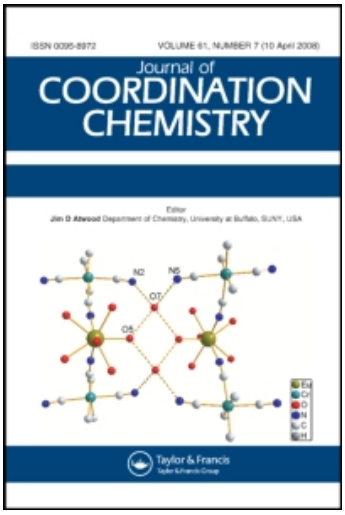

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NEW TRIAMINE-TYPE PLATINUM(II) COMPLEXES OF PHENYL-SUBSTITUTED ETHYLENEDIAMINE: REACTIVITY WITH 5′-GMP

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New triamine-type platinum(II) complexes, [PtCl(amine)(diamine)]$^+$ (amine = 2-aminoethanol (ae-OH) or 2-methoxyethylamine (ae-OMe); diamine = $(NH_3)_2$, ethylenediamine (en), *N,N′*-dibenzylethylenediamine (dibenzylen) or 1,2-diphenylethylenediamine (stien)) were synthesized and their reactions with 5′-guanosine monophosphate (5′-GMP) were studied through ^{1}H NMR measurements. The rate constants for reactions of stien complexes are half those for the en complexes. The dibenzylen complex has lower reactivity because of the bulky benzyl groups. The resulting order of reactivities is en > stien > $(NH_3)_2$ ≥ dibenzylen. In comparison of monoamine ligands, the complexes of 2-methoxyethylamine have higher reactivities than those of 2-aminoethanol.

Keywords: triamine-type Pt(II) complex; reactivity with nucleotide; antitumor activity

INTRODUCTION

While cisplatin-type platinum(II) complexes, *cis*-[Pt(Am)$_2$X$_2$] (Am = amine or 1/2 chelating diamine, X = leaving group) are widely known as antitumor agents,[1–4] few excellent antitumor complexes have ligands with aromatic rings. However, there are some studies of antitumor behavior for other types of Pt complexes such as [Pt(en) (2,2′-bpy)]$^{2+}$ and *cis*-[PtCl(NH$_3$)$_2$(9-AA)]$^+$ (9-AA = 9-aminoacridine), where DNA-aromatic ring interactions such as intercalation or stacking are suggested to play an important role in the antitumor activity.[5–6]

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Antitumor properties of platinum complexes with three nitrogen donors having the general formula, *cis*-[PtCl(Am)$_2$(N-het)]Cl (N-het = heterocyclic amine such as pyridine or cytosine) were reported recently. These complexes are more soluble in water than the neutral complexes.[7] We expect a new mechanism of antitumor activity for these complexes differing from that of *cis*-DDP based on their lack of cross-resistance with cisplatin-resistant tumor lines.

In this paper, we report the syntheses of new triamine-type platinum complexes containing phenyl-substituted ethylenediamine (*N,N'*-dibenzylethylenediamine (dibenzylen) and *rac*-1,2-diphenylethylenediamine (stien), and the effects of non-leaving groups on their reactivities with 5'-guanosinemonophosphate (5'-GMP) measured by ^{1}H NMR. The present complexes are expected to be antitumor agents which display a new-type of antitumor activity due to both Pt-DNA binding and an aromatic ring interaction with the DNA base.

EXPERIMENTAL

All *cis*-[PtCl$_2$(Am)$_2$] starting materials were prepared from K_2PtCl_4 by literature methods.[8-9] [PtCl$_2$ (dibenzylen)] was prepared by the same procedure as [PtCl$_2$(stien)].[9]

[PtCl(ae-OH)(dibenzylen)]Cl (1)

To a solution of [PtCl$_2$(dibenzylen)] (0.5 g, 1 mmol) in 50 mL of DMF was added 2-aminoethanol (0.065 g, 1 mmol). The solution was heated (40–50 °C) for 2 days. The resulting yellow solution was concentrated to *ca.* 5 mL by evaporation, and then about 50 mL of ether was added to the concentrate. The precipitate was filtered, and after drying, it was suspended in 10 mL of methanol. The solution was filtered and the filtrate was evaporated to dryness. The resulting white precipitate was recrystallized from ether-ethanol (1:3). (Yield = 21%)

^{1}H NMR (D_2O) δ = 7.70 - 7.25 (10H, m), 3.66, 3.34 (each 2H, s), 3.59 (2H, t, J = 4.6 Hz), 2.90 (2H, t, J = 4.6 Hz), 2.70 - 2.55 (4H, m). *Anal.* Calcd. for $C_{18}H_{27}N_3Cl_2OPt$(%): C,38.1; H,4.85; N,7.55. Found: C,37.7; H,4.76; N,7.41.

[PtCl(ae-OH or ae-OMe)(stien)]NO_3 (2a) (2b)

A solution of $AgNO_3$ (0.14 g, 0.8 mmol) in 10 mL of DMF was added gradually to a slurry of 0.38 g (0.8 mmol) of [PtCl$_2$(stien)] in 30 mL of DMF at 40 °C for 12 h. The solution was stirred for another 12 h. The AgCl which precipitated was filtered off, and an equimolar amount of 2-aminoethanol (0.05 g) or 2-methoxyethylamine (0.06 g) was added. The mixture was stirred for 24 h. The resulting yellow solution was reduced in

volume, mixed with about 60 mL of ether and allowed to stand overnight. The precipitate was filtered and then was added to 10 mL of methanol. The solution was filtered and evaporated. The resulting white crystals were recrystallized once from water, once from methanol. (Yield = 28%)

^{1}H NMR (**2a**) (D_2O) δ = 7.40 - 7.24 (10H, m), 4.40, 4.33 (each 1H, d, J = 12.3 Hz), 3.83 (2H, t, J = 5.2 Hz), 2.91 (2H, t, J = 5.2 Hz); (**2b**) (D_2O) δ = 7.40 - 7.24 (10H, m), 4.39, 4.33 (each 1H, d, J = 11.7 Hz), 3.67 (2H, t, J = 5.4 Hz), 3.38 (3H, s), 2.91 (2H, t, J = 5.4 Hz). *Anal.* Calcd. for $C_{16}H_{23}N_4ClO_4Pt$ (**2a**) (%): C,34.0; H,4.07; N,9.90. Found: C,34.2; H,4.06; N,10.1. *Anal.* Calcd. for $C_{17}H_{25}N_4ClO_4Pt$ (**2b**)(%): C,35.2; H,4.31; N,9.66. Found: C,35.6; H,4.24; N,9.21.

[PtCl(ae-OH)(en)]Cl (3a)

To a solution of [$PtCl_2$(en)] (0.33 g, 1 mmol) in 10 mL of DMF was added $AgNO_3$ (0.17 g, 1 mmol). The solution was stirred for 16 h. The AgCl was filtered off and 0.065 g(1 mmol) of 2-aminoethanol was added to the filtrate. The mixture was stirred for 24 h. The resulting yellow solution was evaporated to dryness, and then the residue was mixed with about 50 mL of ether. After stirring overnight, the precipitate was filtered and then was added to 10 mL of methanol. The solution was filtered and evaporated to dryness. The residue was dried under vacuum. The oily residue was recrystallized from 0.1 M HCl. The resulting light yellow solid was further recrystallized from methanol. (Yield = 23%)

^{1}H NMR (D_2O) δ = 3.81 (2H, t, J = 5.8 Hz), 2.84 (2H, t, J = 5.8 Hz), 2.70, 2.64 (each 2H, t, J = 5.2 Hz). *Anal.* Calcd. for $C_4H_{15}N_3Cl_2OPt$(%): C,12.4; H,3.89; N,10.9. Found: C,12.1; H,3.88; N,11.1.

[PtCl(ae-OMe)(en)]NO_3 (3b)

To a solution of [$PtCl_2$(en)] (0.33 g, 1 mmol) in 10 mL of DMF was added $AgNO_3$ (0.17 g, 1 mmol). The solution was stirred for 16 h. The AgCl was filtered off and 0.075g (1 mmol) of 2-methoxyethylamine was added. The mixture was stirred for 24 h. The resulting yellow solution was evaporated to dryness, and then the residue was mixed with about 50 mL of CH_2Cl_2. After stirring for 2 h, the precipitate was filtered and then was dissolved in 10 mL of methanol. The solution was filtered and concentrated. To the residue was added a small amount of ethanol. The resulting light yellow solid was recrystallized from methanol. (Yield = 39%)

^{1}H NMR (D_2O) δ = 3.68 (2H, t, J = 4.9 Hz), 3.40 (3H, s), 2.88 (2H, t, J = 4.9 Hz), 2.68, 2.59 (each 2H, t, J = 5.2 Hz). *Anal.* Calcd. for $C_5H_{17}N_4ClO_4Pt$(%): C,14.0; H,3.98; N,13.1. Found: C,13.8; H,3.74; N,13.3.

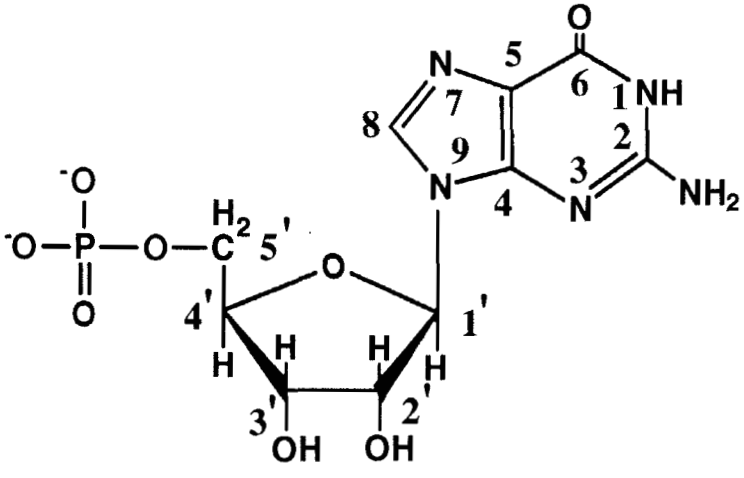
cis-[PtCl(ae-OMe)$(NH_3)_2$]NO_3 (4)

To a solution of *cis*-[$PtCl_2(NH_3)_2$] (0.3 g, 1 mmol) in 10 mL of DMF was added $AgNO_3$ (0.17 g, 1 mmol). The solution was stirred for 16 h. The AgCl was filtered off and 0.075 g (1 mmol) of 2-methoxyethylamine was added. The mixture was stirred for 24 h. The resulting yellow solution was evaporated and then mixed with about 50 mL of ether. After stirring for 2 h, the precipitate was collected and dissolved in 10 mL of methanol. The solution was filtered and concentrated. To the residue was added a small amount of ethanol. The resulting light yellow solid was recrystallized from methanol. (Yield = 18%)

^{1}H NMR (D_2O) δ = 3.39 (3H, s), 3.69 (2H, t, J = 5.4 Hz), 2.87 (2H, t, J = 5.4 Hz). *Anal.* Calcd. for $C_3H_{15}N_4ClO_4Pt$(%): C,8.97; H,3.74; H,13.9. Found: C,8.64; H,3.69; N,14.0.

Determination of Second-Order Reaction Rate Constants

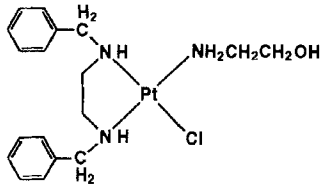
In order to compare the reactivity of these Pt complexes with DNA nucleotide, we determined the second-order rate constants of their reaction with 5′-GMP (sodium salt, see Scheme 1) through ^{1}H NMR measurements. The spectra were recorded with a JEOL JNM-EX270 spectrometer. The measurements were performed on solutions containing the equimolecular complex and each nucleotide in D_2O (10 mM, pD = 6~7) at 37 °C. The rates were followed by monitoring the guanosine H8 signal changes in the ^{1}H NMR spectra. The rate constants were obtained by plotting the reciprocal concentrations *vs.* time. Typical correlation coefficients were in the range 0.994–0.999.



Scheme 1 5′-guanosine monophosphate (5′-GMP)

RESULTS AND DISCUSSION

Figure 1 shows the schematic structures of the triamine Pt (II) complexes used in the present investigation. Some carbon and hydrogen atoms are omitted for simplicity. Figure 2 shows the ^{1}H NMR spectra of 5′-GMP adducts of the triamine-type complexes depicted in Figure 1; their chemical shifts (H8, H1′) appear in Table I. It is clear that their resonances shift slightly to lower field owing to the Pt binding with N7.[10] However, in the case of dibenzylen complex **1**, the H8 resonance of its adduct is split into two signals. The splitting may be ascribed to the presence of diastereomers, because the secondary amine nitrogen atoms of dibenzylen are chiral. Such splitting is not observed in the case of stien complexes **2a** and **2b**, which also exist as optical isomers. In addition, as depicted in Figure 3, the H8 resonance of the reaction mixture between **1** and guanosine, which has no phosphate groups unlike 5′-GMP, shows a single band in the NMR spectrum. Therefore, these findings suggest the existence of rotational isomers due to steric hindrance between the N-substituted benzyl groups of dibenzylen and the phosphate group of 5′-GMP. Moreover, the H1′ resonance of 5′-GMP shifts slightly to higher field upon complexation with **1**. This may be attributed to the ring current effect by the N-substituted benzyl groups.



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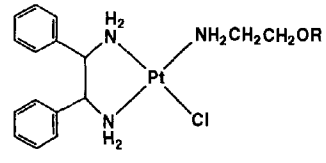

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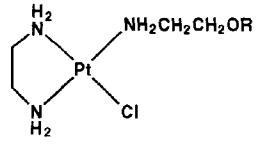
2b R = CH_3



3a R = H
3b R = CH_3

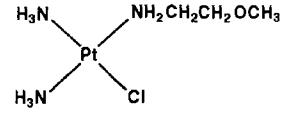


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FIGURE 1 Schematic structures of the triamine Pt(II) complexes. (diamine: 1, dibenzylen; 2, stien; 3, en; 4, diammine).

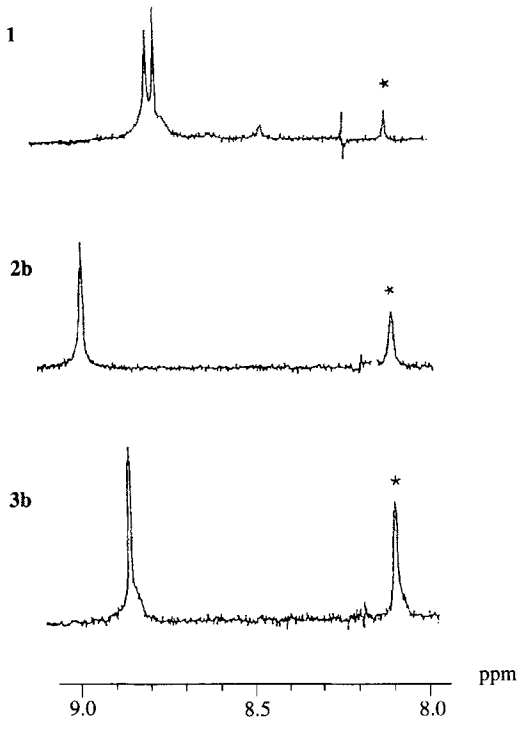

FIGURE 2 ^{1}H NMR H8 signals of 5'-GMP adducts of **1, 2b,** and **3b**. Free 5′-GMP signal is marked with an asterisk.

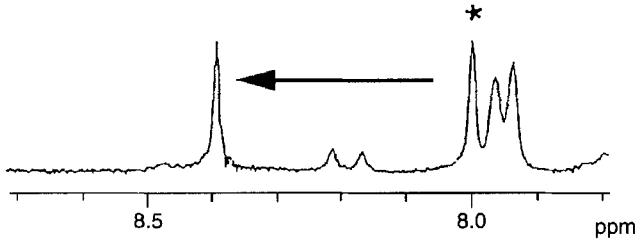

FIGURE 3 ^{1}H NMR spectral change of H8 signals in the reaction between guanosine and **1**. Free guanosine signal is marked with an asterisk.

We studied the relative reactivities of each triamine-type complex with 5′-GMP based on the second-order rate constants k_2 determined through ^{1}H NMR measurements. Typical plots are depicted in Figure 4, and the results are listed in Table I. For these experiments, we used 2-aminoethanol (ae-OH) or 2-methoxyethylamine (ae-OMe) as a monoamine ligand *trans* to diamine in the hope of increasing the solubility in water. Among the three complexes containing ae-OH, it is clear that the reactivity

of the en complex **3a** is the highest. The value of the stien complex **2a** is about half that of the en complex, and the value of the dibenzylen complex **1** is half that of **2a**. On the other hand, the reactivities of the complexes containing ae-OMe show the same trend as those of the ae-OH complexes in order, but these rate constants are larger than those of the ae-OH series. Through the low reactivities of ae-OH complexes, we expect that their hydroxyl groups exert a peculiar influence which may be an electrostatic interaction preventing access of the donor atom (N7) of the nucleotide to the platinum.

TABLE I ^{1}H NMR spectral data and rate constants of reaction with 5'-GMP

compound	*chemical shift δ (ppm)* *H8*	*H1'* [a]	*rate constant* k_2 ($\times 10^{-2} M^{-1} s^{-1}$)
5'-GMP	8.11	5.90	
guanosine	8.00	5.80	
5'-GMP adducts of			
[PtCl(ae-OH)(dibenzylen)]Cl (1)	8.85 8.82	5.88	1.7
[PtCl(ae-OH)(stien)]NO_3 (2a)	9.02	6.05	3.5
[PtCl(ae-OMe)(stien)]NO_3 (2b)	9.05	6.03	7.8
[PtCl(ae-OH)(en)]Cl (3a)	8.92	6.05	6.3
[PtCl(ae-OMe)(en)]NO_3 (3b)	8.86	6.04	13.9
[PtCl(ae-OMe)$(NH_3)_2$]NO_3 (4)	8.93	6.02	4.2

[a] doublet.

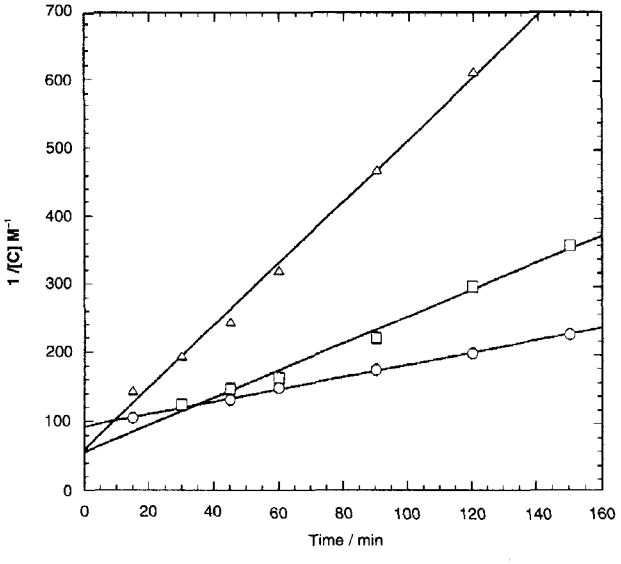

FIGURE 4 Typical kinetic plots of reaction between triamine complexes and 5'-GMP. (○ : **1**, ❑ : **2a**, △ : **2b**)

Based on our kinetic data, we found that the order of reactivity is en > stien > $(NH_3)_2$ ≥ dibenzylen. It has been reported that, in the case of cisplatin-type platinum complexes, the order of reactivities with nucleotides is NH_3 > RNH_2 > R_2 NH, and the ethylenediamine complex is recognized to have higher reactivities with guanosine nucleotides than complexes of diammine or bis alkyl-substituted monoamine.[10–11] Because stien is a chelate NH_2 -type diamine ligand like ethylenediamine, the reaction sites of both complexes are structurally comparable. The difference in reactivity between these complexes is expected to be caused by the *trans* lability relative to the Cl-nucleotide replacement reaction. Although dibenzylen is also a chelate diamine ligand, its complex has lower reactivity. This is in agreement with the case of bis alkyl-substituted monoamine complexes.

Reactions between platinum complexes and nucleotides may depend on the ability to form N—H··· phosphate hydrogen bonds.[12–13] We expected the reactivities to contain a kinetic factor such as a *trans* effect of the non-leaving ammine or amine ligands.

In examinations of our new triamine-type complexes containing substituted ethylenediamine with aromatic rings, the reactivities of the stien complexes with 5′-GMP are higher than that of the dibenzylen complex. In the case of the reactions between these complexes and double-stranded DNA, two structural features differing from that of *cis*-DDP are expected. One is monofunctional Pt-DNA binding. The other is stacking interactions between the aromatic rings of the complexes and DNA-bases surrounding the binding site. Further experiments are required to elucidate this structural mechanism and the resulting biological activity.

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