precursor steps, we emphasize that they are based on assuming similar isomerization dynamics for dimer and its radical anion. Further and more structurally explicit data, such as could come from infrared spectroelectrochemistry, is obviously needed in future investigations.

Finally, we should note that these results are a further example of using cryoelectrochemistry[34-36] to probe chemical reactivities too rapid to observe at room temperature. Recently, we extended[37] the accessible voltammetric temperature range down to 88 K using a new low-melting electrolyte solution. While the full range of temperatures made available by this development is not exploited here, we suggest that cryoelectrochemistry will prove a useful supplement to ultrafast microelectrode voltammetry[38-42] in observing facile chemical reactions and, as in the present case, add significant activation parameter information.

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

Reactivity of Chloro- and Aqua(diethylenetriamine)platinum(II) Ions with Glutathione, *S*-Methylglutathione, and Guanosine 5′-Monophosphate in Relation to the Antitumor Activity and Toxicity of Platinum Complexes

Milos I. Djuran,† Edwin L. M. Lempers, and Jan Reedijk*

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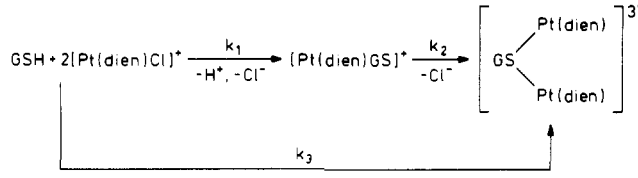
The reactivity of the two platinum(II) complexes $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ with glutathione (GSH), *S*-methylglutathione (GS-Me), and guanosine 5′-monophosphate (5′-GMP) has been investigated and compared. The reactions of GSH and GS-Me with the two platinum complexes are second order, i.e. with a direct nucleophilic attack by the entering ligand on the platinum. For the reaction of 5′-GMP with $[Pt(dien)Cl]^+$ the rate-determining step is the formation of $[Pt(dien)(H_2O)]^{2+}$ followed by a rapid nucleophilic substitution of 5′-GMP, through its N7 atom. The kinetic data show that 5′-GMP has a strong kinetic preference for $[Pt(dien)(H_2O)]^{2+}$ compared with GSH and GS-Me. On the contrary, $[Pt(dien)Cl]^+$ reacts more rapidly with GSH and GS-Me. The obtained kinetic data have been analyzed in relation to the antitumor activity and toxicity of platinum complexes. As a result, a new strategy for the development of novel platinum drugs with improved antitumor properties and lower toxicities has been suggested.

Introduction

After Rosenberg's discovery[1] of the antitumor activity of [*cis*-$PtCl_2(NH_3)_2$] complex (abbreviated cisplatin), many other platinum(II) complexes have been synthesized and tested with the major aims of obtaining better antitumor activity, increased solubility, and lower toxic side effects. At the same time extensive research has been done to establish the mechanism of antitumor activity and toxicity of such platinum(II) complexes.

It has now been generally accepted that the chloro hydrolysis is the rate-determining step in the reaction of cisplatin with DNA.[2] Concerning the rate-determining step of platinum amine compounds with sulfur-containing biomolecules, the available data are rather controversial. It has been reported that the chloro hydrolysis is the rate-determining step in the reactions of cisplatin with leucine aminopeptidase,[3] γ-glutamyl transpeptidase,[3,4] and albumin.[5] However, it has also been suggested that there may be a direct binding to proteins without prior aquation,[6] as has been observed with cysteine,[7,8] glutathione,[7,8] adenosine triphosphatase,[3] and with metallothionein.[9] Given the importance of sulfur-containing biomolecules and their likely responsibility for the development of resistance, inactivation, and toxic side effects of cisplatin, it appears necessary to establish the details of their mechanism of reactions with platinum complexes.

Scheme I



The non-antitumor-active monofunctional [Pt(dien)Cl]Cl complex, with the dien (diethylenetriamine) acting as a non-removable tridentate ligand, has proved to be a very useful model for the first-binding step of platinum antitumor compounds to DNA.[10-12]

† On leave from the University of Svetozar Markovic, Faculty of Science Kragujevac, YU-34000 Kragujevac, Yugoslavia.

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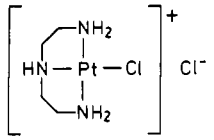
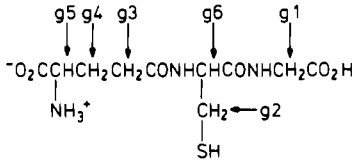


Recently, the reactions of this complex with the tripeptide glutathione (GSH) and its derivative *S*-methylglutathione (GS-Me) has been investigated.[13]



It has been reported that this complex, over the pH range 2–12, has a high affinity for the sulfhydryl group and that the binding to GSH proceeds in two steps (see Scheme I). The first step is forming a mononuclear unit $[Pt(dien)GS]^+$, and in the second step a second $[Pt(dien)Cl]^+$ unit binds to $[Pt(dien)GS]^+$, forming an S-bridged dinuclear unit $[\{Pt(dien)\}_2GS]^{3+}$. It was concluded that at pH <7 the rate of the second platinum-binding step is fast compared to the rate of the first platinum-binding step, while at pH >10 the first binding step becomes faster than the second binding step. Previously, most attention has been given to characterization of the formed complexes, while the mechanism of binding has not been studied in great detail.

In the present paper the rate of reaction and the mechanism of binding of both $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ to GSH and GS-Me have been studied and the results have been compared with those obtained for guanosine 5′-monophosphate (5′-GMP). The obtained kinetic data are discussed in relation to the antitumor activity and toxic side effects of platinum amine complexes.

Experimental Section

Chemicals. Glutathione, *S*-methylglutathione, and guanosine 5′-monophosphate were obtained from Sigma Chemicals and used without further purification.

Preparation of [Pt(dien)Cl]Cl. This complex was prepared by a modification of the method of van Eldik et al.[14a] K_2PtCl_4 (1.00 g, 2.42 × 10^{-3} mol) was dissolved in 30 mL of water, and to this solution 1.0 mL (98%) of diethylenetriamine was added. The pH of the solution was adjusted to ca. 3 by the addition of 1 M HCl, which was followed by further refluxing for 6 h. The yellow solution was filtered, concentrated to 4 mL, and left overnight in a refrigerator. The crystals were removed by filtration, washed with a small amount of ethanol, and air-dried. Yield: 0.6 g (67%). The pure complex was obtained by recrystallization from a small amount of water and cooling. Anal. Calcd for [Pt(dien)Cl]Cl = $C_4H_{13}N_3Cl_2Pt$ (fw = 369.16): C, 13.01; H, 3.54; N, 11.38; Cl, 19.21. Found: C, 13.11; H, 3.52; N, 11.04; Cl, 19.23.

Preparation of [Pt(dien)(NO_3)]NO_3. For preparation of [Pt(dien)(NO_3)]NO_3 the corresponding chloro complex was used and treated in water solution with the appropriate amount of $AgNO_3$ (2 equiv) to precipitate all chloride as AgCl. The mixture was stirred at room temperature in the dark for up to 24 h. The precipitate was removed and the filtrate was evaporated to dryness. In case of hygroscopic residues, a few milliliters of alcohol were added and the evaporation to dryness was repeated. Anal. Calcd for [Pt(dien)(NO_3)]NO_3 = $C_4H_{13}N_5O_6Pt$ (fw = 422.27): C, 11.37; H, 3.10, N, 16.59. Found: C, 11.28; H, 3.12; N, 16.75; Cl, 0.0.

Preparation of [Pt(dien)GS]Cl. This complex was prepared by mixing an equimolar amount of [Pt(dien)Cl]Cl with GSH in D_2O at pH > 10. The reaction mixture, after being left for 15 min at room temperature, was checked for $[Pt(dien)GS]^+$ by ^1H NMR spectroscopy. Any noncoordinated GSH, or $[Pt(dien)Cl]^+$, could be reacted further by addition of one of the two components. The pH of the solution was reduced to ca. 7 by DNO_3, and the filtrate was lyophilized. The resulting yellow solid was kept at −20 °C and was used without further purification.

Analyses. Elemental microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University College, Dublin.

pH Measurements. All pH measurements were performed at 298 K. The pH meter was calibrated with Fischer certified buffer solutions of pH 4.00, 7.00, and 10.00. No corrections were made for the use of D_2O.

Absorption Measurements. The rate constants of the reaction between 5′-GMP and $[Pt(dien)(H_2O)]^{2+}$ were obtained by using a VARIAN DMS 200 UV-visible spectrophotometer. The concentration of 5′-GMP was held constant at 9.84 × 10^{-5} M, and the concentration of $[Pt(dien)(H_2O)]^{2+}$ was varied between 1.2 × 10^{-3} and 4.4 × 10^{-3} M. The reaction was monitored by changes in the absorption at 294 nm in 100 mM phosphate buffer at pH 5.00. The observed rate contants, k_{obs}, were obtained from pseudo-first-order Guggenheim plots. The value of the rate constant for this reaction was determined from the plot of k_{obs} versus concentration of $[Pt(dien)(H_2O)]^{2+}$.

^1H NMR Measurements. All other rate constants presented in Table I were obtained from proton NMR measurements by using a Bruker WM 300 spectrometer. The reactions were carried out in NMR tubes at 295 K in D_2O as a solvent. The concentrations of the reaction components have been determined by measuring the areas of suitable signals with a planimeter. The following signals have been used: g_6 for GSH (1.39 ppm) and $[Pt(dien)GS]^+$ (1.30 ppm), g_5 for $[\{Pt(dien)\}_2GS]^{3+}$ (0.59 ppm), the CH_3 signal for GS-Me (−1.06 ppm) and $[Pt(dien)GS\text{-}Me]^{2+}$ (−0.59 ppm), and H_1' for 5′-GMP (2.75 ppm) and [Pt(dien)(5′-GMP-N7)]$^{2+}$ (2.85 ppm).

For the reactions of GSH with Pt, the respective concentrations were 5.10 and 10.00 mM. For the reactions of $[Pt(dien)GS]^+$ with $[Pt(dien)Cl]^+$, concentrations of 5.00 mM were used for both reactants. The reaction of $[Pt(dien)(H_2O)]^{2+}$ with $[Pt(dien)GS]^+$ was too fast; therefore only the $t_{1/2}$ value is given. The k_3 and k_2 values presented in Table I were obtained at pH 2.00 in 0.01 M DNO_3.

For the reactions of GS-Me with Pt, concentrations of 5.00 mM were used for both reactants. All reactions were carried out at pH 2.00 in 0.01 M DNO_3 and at pH 5.00 in 100 mM phosphate buffer. Care was taken that no phosphate was bound to Pt. (Although one could expect some interaction between phosphate and $[Pt(dien)(H_2O)]^{2+}$, our conditions are much more dilute in platinum (50×) and PO_4^{3-} (6×) then those were binding was observed.[14b]) The reaction between 5′-GMP and $[Pt(dien)Cl]^+$ complex was carried out at pH 5.00 in 100 mM phosphate buffer with 5.00 mM initial concentrations of both reactants.

Table I. Kinetic Data for the Reaction of $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ with GSH, GS-Me, and 5′-GMP, Where *k* Values Are Defined in Scheme I

complex	k(GSH),[a] M^{-1} s^{-1}	k(GSMe),[b] M^{-1} s^{-1}	k(5′-GMP)[b]
$[Pt(dien)Cl]^+$	k_2 = 0.47		
	k_3 = 0.006	k = 0.033	k = 6.2 × 10^{-5} s^{-1}
$[Pt(dien)(H_2O)]^{2+}$	k_2[c] ($t_{1/2}$ < 2 min)		
	k_3 = 0.18	k = 0.51	k = 3.6 M^{-1} s^{-1}

[a] pH 2.00 in 10 mM DNO_3; T = 295 K. [b] pH 5.00 in 100 mM phosphate buffer; T = 295 K. [c] Rate constant could not be determined by ^1H NMR and UV spectroscopy.

Results and Discussion

Determination of the Rate Constants. The two-step mechanism of binding of the monofunctional $[Pt(dien)Cl]^+$ ion to the sulfhydryl group of the tripeptide glutathione can be represented by Scheme I.[13] The rate of formation of the mononuclear $[Pt(dien)GS]^+$ complex, as an intermediate product at pH <7 in comparison with the rate of the second binding step, is slow. At pH >7, on the other hand, the rate of the first binding step is faster than the rate of the second binding step. These, in combination with the fact that at higher pH values (pH >7) the S-bridged dinuclear unit is unstable and dissociates, forming the mononuclear $[Pt(dien)GS]^+$ unit,[13] do not allow for determining k_1 and k_2 separately at physiological pH. Since no platinum exchange reactions between the various species are likely to occur, i.e. at pH <7, the present work is concentrated mainly on the area pH <7. In this pH range, the magnitude of k_3 is nearly equal to k_1

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(14) (a) Mahal, G.; van Eldik, R. *Inorg. Chim. Acta* **1987**, *127*, 203. (b) Appleton, T. G.; Beryy, R. D.; Davis, C. A.; Hall, J. R.; Kimlin, H. A. *Inorg. Chem.* **1984**, *23*, 3514.

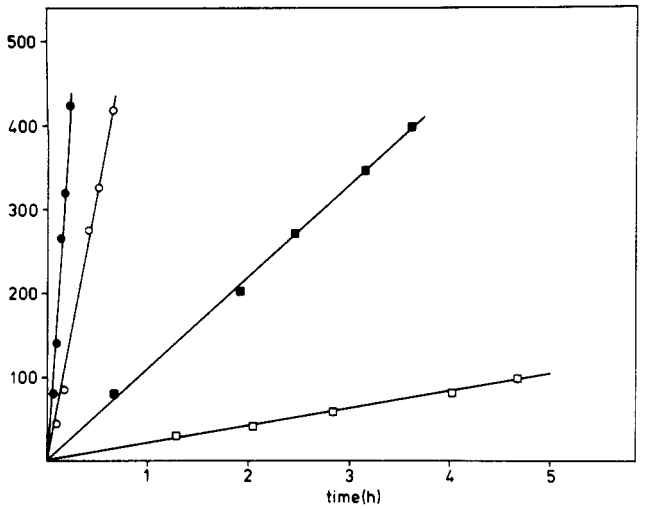

Figure 1. Second-order plot for the reaction of GSH and GS-Me with $[Pt(dien)Cl]^+$ (□, ■) and with $[Pt(dien)(H_2O)]^{2+}$ (○, ●), where open symbols represent GSH and closed symbols represent GS-Me. The y axis represents the right-hand-side term of eq 1 for GSH and eq 2 for GS-Me. Conditions: pH 2.00 in 10 mM DNO_3 for GSH and pH 5.00 in 100 mM phosphate buffer for GS-Me.

(vide supra). Fortunately, the intermediate species $[Pt(dien)GS]^+$ could be prepared spearately (i.e. at pH >10) and therefore k_2 could be determined independently. On the basis of the k_3 and k_2 values, the reactivity and mechanism of binding of $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ complexes with GSH can now be discussed.

The values of k_3 for $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ reactions with GSH (Table I) were obtained from proton NMR measurements of the reaction containing GSH and platinum complex under second-order conditions. For determination of k_3 eq 1 has been applied.[15] In this equation x is the amount of

$$k_3 t = \frac{1}{2a_0 - b_0} \ln \frac{b_0(a_0 - x)}{a_0(b_0 - 2x)} \qquad (1)$$

product, i.e. $[\{Pt(dien)\}_2GS]^{3+}$, and a_0 and b_0 are initial concentrations of GSH and platinum complex, respectively. A plot of the right side of eq 1 versus time yields a straight line passing through the origin, as shown in Figure 1. The values of k_3 (Table I) were obtained from the slope of the straight line.

The reactivity of both the $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ complexes with GSH has been studied over the pH range 2–7. It has been shown that the rate of reaction of these two complexes is nearly pH independent between pH 2 and 5 (suggesting that the protonation of the carboxyl groups in GSH does not affect the reaction velocity), while at pH >5 the aqua complex immediately forms a μ-OH-bridged dimer, which does not react further on the time scale used.[16] In the present study pH 2.00 has been selected, because of better separation of the g_5 and g_6 NMR signals of the various products.

The value of k_2 was determined by ^1H NMR measurements of the reaction containing freshly prepared $[Pt(dien)GS]^+$ and $[Pt(dien)Cl]^+$ complex in the ratio 1:1. For determination of k_2, eq 2 has been used.[15] In this equation x is the amount of S-bridged

$$k_2 t = \frac{x}{a_0(a_0 - x)} \qquad (2)$$

dinuclear complex and a_0 is the initial concentration of $[Pt(dien)GS]^+$. The value of k_2 was determined from the slope of the straight line obtained by plotting the right side of eq 2 versus time (Table I).

For comparison, parallel work has been done with GS-Me. Here only the first step in Scheme I can occur. The values of k were determined by proton NMR measurements of the reaction

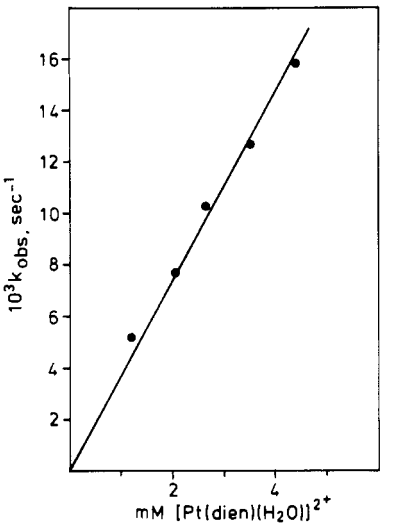

Figure 2. Plot of k_{obs} versus concentration of $[Pt(dien)(H_2O)]^{2+}$ in the reaction with 5′-GMP. Conditions: pH 5.00 in 100 mM phosphate buffer.

containing GS-Me and $[Pt(dien)Cl]^+$, or $[Pt(dien)(H_2O)]^{2+}$, in the ratio 1:1. For determination of the rate constants, eq 2 has been used,[15] where x is the amount of $[Pt(dien)GS\text{-}Me]^{2+}$ and a_0 is the initial concentration of GS-Me. A plot of the right side of eq 2 versus time yields a straight line passing through the origin as shown in Figure 1. The values of k were obtained from the slope of the straight line (Table I). The reaction of $[Pt(dien)Cl]^+$ with GS-Me has been followed also at pH values of 2, 5, and 7 and under different concentrations of phosphate buffer. No significant influence of these two parameters on the magnitude of the rate constant has been observed.

The rate constant for the reaction of 5′-GMP and $[Pt(dien)Cl]^+$ (Table I) was obtained by ^1H NMR measurements. The reaction has been treated under first-order conditions, and for determination of the rate constant, eq 3 has been used.[15] In this equation x is

$$kt = \ln \frac{a_0}{a_0 - x} \qquad (3)$$

the amount of $[Pt(dien)(5'\text{-GMP-N7})]^{2+}$ and a_0 is the initial concentration 5′-GMP. The rate constant was calculated from the slope of the straight line obtained by plotting the right side of eq 3 versus time (Table I).

The reaction of $[Pt(dien)(H_2O)]^{2+}$ with 5′-GMP was too fast to follow by ^1H NMR spectroscopy, and therefore, k_{obs} was obtained from pseudo-first-order conditions by using UV spectrometry. The second-order rate constant was determined from the slope of the straight line obtained by plotting of k_{obs} versus concentration of the $[Pt(dien)(H_2O)]^{2+}$ complex (Figure 2).

Mechanistic Considerations. The reaction of $[Pt(dien)Cl]^+$ with 5′-GMP proceeds in two steps. The first step involves the rate-determining formation of the $[Pt(dien)(H_2O)]^{2+}$ complex, followed in the second step by rapid reaction with 5′-GMP (see Table I). This is a generally accepted mechanism for binding of cisplatin to DNA.[2] To confirm this mechanism for the present case, two sets of experiments were performed. First the determination of the rate of reaction was performed as a function of added NaCl concentration. The rate constant decreases with increasing NaCl concentration, eventually resulting in complete reaction inhibition for a saturated NaCl solution (Figure 3a).

A second experiment was carried out with different $[Pt(dien)Cl]^+$:5′-GMP molar ratios (1:1; 2:1; 1:2). The results presented in Figure 4a clearly confirm that the bimolecular path can be neglected and that the reaction is governed by the solvolytic path.

The reactions of the platinum complexes with GSH and GS-Me are second order, as is shown by the influence of both reactants on the rate of forming the platinum–protein complex (see Figure 4b and Table I). Thus, the reaction of $[Pt(dien)Cl]^+$ with GSH

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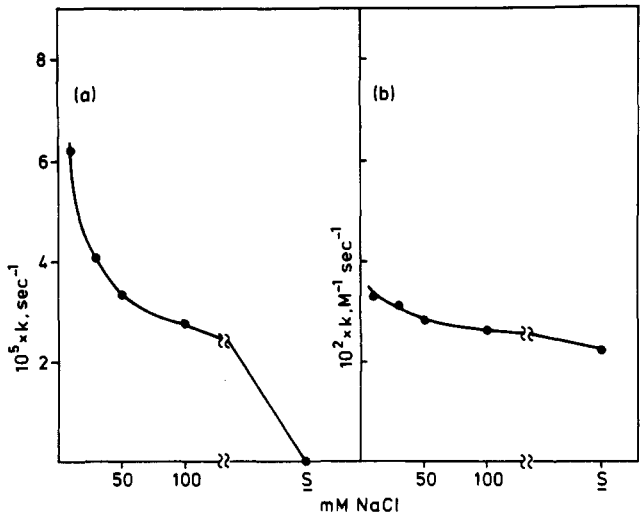

Figure 3. Dependence of the rate constant of the reaction of 5'-GMP (a) and GS-Me (b) with $[Pt(dien)Cl]^+$ on the concentration of NaCl. Conditions: T = 295 K; pH 5.00 in 100 mM phosphate buffer. S represents the concentration of a saturated NaCl solution.

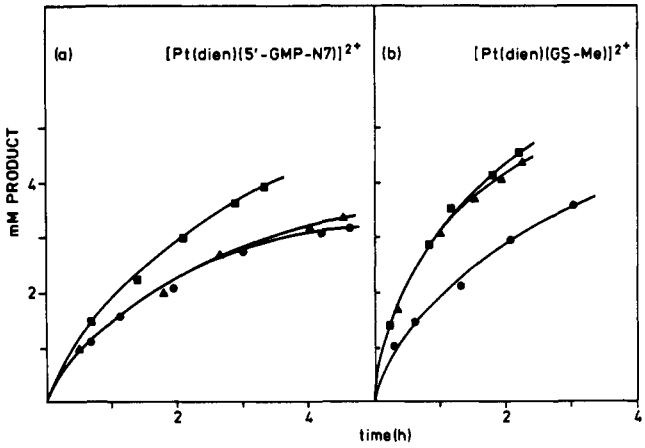

Figure 4. Time dependence of product formation between 5'-GMP (a) or GS-Me (b) with $[Pt(dien)Cl]^+$ in different molar ratio, where 5'-GMP/GS-Me:$[Pt(dien)Cl]^+$ ratio = 1:1 (●), 2:1 (▲), and 1:2 (■). Conditions: T = 295 K; pH 5.00 in 100 mM phosphate buffer. In each case, 1 unit corresponds to 5 mM.

or GS-Me involves direct nucleophilic attack by the entering ligand. Influence of the NaCl concentration on the reaction rate between GSH and the $[Pt(dien)Cl]^+$ complex could not be observed due to experimental problems (i.e. the signal of the g_6 proton overlaps with the water peak). A small effect of the NaCl concentration on the rate constant for the reaction between GS-Me and chloro complex was observed, which is rationalized by assuming that a part of the reaction goes through the hydrolysis path (Figure 3b).

From Table I it is concluded that GS-Me reacts faster with $[Pt(dien)Cl]^+$ and $[Pt(dien)(H_2O)]^{2+}$ compared to GSH (e.g. 0.033 vs 0.006 M^{-1} s^{-1} for reaction with $[Pt(dien)Cl]^+$). Apparently, GS-Me is a stronger nucleophile than GSH, which is rationalized by the more positive inductive effect of the methyl group. It has been proven that GS^- reacts remarkably faster than GSH with $[Pt(dien)Cl]^+$,[13] which is indicative for a slightly higher reactivity of glutathione at physiological pH compared to the present results. $[Pt(dien)GS]^+$ is extremely reactive toward another $[Pt(dien)Cl]^+$ unit (0.47 M^{-1} s^{-1}). The strong nucleophilicity of $[Pt(dien)GS]^+$ can be correlated with a decrease of the electrons density on the platinum, caused by the overlap of a filled d orbital of platinum and a vacant d orbital of sulfur.[17]

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The reactions of 5'-GMP, GSH, and GS-Me with $[Pt(dien)(H_2O)]^{2+}$ are more rapid than the corresponding reactions with $[Pt(dien)Cl]^+$ (Table I). This is further evidence that water is a better leaving ligand than chloride. The present results are in agreement with previous results for similar complexes with different entering ligands.[18,19] Highly surprising is the fact that the order of reactivity of GS-R (R = H, Me) and 5'-GMP is opposite for $[Pt(dien)Cl]^+$ compared with $[Pt(dien)(H_2O)]^{2+}$. GS-R reacts mainly directly with $[Pt(dien)Cl]^+$, and therefore, its overall reaction is faster compared to 5'-GMP. Illustrative for this is the competition experiment as carried out between 5'-GMP and GS-Me with $[Pt(dien)Cl]^+$ (1:1:1). A GS-Me:5'-GMP reactivity ratio = 5:1 was observed. On the other hand, from the data in Table I it is evident that 5'-GMP is the most reactive nucleophile toward $[Pt(dien)(H_2O)]^{2+}$, as was also concluded from a competition experiment as carried out by 5'-GMP and GS-Me with $[Pt(dien)(H_2O)]^{2+}$ (1:1:1). Only binding to 5'-GMP was observed. This apparent contradiction is difficult to explain. Possibly the aqua ligand needs not be polarized (because of the extreme lability), and therefore, the transition state is stabilized most for 5'-GMP. Steric effects and the negative charge on GMP, however, can also be of importance. In vivo, the −1 charge per phosphate on DNA can have a similar effect.

Reactivity of Platinum Complexes in Relation to the Antitumor Activity and Toxicity. When cisplatin is dissolved in water, the labile chloro ligands are slowly replaced by water molecules and mainly two aquated platinum species will be formed in solution, i.e. $[cis\text{-}Pt(NH_3)_2Cl(H_2O)]^+$ and $[cis\text{-}Pt(NH_3)_2(H_2O)_2]^{2+}$.[20] Since water is a better leaving group than chloride,[18,19] the aqua species are most likely the reactive form of cisplatin in vivo. Thus, the hydrolysis is the rate-limiting step in the reaction of cisplatin with biomolecules like DNA.[2] In fact, recent results of House and Lippard et al.[21] indicate that most likely $[cis\text{-}Pt(NH_3)_2Cl(H_2O)]^+$ is the predominant species that reacts with DNA. Our present results, showing that $[Pt(dien)Cl]^+$ reacts with 5'-GMP through the hydrolysis pathway, are in agreement with the above-mentioned hypothesis.

In contrast to their reactions with DNA, it has been suggested that the reaction of cisplatin and related platinum complexes with S-containing nucleophiles goes primarly without prior aquation.[6] Direct nucleophilic substitution of a chloride ligand has been observed in the reaction with cysteine,[7,8] GSH,[7,8] adenosine triphosphatase,[3] and metallothionein.[9] The results from this work for the reaction between $[Pt(dien)Cl]^+$ and GSH and GS-Me also showed second-order behavior, which is evidence for a direct binding without prior aquation.

The selective preference of the aqua and chloro platinum species to different donor atoms (i.e. the aqua complex reacts mainly with 5'-GMP, whereas the chloro complex reacts predominantly with GSH and GS-Me) can have important consequences for the behavior of antitumor platinum complexes after administration in the human body. This means that in the blood plasma, where the concentration of the chloride ion is sufficiently large to prevent hydrolysis, only sulfur-containing proteins will react with the platinum complex, but inside the cell, with a much lower concentration of the chloride ion (about 4 mM), N7 of the guanine base of DNA will be able to compete with S-donor biomolecules.

Increasing the steric crowding in the planar complex is known to result in a decrease of the rate of the substitution reaction. The recent analysis of van Eldik[22] and our present data are of great importance for the strategy of the development of new platinum drugs. If it would be possible to develop a compound with structural properties such that the direct attack by sulfur is in-

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hibited, but with a similar rate of chloro hydrolyses compared to cisplatin, this would lead to species with improved antitumor properties and lower toxicities.

The promising antitumor activities of the new platinum complexes with general formulas [Pt(diam)(R'R''SO)Cl](NO$_3$) (diam = bidentate amine and R'R''SO = substituted sulfoxide)[23] and [*cis*-Pt(NH$_3$)$_2$(N-het)Cl]Cl (N-het = heterocyclic amine)[24] could in view of the above have favorable nitrogen over sulfur binding ratios. In conclusion, important information is presented that could ultimately lead to new antitumor complexes such that the binding to sulfur-containing biomolecules is inhibited. This could lead to lower amounts of inactivation and diminished toxic side effects.

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Contribution from the Department of Chemistry, Pohang Institute of Science and Technology, P.O. Box 125, Pohang, 790-330 South Korea, and School of Chemical Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Synthesis and Structure of Transition-Metal Bis(porphyrinato) Complexes. Characterization of Zr(TPP)$_2$ and Zr(OEP)$_2$

Kimoon Kim,*,† Won S. Lee,† Hee-Joon Kim,† Sung-Hee Cho,† Gregory S. Girolami,*,‡ Philip A. Gorlin,‡ and Kenneth S. Suslick*,‡

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Treatment of Zr(NEt$_2$)$_4$ with the free-base porphyrins 5,10,15,20-tetraphenylporphyrin (H_2TPP) or 2,3,7,8,12,13,17,18-octaethylporphyrin (H_2OEP) gives the transition-metal bis(porphyrinato) complexes Zr(TPP)$_2$ and Zr(OEP)$_2$. The hafnium analogue Hf(OEP)$_2$ may be prepared similarly from Hf(NEt$_2$)$_4$. The complexes have been characterized by UV-vis and ^{1}H NMR spectroscopy, and the molecular structure of Zr(TPP)$_2$ has been determined crystallographically. The Zr-N distances of 2.40 (1) Å and the porphyrin-porphyrin interplanar spacing of 2.56 Å are the shortest such distances in all known M(porphyrinato)$_2$ complexes. The cyclic voltammograms indicate that Zr(TPP)$_2$ and Zr(OEP)$_2$ each undergo two oxidations and two reductions; the redox potentials suggest that there is significant overlap between the π-systems of the two porphyrin rings. Chemical oxidation of the Zr(porphyrinato)$_2$ complexes with phenoxathiinylium hexachloroantimonate has led to the isolation of the π-radical-cation complexes [Zr(TPP)$_2^+$][SbCl$_6^-$] and [Zr(OEP)$_2^+$][SbCl$_6^-$]. The UV-vis, near-IR, EPR, and IR spectra of these cations are consistent with oxidation of the porphyrin-porphyrin π-system; most notable are the unusually high energy near-IR bands at 1110 and 962 nm in the TPP and OEP complexes, respectively. The high energy of these bands with respect to those of other [M(porphyrinato)$_2^+$] cations with larger metal atoms again can be rationalized on the basis of unusually strong overlap between the π-systems of the two porphyrin rings. Crystallographic data for Zr(TPP)$_2$·C$_5$H$_{12}$: monoclinic, space group $C2/c$, with a = 21.183 (3) Å, b = 21.263 (4) Å, c = 18.688 (3) Å, β = 124.57 (1)°, V = 6930.9 Å^3, Z = 4; R_F = 0.077 and R_{wF} = 0.083 for 1578 independent reflections with $I > 3\sigma(I)$.

Introduction

Complexes that possess two phthalocyanine[1] or two porphyrin[2] macrocycles bound to a single metal center are proving useful as structural and spectroscopic models of the bacteriochlorophyll special pair in the reaction center[3] of photosynthesis. To date, such bis(porphyrinato)metal complexes have only been prepared with metals that possess very large ionic radii (>1.0 Å) such as yttrium,[4] the lanthanides,[5] and the actinides (U and Th).[6] We now report the synthesis, characterization, and X-ray structure of *transition-metal* bis(porphyrinato) complexes, Zr(TPP)$_2$ and Zr(OEP)$_2$.[7] In these compounds, the two porphyrin rings are held in unusually close proximity due to the smaller ionic radius of zirconium (ca. 0.84 Å). These complexes exhibit interesting and unusual properties as a result of the small distance between the two porphyrin ring planes.

Results and Discussion

The preparation of the bis(porphyrinato)zirconium and -hafnium complexes follows our previously described synthesis of the thorium and uranium analogues.[6] Thus, treatment of the diethylamido complex[8] Zr(NEt$_2$)$_4$ with the free porphyrins H_2TPP and H_2OEP, followed by chromatography on alumina or silica gel, yields Zr(TPP)$_2$ and Zr(OEP)$_2$ in 54% and 55% yields, re-

† Pohang Institute of Science and Technology.
‡ University of Illinois at Urbana-Champaign.

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