

Synthesis, Antitumor Activity, and Chemical Properties of Silaplatin and Related Platinum(II) and Platinum(IV) Complexes Derived from β -Silyl Amines

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Received April 14, 1994[®]

Platinum(II) and platinum(IV) coordination complexes derived from β -silyl-substituted amines were prepared. The solubility of selected complexes in water and physiological saline was measured, and the effect of the β -silicon on the reactivity of the complex in aqueous solution was determined by HPLC. The stabilities of selected silyl complexes were compared to the carbon analogues. The cyclic complexes **2a** ("silaplatin") and its Pt(IV) analogue, **2b**, were very active against L1210 leukemia in vivo. Both the platinum(II) complex **2a** and the platinum(IV) complex **2b** produced a significant number of cures over the dose range 10–40 mg/kg. The platinum(II) complex **2a**, silaplatin, was very active in vivo against an L1210 leukemia subline that was resistant to cisplatin; **2a** was also active, when given ip, against ic implanted L1210. The cyclobutanedicarboxylic acid complex **3c** was synthesized; this complex was active against both cisplatin sensitive and resistant L1210 leukemia but was less potent than the analogous dichloro compound **2a**. The acyclic platinum(II) and platinum(IV) complexes **1a,b** were synthesized and unexpectedly found to be inactive in vivo against L1210 leukemia. More lipophilic silaplatin analogues were prepared—Pt(II) complex **2c** and Pt(IV) complex **2d** have one additional methylene carbon compared to **2a,b**, whereas Pt(II) complex **2e** and Pt(IV) complex **2f** have two additional methylene carbons. Cyclization of the alkyl groups attached to the silicon gave the spiro bicyclic Pt(II) complexes **10a** and **11a** and the Pt(IV) complexes **10b** and **11b**.

The clinical efficacy of *cis*-dichlorodiammineplatinum(II), cisplatin, has provided the impetus for the search for additional metal coordination complexes to be used in cancer chemotherapy. This has led to the investigation of a wide range of platinum complexes as well as complexes of other metals (e.g., gold, palladium, cobalt, and chromium, etc.). The goals are to develop complexes with a different spectrum of antitumor activity than cisplatin, to develop compounds with activity against tumor sublines that have acquired resistance to cisplatin, and to develop compounds that are less toxic than cisplatin. The toxic effects of cisplatin include nephrotoxicity, ototoxicity, myelosuppression, neurotoxicity, and severe nausea and vomiting. We reported the synthesis and antitumor activity of tetraplatin (a tetrachloroplatinum(IV) complex of *trans*-1,2-diaminocyclohexane), a platinum complex with reduced renal toxicity compared to cisplatin and with activity against cisplatin resistant sublines of murine P388 and L1210 leukemias.¹ Tetraplatin also has shown to possess suitable physicochemical properties for pharmaceutical formulation development.²

This report describes the synthesis and evaluation of platinum complexes derived from β -silyl-substituted amines.³ The effect of the silicon in the β -position is one of a powerful electron-releasing substituent that can stabilize positively charged species through a hyperconjugative interaction (the so-called β -effect of silicon).⁴ The β -effect increases the base strength of amines: 2,2-dimethylaminopropane has a $pK_a = 10.21$ compared to

a $pK_a = 10.96$ for (aminomethyl)trimethylsilane.⁵ We prepared platinum-coordinated compounds derived from β -silyl amines to determine the effect of this substitution on the biological activity and chemical properties of the complexes. Our approach was to prepare platinum(II) and platinum(IV) complexes derived from monodentate and bidentate amine ligands. The bidentate amine ligands were of particular interest because cyclic platinum complexes derived from diamines frequently show activity against tumor sublines with acquired resistance to cisplatin and because cyclic complexes are less hindered around the reactive center, platinum, than corresponding acyclic analogues. The reactivity of platinum(II) complexes is known to be influenced by steric effects.⁶ This point raises another important feature of silicon, namely, the carbon–silicon bond is longer than a carbon–carbon bond (the carbon–carbon bond length in 2,2-dimethylpropane is 1.54 Å, whereas the carbon–silicon bond length in tetramethylsilane is 1.89 Å). The longer carbon–silicon bond reduces the steric hindrance around platinum in a β -silyl compound relative to an analogous carbon compound. The reduction of steric hindrance in square-planar complexes generally results in an increased rate of ligand substitution by the associative mechanism.^{1,7}

The final difference between carbon and silicon that may be relevant in drug design is the increased lipophilic character of silicon (the hydrophobic fragment constants for C and Si are 0.20 and 0.65, respectively). This latter difference is not easily assessed in the complexes because of the uncertainty of the overall effect of the β -silicon/ammonium interaction on lipophilicity.

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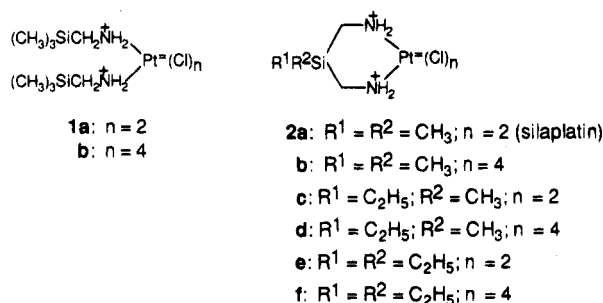
[‡] National Institutes of Health.

[®] Abstract published in *Advance ACS Abstracts*, September 1, 1994.

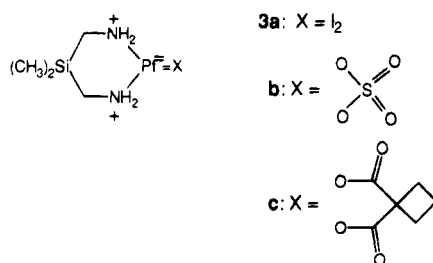
The series of platinum complexes reported in this study also include changes in the alkyl groups on the bis-(aminomethyl)dialkylsilane moiety, designed to represent a series with ascending lipophilicity.

Chemistry

The platinum(II) complexes **1a** and **2a,c,e** were synthesized from pure **4c** and **7a,c,e**, respectively, by treatment with pure potassium tetrachloroplatinate in degassed water-methanol for 16 h at 20 °C (protected from light and under an argon atmosphere). The platinum(II) complexes **1a** and **2a,c,e** were oxidized to the platinum(IV) complexes **1b** and **2b,d,f**, respectively, by treatment with chlorine in 0.5 N HCl at 60 °C.⁸ The

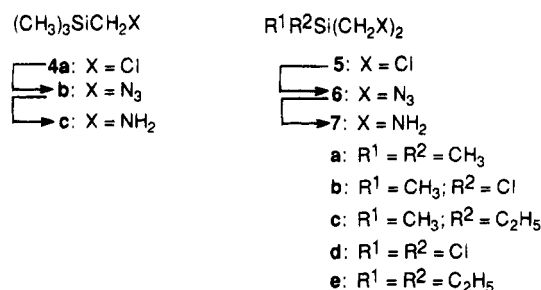


cyclobutanedicarboxylic acid ("CBDCA") complex **3c** was also prepared for comparison with **2a**. Treatment of **7a** with potassium tetrachloroplatinate in the presence of excess potassium iodide gave [bis(aminomethyl)dimethylsilane]diiodoplatinum(II) (**3a**). The diiodoplatinum complex **3a** was treated with silver sulfate, and the resulting sulfate complex **3b** was converted to **3c** by treatment with the barium salt of CBDCA. The *N*-methylimino diacetic acid derivative was also prepared by this method but was not readily purified. The product and three major impurities had similar HPLC retention times (RP8 column eluted with water-acetonitrile, 3:1).

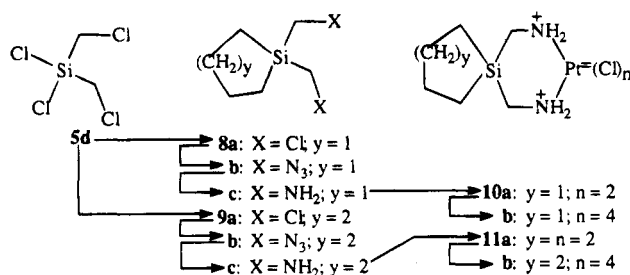


(Aminomethyl)trimethylsilane (**4c**) was synthesized from (chloromethyl)trimethylsilane (**4a**) by treatment with sodium azide^{9,10} in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) followed by reduction of the azide **4b** (lithium aluminum hydride in ether at 0 °C). The bis(chloromethyl)dialkylsilanes **5c,e** were synthesized from bis(chloromethyl)methylchlorosilane (**5b**) and bis(chloromethyl)dichlorosilane (**5d**), respectively, by treatment with ethylmagnesium bromide. The bis-azides **6a,c,e** were prepared from the corresponding bis(chloromethyl)dialkylsilanes (**5a,c,e**, respectively) and NaN_3 in sulfolane rather than DMPU. The bis-azides were isolated from the high-boiling solvent in a low-temperature distillation (low-temperature distillation of **6** from DMPU gave a product that was contaminated with DMPU, and higher temperature distillation

resulted in a severe explosion). The bis-azides **6** were reduced to the diamines **7a,c,e** (lithium aluminum hydride, 0 °C). The volatile diamines **7** are difficult to purify, but purification is essential for success in obtaining pure complexes in the subsequent steps.



The spiro bicyclic complexes **10** and **11** were designed to have enhanced lipophilicity with a minimum increase in steric bulk. The tetramethylenesilane **8a** and the pentamethylenesilane **9a** were prepared from bis(chloromethyl)dichlorosilane (**5d**) by treatment with the bis-Grignard reagents derived from 1,4-dibromobutane and 1,5-dibromopentane, respectively (the corresponding lithio reagents gave inferior results). Treatment of the bis(chloromethyl) compounds **8a** and **9a** with sodium azide in sulfolane followed by low-temperature hydride reduction of the bis(azidomethyl) derivatives **8b** and **9b** gave the requisite diamines **8c** and **9c**. The platinum(II) complexes **10a** and **11a** were prepared from the corresponding diamine by treatment with potassium tetrachloroplatinate; chlorine oxidation of the platinum(II) complexes afforded the platinum(IV) complexes **10b** and **11b**.



Early efforts to prepare **9a,b,c** from 1,1-dichlorosilacyclohexane were unsuccessful. Treatment with the organomagnesium, -lithium, or -sodium derivatives derived from *N*-(bromomethyl)phthalimide or with the anion derived from nitromethane failed to give desired product (only intractable product mixtures). The lithium salt derived from thioanisole did react with 1,1-dichlorosilacyclohexane to give 1,1-bis(thiophenyl)silacyclohexane (49%), and alkylation of the bis(thiophenyl) derivative (methyl triflate) gave the bis-sulfonium salt. However, treatment of the bis-sulfonium salt with azide under a variety of conditions always led to displacement through attack at silicon instead of carbon. Similarly, treatment of 1,1-dichlorosilacyclohexane with KCN afforded 1,1-dicyanosilacyclohexane, but lithium aluminum hydride reduction led to reductive cleavage of the Si-CN bond instead of nitrile reduction to the amine.

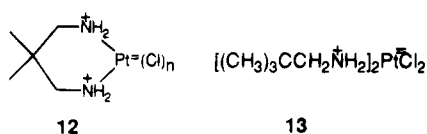
The carbocyclic analogue **12** of silaplatin was prepared from 1,3-diamino-2,2-dimethylpropane by treatment with K_2PtCl_4 . 1,3-Diamino-2,2-dimethylpropane was prepared in three steps (43% overall yield) from 2,2-

Table 1. Solubility of the Platinum Complexes in Water and Normal Saline

compd	solubility (mg/mL)	
	water	0.9% NaCl
1a	9.89	11.90
1b	4.32	4.20
2a	0.30	0.33
2b	5.04	4.84
3c	9.14	9.30

^a Standard plots of concentration vs absorbance (210 nm) were prepared for each complex. A saturated solution ($23 \pm 2^\circ\text{C}$) of the complex was diluted quantitatively, the UV absorbance of the solution was measured, and the concentration was calculated from the standard plot.

dimethylmalonic acid [(1) SOCl_2 ; (2) $\text{NH}_3/\text{H}_2\text{O}$; (3) $\text{BH}_3\text{-SMe}_2\text{-THF}$]. The carbon analogue of **1a** was also prepared. Thus, treatment of 2 equiv of 2,3-dimethylaminopropane with K_2PtCl_4 in degassed water at 20°C gave crude **13** that was purified by crystallization from DMF.



The solubility of selected platinum complexes prepared in this study was determined in water and 0.9% aqueous sodium chloride solution. These data are given in Table 1. The CBCDA complex **3c** was more soluble than the corresponding dichloro complex **2a** (a trend which is also evident for cisplatin and its CBCDA analogue, carboplatin), and the platinum(IV) complex **2b** was more soluble than the corresponding platinum(II) complex **2a**.

Qualitative hydrolysis studies show that silaplatin (**2a**) is less stable than the corresponding platinum(IV) analogue **2b**. This was expected on the basis of the known stability of platinum(IV) complexes relative to platinum(II) complexes.^{1,11} Quantitative HPLC studies reveal that there is no significant difference between the hydrolytic stability of silaplatin (**2a**) and the carbocyclic platinum(II) analogue **12**. Silaplatin (**2a**) was hydrolyzed in water ($24.3 \pm 0.4^\circ\text{C}$) with a half-life of 208 min (10% hydrolysis in 33 min). The carbocyclic analogue **12** had a half-life of 238 min ($25.3 \pm 0.5^\circ\text{C}$) (10% hydrolysis in 35 min).

The acyclic platinum(II) complex **1a**, derived from (aminomethyl)trimethylsilane, was unexpectedly stable. An aqueous solution of **1a** showed no significant decomposition (HPLC) over a 24 h period, but the origin of this stability is unclear. The low reactivity of **1a** (stability toward hydrolysis) is clearly consistent with the observed in vivo biological inactivity (but not with the observed in vitro activity) of this complex.

Biological Results and Discussion

The platinum complexes prepared in this study were evaluated in the NCI in vitro disease-oriented primary screen comprised of 60 human tumor cell lines derived from seven cancer types (brain, colon, leukemia, lung, melanoma, ovarian, and renal). Overall potencies of the complexes in this assay are summarized in Table 2. The complexes demonstrated similar potencies to that of cisplatin and were more cytotoxic than carboplatin.

Table 2. Potency of the Platinum Complexes in the in Vitro Disease-Oriented Anticancer Screen^a

compd	log GI ₅₀ ^b	log TGI ^b	log LC ₅₀ ^b
1a	-5.35	-4.72	> -4.07
1b	-5.23	-4.64	> -4.06
2a	-4.69	-4.08	> -4.01
2b	-5.32	-4.38	> -4.02
2c	-5.49	-4.50	> -4.03
2d	-5.21	-4.40	> -4.02
2e	-4.71	-4.09	> -4.01
2f	-5.52	-4.33	> -4.02
3c	nt ^c	nt	nt
10a	-4.59	-4.05	> -4.00
10b	-5.35	-4.31	> -4.00
11a	-4.93	-4.17	> -4.01
11b	-5.38	-4.30	> -4.01
cisplatin	-5.35	-4.47	> -3.35
carboplatin	-3.97	-3.67	> -3.61

^a Assays were conducted according to published procedures (Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langlay, J.; Cronise, P.; Vaigro-Wolf, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757-766) and involved a 24 h preincubation of cells, addition of test agent in five 10-fold dilutions, incubation for 48 h followed by in situ fixation, staining, and measurement of solubilized stain spectrophotometrically. Concentrations of platinum complexes ranged from 0.01 to 100 μM (log -8 to -4), except for cisplatin (0.05-500 μM) and carboplatin (0.025-250 μM). The cell lines used in these experiments were leukemia lines CCRF-CEM, HL-60 (TB), K-562, MOLT-4, and RPMI-8226; non-small-cell lung tumor lines A549/ATCC, EK VX, HOP-18, HOP-62, HOP-92, NCI-H23, NCI-H226, NCI-H322M, NCI-H460, NCI-H522, and LXFL 529; small cell lung carcinoma lines DMS-114 and DMS 273; colon carcinoma lines COLO 205, HCC-2998, DLD-1, HCT-15, HCT-116, HT29, KM12, KM20L2, and SW-620; CNS cancer lines SF-268, SF-295, SF-539, SNB-19, SNB-78, U251, and XF 498; melanoma lines LOX IMVI, MALME-3M, M14, M19-MEL, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-62, and UACC-257; ovarian carcinoma lines IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OK-3; and renal carcinoma lines 786-0, ACHN, CAKI-1, RXF-631, SN12C, TK-10, and UO-31. ^b The log₁₀ molecular concentration that caused 50% tumor growth inhibition (GI₅₀), total growth inhibition (TGI), and 50% cell kill (LC₅₀). The concentrations shown are mean values calculated by averaging log GI₅₀ (or TGI or LC₅₀) values obtained with each test agent in each cell line in a specific experiment. Compounds **1a-2d** were tested in one experiment and compounds **2e-11b** in a second experiment. Values for cisplatin and carboplatin are means, calculated from three experiments conducted in the same time period. ^c Not tested.

There were no substantial differences between the spiro-silanes **10** and **11** and the monocyclic silanes **2** in the in vitro assays; the platinum oxidation state did influence activity—four of the platinum(IV) analogues were more potent than the corresponding platinum(II) complex, but two Pt(II) complexes were slightly more active than the Pt(IV) analogues, so there was no clear trend. Similarly, there was no clear trend in activity as the lipophilicity increased (cf. **2a** vs **11a**). Although no striking differential cytotoxicity was observed, all but two (**1a** and carboplatin) of the platinum complexes demonstrated some specificity for the leukemia panel (on the basis of concentrations causing 50% growth inhibition).

Five of the platinum complexes were evaluated for antitumor activity in mice bearing ip implants of the murine L1210 leukemia (L1210/0).¹² The two acyclic complexes **1a,b** demonstrated no activity following ip administration of dosage levels ranging from 10 to 400 mg/kg on days 1, 5, and 9 (data not shown). Complex **1b** was toxic at 400 mg/kg/injection, causing 100% lethality prior to the first death in tumorous control mice. In marked contrast to the acyclic complexes **1b**,

Table 3. Activity of **2a** (silaplatin), **2b**, and **3c** Against Cisplatin Sensitive and Resistant L1210 Leukemia in Vivo^a

compd	dose (mg/kg) ^b	L1210/0			L1210/cisplatin		
		BWC (g) ^c	MST (days) ^d	% ILS (day 30 survivors/total)	BWC (g)	MST (days)	% ILS (day 30 survivors/total)
2a	30	-1.1	21.5	141 (5/6)	-2.5	14.8	60 (0/6)
	20	-1.0	16.8	88 (2/6)	-2.7	13.8	50 (2/6)
	15	-1.7	16.3	83 (6/10)	-0.4	18.3	98 (6/10)
	10	-1.5	22.5	152 (3/10)	-0.8	10.5	14 (9/10)
	5	-0.4	21.5	141 (3/10)	0.1	12.5	35 (1/10)
cisplatin	10	-1.3	17.3	94 (3/10)	-1.3	10.0	8 (0/10)
control	—	0.5	8.9	— (0/20)	0.7	9.2	— (0/20)
2a	80	-3.5	11.8	37 (0/6)			
	40	-0.9	30.0	248 (4/6)			
	20	-0.6	20.5	138 (0/6)			
	10	-0.9	18.0	109 (3/6)			
	80	-5.0	8.3	-4 (0/6)			
2b	40	-2.4	27.0	214 (4/6)			
	20	-1.2	21.0	144 (4/6)			
	10	0.0	18.5	115 (3/6)			
	20	-2.7	15.0	74 (4/6)			
	—	0.6	8.6	— (0/30)			
cisplatin	20	-0.6	8.6	30 (0/10)			
control	—	0.6	8.6	30 (0/10)			
2a	80	-4.3	6.3	30 (0/10)			
	40	-2.9	11.7	31 (0/10)			
	20	-0.2	22.5	153 (5/10)			
	10	-0.2	15.5	74 (3/10)			
	80	-3.4	10.0	12 (0/10)			
2b	40	-1.3	21.0	136 (4/10)			
	20	-0.6	19.0	113 (1/10)			
	10	0.1	15.0	69 (0/10)			
	20	-0.3	17.5	97 (1/10)			
	—	0.9	8.9	— (0/20)			
cisplatin	10	-0.3	17.5	97 (1/10)			
control	—	0.9	8.9	— (0/20)			
3c	80	0.9	22.0	144 (0/6)	1.5	16.0	73 (0/6)
	60	0.5	16.3	81 (0/6)	1.0	16.0	73 (0/6)
	40	1.0	16.0	77 (0/6)	0.7	13.0	41 (0/6)
	20	1.5	12.0	33 (0/6)	1.1	10.8	17 (0/6)
	10	0.8	11.0	22 (0/6)	1.1	9.9	7 (0/6)
cisplatin	20	-3.5	18.0	100 (0/6)	-4.6	9.8	6 (0/6)
control	—	1.2	9.2	— (0/20)	0.8	9.2	— (0/20)

^a 10⁵ L1210/0 (parent) or L1210/cisplatin (resistant) leukemia cells were implanted ip in dosage groups of 6 or 10 CD₂F₁ mice (20 or 30 controls) on day 0.^{12,13} The sensitive and resistance leukemia studies were conducted simultaneously and used the same test agent preparations. ^b Platinum complexes were administered ip on days 1, 5, and 9 in saline plus Tween 80. Several dosage levels of cisplatin, administered as solution in saline, were included in each comparison of sensitive and resistance leukemias; only data for the optimal dose are shown. ^c Mean body weight change per group (day 5 minus day 1). ^d Median survival time (MST) and percent increase in life span (ILS, calculated from MST) based on dying mice only (excludes day 30 survivors).

all three cyclic complexes derived from the diamine **7a**, silaplatin (**2a**), the platinum(IV) analogue **2b**, and the CBDCA analogue **3c** demonstrated good reproducible activity against this cisplatin sensitive L1210 leukemia in vivo. Data illustrative of these activities are summarized in Table 3. These data indicate that the therapeutic efficacy of the platinum(IV) complex **2b** was comparable to that of the platinum(II) complex **2a**, and it can be presumed that **2b** is reduced to **2a** in vivo by facile inner sphere redox mechanism. Both complexes demonstrated host toxicity (weight loss and early deaths) at a dosage level of 80 mg/kg/injection and antitumor activities at doses ranging from 2.5 to 40 mg/kg/injection (data for lower dose levels not shown). The CBDCA complex **3c** was less potent, and possibly less active, than the corresponding dichloro complex **2a**. In contrast to complex **2a**, the 80 mg/kg dosage level of complex **3c** was well-tolerated but produced no 30 day survivors.

The two platinum(II) complexes **2a** and **3c** were evaluated in vivo against the ip implanted L1210 leukemia subline with acquired resistance to cisplatin (L1210/cisplatin).¹³ As illustrated by the data in Table

3, L1210/cisplatin appeared to be as sensitive to the complexes as was the parent L1210/0 leukemia when both experiments were conducted simultaneously. The L1210/cisplatin leukemia demonstrated complete resistance to cisplatin tested in the same experiments. The dichloroplatin(II) complex **2a** also was evaluated against intracerebrally implanted L1210/0 leukemia. Although a 10 mg/kg dosage level administered ip on days 1, 5, and 9 demonstrated marginal activity (ILS = 40%) in this model, activity probably was associated with effects against systemic leukemia cells and not to drug penetration of the CNS. In the same study, the 10 mg/kg dosage level administered to mice bearing the ip implanted tumor produced a T/C of 235% and 3/10 day 30 survivors.

In conclusion, silaplatin represents a new class of platinum coordination compounds with activity against cisplatin resistant cancer cell lines in vitro and in vivo. The compound has been selected as a potential clinical candidate, and further studies on the preclinical toxicology of silaplatin and related congeners will be carried out and reported at a later date.

Experimental Section

NMR spectra were determined using a Varian EM390 spectrometer. IR spectra were obtained for KBr pellets (unless otherwise indicated) with a Nicolet FT-IR system. HPLC data were obtained with a Spectrophysics 8000 system using a Varian Varichrome variable wavelength UV-visible detector (unless otherwise specified) and an HP-3392A electronic integrator. UV spectra were obtained with a Varian/Cary 118c UV-vis spectrophotometer. Elemental analysis data were obtained from Atlantic Microlabs, Inc., Atlanta, GA.

cis-Bis[[[(trimethylsilyl)methyl]amino]dichloroplatinum(II)] (1a). A solution of trimethylsilylmethylamine (**4c**; 2.09 g, 0.012 mol) in methanol (8 mL) and water (4 mL) was added to a filtered solution of potassium tetrachloroplatinate (4.185 g, 0.01 mol) in helium-degassed water (28 mL) that was stirred in the dark under an argon atmosphere. The mixture was stirred under these conditions for 18 h at 18–20 °C. The precipitated product was collected on a sintered glass funnel and washed sequentially with cold water, cold 1 N HCl, cold (0 °C) ethanol, and ether. The grayish-white solid was purified in DMF–water to give a pale yellow-white solid that was dried in vacuo to give **1a** (2.78 g, 58%); mp 163–176 °C (shrinks), 180–181 °C dec (melts); ¹H NMR [DMSO-*d*₆ (external TMS)] δ 0.0 (s, 18 H, H₃C-Si), 1.9–2.7 (br m, 8 H, CH₂ and DMSO); ¹H NMR (DMF-*d*₇/TMS) δ 0.13 (s, 18 H, Si-CH₃), 2.43 [(2.13–2.73), t br t, 4 H, Si-CH₂-N, *J*_{NHCH} = 6–7 Hz, *J*_{PNCH} = 18 Hz], 4.70 [(4.0–5.4) br t, 4 H, NH₂, *J*_{PNH} = 33 Hz]; IR 3274, 3232, 3197, 3140, 3126, 2901, 2957, 1584, 1415, 1253, 1189, 1161, 859, 844, 734, 745, 696, 654 cm⁻¹. Anal. (C₈H₂₆N₂Cl₂Si₂Pt) C, H, N, Cl.

cis-Bis[[[(trimethylsilyl)methyl]amino]tetrachloroplatinum(IV)] (1b). Chlorine gas was slowly bubbled (ca. 2–3 bubbles/s) through a stirred suspension of bis[[[(trimethylsilyl)methyl]amino]dichloroplatinum(II)] (**1a**; 0.5 g, 1.059 mmol) in 0.5 N HCl (10 mL) maintained at 60 °C. The solid immediately became yellow in color. The chlorine gas was bubbled into the suspension (55–60 °C) for 2 h. The mixture was cooled to room temperature, and excess chlorine was removed by bubbling air rapidly through the reaction mixture for 2 h. The mixture was concentrated to dryness in vacuo, and the solid yellow residue was dissolved in methanol. The methanol solution was filtered and concentrated to dryness in vacuo to yield a yellow solid that was crystallized from acetone–water (1:3) to give **1b** (0.496 g, 82%); ¹H NMR [DMSO-*d*₆ (external TMS)] δ 0.05 (s, 18 H, Si-CH₃), 1.67–1.85 (m, 4 H), 2.08 (s, 4 H, CH₂); IR 3274, 3253, 3218, 3204, 2957, 1422, 1570, 1253, 1196, 851, 774, 738, 703, 648 cm⁻¹. Anal. (C₈H₂₆N₂Cl₄Si₂Pt) C, H, N, Cl.

[Bis(aminomethyl)dimethylsilane]dichloroplatinum(II) (2a). A solution of bis(aminomethyl)dimethylsilane (**7a**; 1.0 g, 8.62 mmol) in argon-degassed methanol (9 mL) was added rapidly to a stirred solution of potassium tetrachloroplatinate (3.58 g, 8.62 mmol) in argon-degassed water (36 mL) that was maintained under an argon atmosphere and protected from light. The mixture was stirred at 20 °C for 16 h. The solid was collected on a sintered glass funnel, washed with water, 1 N HCl, cold ethanol, and ether, and then dried to give **2a** as an off-white solid (2.5 g, 75%): mp 185 °C (shrinks), 230 °C dec (melts); ^1H NMR (DMF- d_7 /TMS) δ 0.29 (s, 6 H, $\text{H}_3\text{C-Si}$), 2.41 (t br t, $J_{\text{HNCH}} = 6$ Hz, $J_{\text{PNCH}} = 28.5$ Hz, 4 H, CH_2), 4.93 (br t, $J_{\text{PNH}} = 37.5$ Hz, 4 H, NH_2); IR 3239, 3211, 3133, 1598, 1422, 1281, 1253, 1140, 865, 844, 788, 752, 689 cm^{-1} . Anal. ($\text{C}_4\text{H}_{14}\text{N}_2\text{Cl}_2\text{SiPt}$) C, H, N, Cl.

[Bis(aminomethyl)dimethylsilane]tetrachloroplatinum(IV) (2b). The oxidation of *cis*-[bis(aminomethyl)dimethylsilane]dichloroplatinum(II) (**2a**; 1.0 g, 2.62 mmol) was conducted as described for **1b**. The bright yellow solid obtained when the mixture was concentrated to dryness in vacuo was dissolved in acetonitrile–water (3:2); the solution was filtered and concentrated in vacuo until only a small amount of solvent remained. The mixture was filtered. The solid was washed with methanol and then with ether and dried to give **2b** (0.932 g, 79%) as a yellow solid: mp 192 °C (shrinks), 235 °C dec (melts); ^1H NMR (DMF- d_7 /TMS) δ 0.30 (s, 6 H, $\text{H}_3\text{C-Si}$), 2.42 (t br t, $J_{\text{HNCH}} = 5.3$ Hz, $J_{\text{PNCH}} = 19.5$ Hz, 4 H, CH_2), 6.73 (br t, $J_{\text{PNH}} = 30$ Hz, 4 H, NH_2); IR 3211, 3190, 3119, 2964, 2894, 1577, 1415, 1337, 1302, 1260, 1168, 999, 858, 816, 781, 752, 689 cm^{-1} . Anal. ($\text{C}_4\text{H}_{14}\text{N}_2\text{Cl}_4\text{SiPt}$) C, H, N, Cl.

[Bis(aminomethyl)ethylmethylsilane]dichloroplatinum(II) (2c). A solution of bis(aminomethyl)ethylmethylsilane (**7c**; 2.3 g, 17.39 mmol) in nitrogen-degassed methanol (26 mL) was added rapidly to a stirred solution of potassium tetrachloroplatinate (7.52 g, 36 mmol) in nitrogen-degassed water (77 mL) that was maintained under a nitrogen atmosphere. After 20 min, formation of a white solid was observed. The mixture was stirred at 20 °C and protected from light for 16 h. The solid was collected, washed with water, 1 N HCl, cold ethanol, and ether, and dried to give [bis(aminomethyl)ethylmethylsilane]dichloroplatinum(II) (**2c**) as an off-white solid [4.11 g, 59% (an additional 0.157 g of off-white solid was obtained from the original aqueous filtrate and washings to give a total crude yield of 62%): mp 225 °C (shrunk and turned brown), 227 °C dec (melts). Anal. Calcd for $\text{C}_6\text{H}_{16}\text{N}_2\text{Cl}_2\text{SiPt}$: C, 15.08; H, 4.05; N, 7.03. Found: C, 15.09; H, 3.85; N, 6.81.

The off-white solid was dissolved in DMSO and precipitated with water to give a light yellow solid (2.773 g, 40%) which was then purified twice by dissolution in DMF and precipitated slowly by the addition of ether to yield a crystal-like yellow solid (1.617 g, 23%): mp 241–247 °C (shrinks), 250 °C dec; ^1H NMR (DMF- d_7 /TMS) δ 0.30 (s, 3 H, Si-CH_3), 0.94 [(0.61–1.21) m, 5 H, $\text{Si-CH}_2\text{-C} + \text{C-CH}_3$], 2.45 (t br t, $J_{\text{PNCH}} = 27$ Hz, $J_{\text{HNCH}} = 6$ Hz, 4 H, $\text{Si-CH}_2\text{-N}$), 4.86 (br t, $J_{\text{PNH}} = 39$ Hz, 4 H, NH_2); IR (KBr) 3217, 3138, 2951, 2879, 1597, 1437, 1154 cm^{-1} . Anal. ($\text{C}_6\text{H}_{16}\text{N}_2\text{Cl}_2\text{SiPt}$) C, H, N.

[Bis(aminomethyl)ethylmethylsilane]tetrachloroplatinum(IV) (2d). Chlorine gas was bubbled through a stirred suspension of [bis(aminomethyl)ethylmethylsilane]dichloroplatinum(II) (**2c**; 1.4 g, 3.65 mmol) in 0.5 N HCl (100 mL) maintained at 60 °C. The solid immediately became yellow in color. The chlorine gas was bubbled into the suspension (50–60 °C) for 2 h. The mixture was cooled to room temperature, and excess chlorine was removed by bubbling air rapidly through the reaction mixture for 1–2 h. The yellow solid was filtered and washed with water, methanol, and ether to give [bis(aminomethyl)ethylmethylsilane]tetrachloroplatinum(IV) (**2d**) as a yellow solid (1.28 g, 78%): mp 214 °C (shrinks, brown), 221–222 °C dec. The yellow solid was dissolved in hot acetonitrile–water (3:2) and concentrated in vacuo. The solid was filtered and washed with methanol and ether to give [bis(aminomethyl)ethylmethylsilane]tetrachloroplatinum(IV) (**2d**) as a yellow solid (1.01 g, 61%): mp 213–215 °C (shrunk, brown), 223 °C dec; ^1H NMR (DMF- d_7 /TMS) δ 0.32 (s, 3 H, Si-CH_3), 0.93 [(0.71–1.1), m, 5 H, $\text{Si-CH}_2\text{-C}$, SiC-CH_3],

2.41 (t br t, $J_{\text{PNCH}} = 20$ Hz, $J_{\text{HNCH}} = 6$ Hz, 4 H, $\text{Si-CH}_2\text{-N}$), 6.69 (br t, $J_{\text{PNH}} = 30$ Hz, 4 H, NH_2); ^1H NMR (DMSO- d_6) δ 0.16 (s, 3 H, Si-CH_3), 0.79 (m, 5 H, $\text{Si-CH}_2\text{-C}$ and C-CH_3), 2.04 (br t, $J_{\text{PNCH}} = 20$ Hz, 4 H, $\text{Si-CH}_2\text{-N}$), 6.55 (br t, $J_{\text{PNH}} = 30$ Hz, 4 H, NH_2); IR (KBr) 3214, 3191, 3120, 2953, 1570, 1412, 1165 cm^{-1} . Anal. ($\text{C}_5\text{H}_{16}\text{N}_2\text{Cl}_4\text{SiPt}$) C, H, N.

[Bis(aminomethyl)diethylsilane]dichloroplatinum(II) (2e). A solution of bis(aminomethyl)diethylsilane (**7e**; 4.731 g, 32 mmol) in nitrogen-degassed methanol (32 mL) was added rapidly to a stirring solution of potassium tetrachloroplatinate (13.42 g, 32 mmol) in nitrogen-degassed water (136 mL) under an argon atmosphere. The reaction mixture was protected from light. Formation of a white solid was observed immediately. The mixture was stirred in the dark under argon for 16 h at 18–20 °C. The precipitated product was collected and washed sequentially with cold water, cold 1 N HCl, cold water, cold ethanol, and ether to yield a pale yellow solid (12.3 g, 92%). The solid was dissolved in a minimum amount of DMF, ether was added, and the precipitate was collected and washed with acetonitrile and ether to give [bis(aminomethyl)diethylsilane]dichloroplatinum(II) (**2e**) as a pale yellow solid [7.98 g, 60%; the filtrate (DMF–ether) was concentrated, and ether was added to yield an off-white precipitate (0.915 g, for a total yield of 70%): mp 244–247 °C (shrinks), 283–284 °C dec (melts); ^1H NMR (DMF- d_7 /TMS) δ 0.96 [(0.63–1.13), m, 10 H, $\text{CH}_2 + \text{CH}_3$], 2.43 (t br t, 4 H, SiCH_2N , $J = 6$ Hz, $J = 27$ Hz), 4.90 (br t, 4 H, NH_2 , $J = 34.5$ Hz); IR (neat) 3213, 3134, 2952, 2905, 1593, 1413, 1156, 1014, 764 cm^{-1} . Anal. ($\text{C}_6\text{H}_{18}\text{Cl}_2\text{N}_2\text{SiPt}$) C, H, N.

[Bis(aminoethyl)diethylsilane]tetrachloroplatinum(IV) (2f). Chlorine gas was bubbled through a stirred suspension of [bis(aminomethyl)diethylsilane]dichloroplatinum(II) (**2e**; 3.861 g, 9.364 mmol) in 0.5 N HCl (154 mL) at 50–60 °C for 1 h. The mixture was cooled to room temperature, and the excess chlorine was removed by bubbling air through the reaction mixture for 1 h. The yellow solid was filtered and washed with water and ether to give a yellow solid (3.09 g, 68%). The aqueous filtrate and water washings were combined and concentrated in vacuo at 40 °C. Several crops of yellow solids (0.356 g, 7.9%) were collected. A semicrystallization of the combined yellow solid (3.45 g, 76%) from warm acetonitrile yielded [bis(aminoethyl)diethylsilane]tetrachloroplatinum(IV) (**2f**) (2.904 g, 64%) as a yellow solid: mp 190–193 °C (sintered), 201–202 °C dec (melted); ^1H NMR (DMF- d_7 /TMS) δ 0.97 [(0.6–0.75), m, 10 H, $\text{CH}_2 + \text{CH}_3$], 2.47 (t br t, 4 H, SiCH_2 , $J = 5.3$ Hz, $J = 19.5$ Hz), 6.75 (br t, 4 H, $J = 27$ Hz); IR (neat) 3215, 3191, 3132, 2956, 2928, 2888, 1559, 1412, 1163, 1018, 833, 764 cm^{-1} . Anal. ($\text{C}_6\text{H}_{18}\text{N}_2\text{Cl}_4\text{SiPt}$) C, H, N.

***cis*-[Bis(aminomethyl)dimethylsilane]diiodoplatinum(II) (3a).** Solid anhydrous potassium iodide (6.644 g, 40 mmol) was added to a solution of potassium tetrachloroplatinate (4.15 g, 10 mmol) in argon-degassed water (60 mL). The mixture was stirred in the dark under argon for 15 min. A solution of bis(aminomethyl)dimethylsilane (1.16 g, 10 mmol) in argon-degassed water (2 mL) was added to the mixture in a single aliquot. Immediately, a yellow solid began to precipitate. The mixture was stirred at 16 °C for 70 min. The solid was filtered and washed with 2 mL portions of water until the washings were colorless. The product was washed with cold ethanol (5 mL) and anhydrous ether and air-dried. The yellow electrostatic solid (4.35 g, 77%) was used in the next step without further purification.

***cis*-[Bis(aminomethyl)dimethylsilane]platinum(II) Sulfate (3b).** *cis*-[Bis(aminomethyl)dimethylsilane]diiodoplatinum(II) (**3a**; 4.536 g, 8 mmol) was added to a solution containing slightly less than the stoichiometric amount of silver sulfate (2.49 g, 7.98 mmol) in distilled water (400 mL). The mixture was stirred for 4 h in the dark. The mixture was filtered initially through a fine sintered glass funnel and then through a 0.45 μm nylon filter membrane. The clear solution was concentrated to 400 mL and used immediately in the next step.

Barium 1,1-Cyclobutanedicarboxylate. 1,1-Cyclobutanedicarboxylic acid (1.184 g, 8 mmol) was added in one portion to a solution of barium hydroxide octahydrate (2.524 g, 8 mmol) in water (120 mL). The resulting solution was stirred for 10 min and used immediately in the next step.

Platinum Bis(aminomethyl)dimethylsilane Cyclobutane-1,1-dicarboxylate(2-)-O,O' (3c).¹⁴ The aqueous solution of barium 1,1-cyclobutanedicarboxylate (8 mmol) from the previous step was added to the aqueous solution of *cis*-[bis(aminomethyl)dimethylsilane]platinum(II) sulfate (8 mmol) prepared above. The reaction mixture was stirred at 20 °C for 1 h. The resulting suspension was filtered through a 0.45 μ m nylon filter. The clear filtrate was concentrated to dryness to give a white crystalline residue. This was washed with ethanol and then with anhydrous ether to give the desired product (3.61 g) as a white crystalline solid. Reverse phase HPLC analysis indicated the presence of a polar impurity. The crude solid was purified on a Lobar C-8 column using acetonitrile–water (1:9) as the mobile phase. **3c**: ¹H NMR [DMF-*d*₇ (external TMS)] δ -0.12 (s, 6 H), 1.32 (m, 2 H), 1.97 (t, *J* = 6 Hz, 4 H), 3.05 (s, 4 H), 4.82 (br m, 4 H); IR 3260, 3204, 3105, 2992, 2957, 2894, 1675, 1646, 1618, 1428, 1350, 1252, 1111, 907, 857, 780, 745, 695, 667, 568 cm⁻¹. Anal. (C₁₀H₂₀N₂O₄·SiPt) C, H, N.

(Trimethylsilyl)methyl Azide (4b). (Chloromethyl)trimethylsilane (**4a**; 12.26 g, 0.1 mol) was added to a stirred suspension of finely powdered sodium azide (7.16 g, 0.11 mol) in DMPU (50 mL). The mixture was stirred at 80 °C for 14 h. The cloudy reaction mixture was allowed to cool to room temperature, and the reaction mixture was *carefully* distilled (CAUTION, EXPLOSIVE HAZARD) to give (trimethylsilyl)methyl azide (**4b**) as a colorless liquid (10.28 g, 80%): bp 40–42 °C/42 mmHg (lit.¹⁰ bp 58–61 °C/80 mmHg); ¹H NMR [CDCl₃ (external TMS)] δ 0.08 (s, 9 H, Me₃Si), 2.67 (s, 2 H, CH₂); IR (neat) 2957, 2901, 2182, 1253, 851 cm⁻¹.

(Aminomethyl)trimethylsilane (4c). A suspension of lithium aluminum hydride (3.04 g, 0.08 mol) in anhydrous ether (120 mL) was stirred at 0 °C for 30 min under an argon atmosphere. A solution of (trimethylsilyl)methyl azide (**4b**; 10.32 g, 0.08 mol) in anhydrous ether (40 mL) was added dropwise to the stirred lithium aluminum hydride suspension over a period of 45 min while the temperature was maintained at 0 °C. The cooling bath was removed after the addition was completed, and the stirred reaction mixture was allowed to warm to room temperature over a period of 2 h. The reaction was carefully quenched with water (3.5 mL) followed by 10% aqueous sodium hydroxide (4.0 mL). The mixture was filtered, the filtrate was dried (sodium sulfate), and the ether was removed in vacuo (0–5 °C). The crude residue was allowed to stand at room temperature over potassium hydroxide pellets for 1 h with intermittent shaking, and then, without removal of the potassium hydroxide, the product was distilled in an argon atmosphere to give (aminomethyl)trimethylsilane (**4c**; 5.06 g, 61%) that was stored under an argon atmosphere: bp 92–94 °C (lit.⁷ bp 94 °C); ¹H NMR [CDCl₃ (external TMS)] δ 0.04 (s, 9 H, Me₃Si), 0.76 (s, 2 H, NH₂), 1.90 (s, 2 H, CH₂); IR (neat) 3366, 3295, 2964, 2901, 2866, 1612, 1415, 1253, 1055, 696, 668 cm⁻¹.

Bis(chloromethyl)ethylmethylsilane (5c). Bis(chloromethyl)methylchlorosilane (**5b**; 35.5 g, 32.8 mL, 0.2 mol) was added to a solution of ethylmagnesium bromide (50.0 g, 125 mL of a 3 M ether solution, 0.38 mol) in ether (560 mL) at 0 °C under a nitrogen atmosphere. A white precipitate began to form after 5 min. The reaction mixture was heated at reflux for 3 h and allowed to stand at room temperature for 15 h. The reaction mixture was filtered, and the magnesium salts were washed with ether and CH₂Cl₂. The combined organic solution was dried (Na₂SO₄) and concentrated to dryness in vacuo. The light yellow liquid residue was distilled to give bis(chloromethyl)ethylmethylsilane (**5c**; 30.28 g, 89%) as a colorless liquid: bp 26–28 °C/0.15 mmHg (lit.¹⁵ bp 185 °C/atm); ¹H NMR (CDCl₃/TMS) δ 0.20 (s, 3 H, CH₃), 0.78 (q, 2 H, CH₂, *J* = 6 Hz), 1.02 (t, 3 H, CH₃, *J* = 6 Hz), 2.89 (s, 4 H, CH₂); IR (neat) 2958, 2933, 2878, 1458, 1396, 1257 cm⁻¹.

Bis(chloromethyl)dichlorosilane (5d). Anhydrous powdered cupric sulfate (0.58 g) was added to a solution of (chloromethyl)trichlorosilane (40.25 g, 0.219 mol, 27.23 mL) in dry ether (57 mL) at -40 to -45 °C, and then a solution of diazomethane (15 g, 0.357 mol) in dry ether (380 mL) was added dropwise. The temperature was then raised to -25 to -20 °C, and after 2 h, anhydrous cupric sulfate (0.58 g) and

then diazomethane (15 g, 0.357 mol) in dry ether (380 mL) were added at -25 °C. After 1 h, the mixture was warmed to 18 °C, filtered, and distilled using a Vigreux column (1.5 × 10 cm) to give bis(chloromethyl)dichlorosilane (**5d**; 26.48 g, 61%) as a colorless liquid [bp 62–75 °C/18 mmHg (lit. bp 58.5 °C/16 mmHg); ¹H NMR (CDCl₃/TMS) δ 3.30] and tris(chloromethyl)chlorosilane (15.31 g, 33%) as a colorless liquid [bp 90–100 °C/15 mmHg (lit.¹⁶ bp 79 °C/4 mmHg); ¹H NMR (CDCl₃/TMS) δ 3.23].

Bis(chloromethyl)diethylsilane (5e). Bis(chloromethyl)dichlorosilane (**5d**; 13.216 g, 0.0668 mol) was added to a solution of ethylmagnesium bromide (36 g, 90 mL of a 3 M ether solution, 0.27 mol) in ether (360 mL). The reaction mixture was heated at reflux for 5 h and allowed to stand at room temperature for 15 h. The reaction mixture was filtered, and the magnesium salts were washed with ether. The combined organic solution was dried (Na₂SO₄) and concentrated to dryness in vacuo. The concentrated residue contained a large amount of white magnesium salts and was extracted with pentane. The pentane extract was concentrated to dryness in vacuo and distilled (1.5 × 10 cm Vigreux column) to give bis(chloromethyl)diethylsilane (**5e**; 7.87 g, 64%) as a colorless liquid: bp 108–110 °C/30 mmHg; ¹H NMR (CDCl₃/TMS) δ 0.82 (q, 4 H, CH₂, *J* = 6 Hz), 1.03 (t, 6 H, CH₃, *J* = 6 Hz), 2.94 (s, 4 H, CH₂); IR (neat) 2937, 2914, 2878, 1466, 1413, 1395, 1239, 1175, 1107, 1011, 787 cm⁻¹.

Bis(azidomethyl)dimethylsilane (6a). Bis(chloromethyl)dimethylsilane (**5a**; 15.7 g, 0.1 mol) was added in one portion to a stirred suspension of sodium azide (13.0 g, 0.2 mol) in tetramethylenesulfone [(sulfolane) 50 mL] at 40 °C. Solid sodium carbonate (4–5 granules) was added, and the mixture was heated at 55–60 °C for 16 h under a nitrogen atmosphere. The turbid white reaction mixture was cooled to room temperature, and the product was *carefully* distilled directly from the mixture to give **6a** (14.96 g, 88%): bp 64–70 °C/0.1 mmHg; ¹H NMR [CDCl₃ (external TMS)] δ 0.28 (s, 6 H, -CH₃), 2.93 (s, 4 H, -CH₂-); IR (neat) 2964, 2929, 2098, 1383, 1253, 1175, 1405, 851 cm⁻¹. The product was used directly in the next step with no further purification.

Bis(azidomethyl)ethylmethylsilane (6c). Bis(chloromethyl)ethylmethylsilane (**5c**; 1.71 g, 0.01 mol) was added to a stirred suspension of sodium azide (1.35 g, 0.021 mol) in tetramethylenesulfone (5 mL) at 50 °C. A few granules of solid sodium carbonate were added, and the mixture was heated at 60–70 °C for 20 h under a nitrogen atmosphere. The product was distilled directly from the turbid white reaction mixture to give bis(azidomethyl)ethylmethylsilane (**6c**; 1.45 g, 79%) as a colorless liquid: bp 62–64 °C/0.17 mmHg; ¹H NMR (CDCl₃/TMS) δ 0.15 (s, 3 H, CH₃), 0.70 (q, 2 H, CH₂, *J* = 6 Hz), 1.00 (t, 3 H, CH₃, *J* = 6 Hz), 2.91 (s, 4 H, CH₂); IR (neat) 2960, 2879, 2181, 2092, 1413, 1290 cm⁻¹.

Bis(azidomethyl)diethylsilane (6e). A mixture of bis(chloromethyl)diethylsilane (**5e**; 7.87 g, 42.5 mmol), sulfolane (33 mL), sodium azide (8.3 g, 128 mmol), and a small amount of sodium carbonate was stirred at 55–60 °C for 19 h under argon. The resulting clear solution (containing a white solid) was extracted with petroleum ether. The extracts were combined, washed with brine, dried (Na₂SO₄), and freed of solvent in vacuo to give crude bis(azidomethyl)diethylsilane (**6e**; 8.4 g, 100%) as a colorless liquid: ¹H NMR (CDCl₃/TMS) δ 0.74 (q, 4 H, CH₂, *J* = 6 Hz), 1.03 (t, 6 H, CH₃, *J* = 6 Hz), 2.98 (s, 4 H, CH₂); IR (neat) 2959, 2913, 2879, 2179, 2093, 1466, 1413, 1289, 1232, 1012, 795 cm⁻¹.

Bis(aminomethyl)dimethylsilane (7a). A solution of bis(azidomethyl)dimethylsilane (**6a**; 14.96 g, 0.088 mol) in anhydrous ether (50 mL) was added dropwise over a 45 min period to a suspension of lithium aluminum hydride (6.69 g, 0.176 mol) in anhydrous ether (200 mL) at 0 °C under nitrogen. The mixture was then stirred at 0 °C for 30 min and at 20 °C for 30 min. The mixture was cooled to 0 °C, and water (8 mL) was added carefully. A 10% sodium hydroxide solution (7 mL) was added, the mixture was filtered, and the lithium salts were washed repeatedly with ether. The combined ether solution was dried (sodium sulfate), and the ether was removed in vacuo at 0 °C. Potassium hydroxide pellets were added to the colorless liquid residue; the mixture was allowed to stand

overnight and then distilled to give **7a** (4.3 g, 42%) as a colorless liquid: bp 68–72 °C/19 mmHg; ^1H NMR [CDCl_3 (external TMS)] δ 0.08 (s, 6 H, $-\text{CH}_3$), 1.50 (s, 4 H, $-\text{NH}_2$), 2.31 (s, 4 H, $-\text{CH}_2-$); IR (neat) 3359, 3288, 2957, 2901, 2816, 1605, 1436, 1246, 1098, 1055, 914, 844, 724 cm^{-1} . The diamine **7a** was used directly in the next step.¹⁷

Bis(aminomethyl)ethylmethylsilane (7c). A solution of bis(azidomethyl)ethylmethylsilane (**6c**; 1.84 g, 0.01 mol) in ether (5 mL) was added dropwise over 15 min to a suspension of lithium aluminum hydride (0.76 g, 0.02 mol) in ether (40 mL) at -5 °C under nitrogen. The mixture was then stirred at 0 °C for 15 min, at 18 °C for 30 min, and then at 0 °C for 30 min. Ice-cooled saturated NaCl solution (2.2 mL) and 10% NaOH solution (0.8 mL) were added at 0 °C. Solid NaCl and Na_2SO_4 were added. The mixture was filtered, and the salts were washed repeatedly with ether and then with dichloromethane. The combined organic solution was dried, and the solvents were removed in vacuo at 0 °C. The light yellow liquid residue was distilled to give bis(aminomethyl)ethylmethylsilane (**7c**; 1.05 g, 52%) as a colorless liquid: bp 52–54 °C/0.68 mmHg (90–92 °C/18 mmHg); ^1H NMR (CDCl_3/TMS) δ 0.04 (s, 3 H, Si- CH_3), 0.61 (q, 2 H, $J = 6$ Hz, Si- $\text{CH}_2\text{-C}$), 0.99 (t, 3 H, $J = 6$ Hz, C- CH_3), 1.05 (s, 4 H, NH_2), 2.32 (s, 4 H, $-\text{Si-CH}_2\text{-N}$); IR (neat) 3359, 3282, 2952, 2874, 2804, 1599, 1459, 1251 cm^{-1} .

Bis(aminomethyl)diethylsilane (7e). A solution of bis(azidomethyl)diethylsilane (**6e**; crude, 8.43 g, 42.5 mmol) in ether (25 mL) was added dropwise over 5 min to a suspension of lithium aluminum hydride (3.23 g, 85.1 mmol) in ether (170 mL) at -15 °C under argon. The mixture was then stirred at 15 °C for 15 min and at 18 °C for 50 min. Ice-cooled saturated salt solution (9.4 mL) and 10% aqueous sodium hydroxide (3.4 mL) were added at 0 °C. Solid sodium chloride and sodium sulfate were added. The mixture was filtered, and the salts were washed repeatedly with ether. The combined ether solution was dried (Na_2SO_4) and concentrated to dryness in vacuo to give a pale yellow liquid (6.6 g). The liquid was distilled (short path) to give bis(aminomethyl)diethylsilane (**7e**) as a colorless liquid (4.905 g, 79%): bp 83–94 °C/10 mmHg; ^1H NMR (CDCl_3/TMS) δ 0.63 (q, 4 H, CH_2 , $J = 6.8$ Hz), 1.00 (t, 6 H, CH_3 , $J = 6.8$ Hz), 1.30 (s, 4 H, NH_2), 2.35 (s, 4 H, CH_2); IR (neat) 3354, 2951, 2914, 2810, 1596, 1455, 1341, 1237, 1012, 751 cm^{-1} .

Bis(chloromethyl)tetramethylenesilane (8a). A Grignard reagent, prepared from 1,4-dibromobutane (8.483 g, 39.3 mmol, 4.7 mL) and magnesium (2.15 g, 88.4 mmol) in anhydrous ether (40 mL), was added dropwise to bis(chloromethyl)dichlorosilane (**5d**; 7 g, 35.4 mmol, 4.8 mL) in anhydrous ether (100 mL) with stirring under argon. The mixture was heated at reflux for 17 h and filtered, and the magnesium salts were washed with ether. The ether solution was evaporated to dryness in vacuo, and the white solid residue was extracted with a small amount of pentane. The pentane extract was concentrated to dryness in vacuo, and the residue was distilled (1.5 \times 10 cm Vigreux column) to give bis(chloromethyl)tetramethylenesilane (**8a**; 2.92 g, 45%) as a colorless liquid: bp 94–95 °C/11 mmHg; ^1H NMR (CDCl_3/TMS) δ 0.82 (m, 4 H), 1.68 (m, 4 H), 3.0 (s, 4 H); IR (neat) 2933, 2856, 1451, 1397, 1249, 1076, 1029, 824, 787, 723, 628 cm^{-1} .

Bis(azidomethyl)tetramethylenesilane (8b). A mixture of bis(chloromethyl)tetramethylenesilane (**8a**; 2.62 g, 14.31 mmol), sodium azide (2.79 g, 42.92 mmol), sulfolane (11 mL), and a small amount of sodium carbonate was stirred at 50–60 °C for 19 h under argon. The resulting clear solution (containing a white solid) was extracted with petroleum ether. The extracts were combined, washed with brine, dried (Na_2SO_4), and freed of solvent in vacuo to give crude bis(azidomethyl)tetramethylenesilane (**8b**; 2.58 g, 92%) as a colorless liquid: ^1H NMR (CDCl_3/TMS) δ 0.78 (m, 4 H), 1.68 (m, 4 H), 3.05 (s, 4 H); IR (neat) 2934, 2858, 2179, 2092, 1457, 1451, 1287, 1231, 1077, 1029, 823 cm^{-1} .

Bis(aminomethyl)tetramethylenesilane (8c). A solution of bis(azidomethyl)tetramethylenesilane (crude **8b**; 1.896, 9.66 mmol) in ether (8 mL) was added dropwise over 10 min to a suspension of lithium aluminum hydride (1 g, 26.35 mmol) in ether (53 mL) at -5 °C under argon. The mixture was then

stirred at 18 °C for 1 h. Ice-cooled saturated salt solution (3.2 mL) and 10% sodium hydroxide (1.2 mL) were added at 0 °C. Solid NaCl and Na_2SO_4 were added, the mixture was filtered, and the salts were washed repeatedly with ether. The combined ether solution was dried (Na_2SO_4) and concentrated to dryness in vacuo to give a very pale yellow liquid. The liquid was distilled (short path) to give bis(aminomethyl)tetramethylenesilane (**8c**) as a colorless liquid (0.657 g, 47%): bp 100–103 °C/11 mmHg; ^1H NMR δ 0.67 (m, 4 H), 1.1 (s, 4 H, NH_2), 1.61 (m, 4 H), 2.34 (s, 4 H); IR (neat) 3333, 3202, 3191, 2930, 2852, 2808, 1603, 1247, 1073, 1026 cm^{-1} .

Bis(chloromethyl)pentamethylenesilane (9a). A Grignard reagent, prepared from 1,5-dibromopentane (24.26, 0.106 mol) and magnesium (8.2 g, 0.337 g-atom) in anhydrous ether, (120 mL) was added dropwise to bis(chloromethyl)dichlorosilane (**5d**; 18.895 g, 95.91 mmol) in anhydrous ether (270 mL) with stirring under argon. The mixture was heated at reflux for 8 h and then concentrated to dryness in vacuo. The concentrated residue contained a large amount of magnesium salts and was extracted with pentane. The pentane extract was concentrated to dryness in vacuo and distilled (1.5 \times 10 cm Vigreux column) to give bis(chloromethyl)pentamethylenesilane (**9a**) as a colorless liquid (10.879 g, 58%): bp 120–126 °C/15 mmHg; ^1H NMR (CDCl_3/TMS) δ 0.87 (t, 4 H, CH_2 , $J = 6.75$ Hz), 1.47, 1.82 [(1.08–1.95), m, 6 H, CH_2], 2.98 (s, 4 H, CH_2); IR (neat) 2926, 2854, 1460, 1399, 1341, 1265, 1183, 1098, 990, 910, 802 cm^{-1} .

Bis(azidomethyl)pentamethylenesilane (9b). A mixture of bis(chloromethyl)pentamethylenesilane (**9a**; 10.879 g, 55 mmol), sodium azide (10.76 g, 166 mmol), sulfolane (42 mL), and a small amount of sodium carbonate was stirred at 55–65 °C for 22 h under argon. The resulting clear solution (containing a white solid) was extracted with petroleum ether. The extracts were combined, washed with brine, dried (Na_2SO_4), and freed of solvent in vacuo to give crude bis(azidomethyl)pentamethylenesilane (**9b**; 11.04 g, 95%) as a colorless liquid: ^1H NMR (CDCl_3/TMS) δ 0.83 (t, 4 H, $J = 6.75$ Hz), 1.4, 1.75 [(1.07–1.99), m, 6 H], 3.00 (s, 4 H); IR (neat) 2923, 2857, 2179, 2093, 1460, 1409, 1292, 1231, 1183, 1076, 992 cm^{-1} .

Bis(aminomethyl)pentamethylenesilane (9c). A solution of bis(azidomethyl)pentamethylenesilane (crude **9b**; 11 g, 52.5 mmol) in ether (30 mL) was added dropwise over 10 min to a suspension of lithium aluminum hydride (3.98 g, 105 mmol) in ether (210 mL) at -10 °C under argon. The mixture was then stirred at 20 °C for 40 min. Ice-cooled saturated salt solution (12 mL) and 10% sodium hydroxide (4.3 mL) were added at 0 °C. Solid sodium sulfate was added. The mixture was filtered, and the salts were washed repeatedly with ether. The combined ether solution was dried (Na_2SO_4) and concentrated to dryness in vacuo to give a pale yellow liquid (7.497 g). The liquid was distilled (short path) to give bis(aminomethyl)pentamethylenesilane (**9c**) as a colorless liquid (4.9 g, 59%): bp 120–128 °C/17 mmHg; ^1H NMR (CDCl_3/TMS) δ 0.7 (t, 4 H, $J = 7.5$ Hz), 1.2 (s, 4 H, NH_2), 1.45, 1.7 [(1.25–2.1), m, 6 H], 2.45 (s, 4 H); IR (neat) 3360, 3282, 2909, 2850, 2806, 1598, 1402, 1181, 989, 909, 789 cm^{-1} .

[Bis(aminomethyl)tetramethylenesilane]dichloroplatinum(II) (10a). A solution of bis(aminomethyl)tetramethylenesilane (**8c**; 0.657 g, 4.55 mmol) in nitrogen-degassed methanol (4.6 mL) was added rapidly to a stirring solution of potassium tetrachloroplatinate (98%, 1.92 g, 4.55 mmol) in nitrogen-degassed water (19 mL) under an argon atmosphere. The reaction mixture was protected from the light. Formation of white solid was observed immediately. The mixture was stirred in the dark under argon for 19 h. The precipitated product was collected and washed sequentially with cold water, cold 1 N HCl, cold water, cold ethanol, and ether to yield an off-white solid. The solid was dissolved in a minimum amount of DMF; then ether was added, and the precipitate was collected and washed with acetonitrile and ether to give an off-white solid (0.9 g, 48%). The solid was dissolved in a minimum amount of DMF and worked up in a similar manner to yield [bis(aminomethyl)tetramethylenesilane]dichloroplatinum(II) (**10a**) as a very pale yellow solid: mp 190 °C (shrinks), 197–198 °C dec (melts); ^1H NMR ($\text{DMF-}d_7/\text{TMS}$) δ 0.82 (m, 4

H), 1.59 (m, 4 H), 2.57 (t br t, $J = 27$ Hz, $J = 6$ Hz), 5.03 (br t, $J = 33$ Hz); IR (KBr) 3236, 3125, 2925, 2856, 1658, 1597, 1406, 1147, 1077, 771 cm^{-1} . Anal. ($\text{C}_6\text{H}_{16}\text{N}_2\text{Cl}_2\text{PtSi}$) C, H, N.

[Bis(aminomethyl)tetramethylenesilane]tetrachloroplatinum(IV) (10b). Chlorine gas was bubbled through a stirred suspension of [bis(aminomethyl)tetramethylenesilane]dichloroplatinum(II) (crude **10a**; 0.288 g, 0.7 mmol) in 0.5 N HCl (12 mL) at 50 °C for 40 min. The mixture was cooled to room temperature, and the excess chlorine was removed by bubbling air through the reaction mixture for 40 min. The yellow solid was filtered and washed with water and ether to give an orange-yellow solid (0.27 g). The aqueous filtrate and the water washing were combined and concentrated in vacuo to yield a yellow solid (83 mg). The combined yellow solid (0.353 g, 100%) was dissolved in acetonitrile, ether was added, and the precipitate was collected to yield [bis(aminomethyl)tetramethylenesilane]tetrachloroplatinum(IV) (**10b**) as a yellow solid (0.165 g, 49%); mp 187 °C (sintered), 191–195 °C dec (melted); ^1H NMR ($\text{DMF-}d_7/\text{TMS}$) δ 0.83 (m, 4 H), 1.57 (m, 4 H), 2.53 (t br t, 4 H, $J = 20.25$ Hz, $J = 4.5$ Hz), 6.77 (br t, $J = 31.5$ Hz); IR (KBr) 3201, 3113, 2930, 2849, 1630, 1566, 1458, 1407, 1334, 1291, 1167, 1077, 1029 cm^{-1} . Anal. (From $\text{DMF-}d_7/\text{ether}$.) Calcd for $\text{C}_6\text{H}_{16}\text{N}_2\text{Cl}_4\text{SiPt} + 0.25\text{DMF-}d_7$: C, 16.18; H, 3.44; N, 6.28. Found: C, 16.63; H, 3.55; N, 6.16.

[Bis(aminomethyl)pentamethylenesilane]dichloroplatinum(II) (11a). A solution of bis(aminomethyl)pentamethylenesilane (**9c**; 1.5 g, 9.48 mmol) in nitrogen-degassed methanol (9.5 mL) was added rapidly to a stirring solution of potassium tetrachloroplatinate (3.933 g, 9.48 mmol) in nitrogen-degassed water (40 mL) under an argon atmosphere. The reaction mixture was protected from the light. Formation of white solid was observed immediately. The mixture was stirred in the dark under argon for 20 h at 20–23 °C. The precipitated product was collected and washed sequentially with cold water, cold 1 N HCl, cold water, and ether to yield an off-white solid (3.54 g, 88%). The solid was dissolved in a minimum amount of DMF, ether was added, and the precipitate was collected and washed with acetonitrile and ether to give [bis(aminomethyl)pentamethylenesilane]dichloroplatinum(II) (**11a**) as a pale yellow solid (1.43 g, 36%) [the filtrate (DMF-ether) was concentrated, and ether was added to give an off-white precipitate (0.472 g, for a total yield of 47%); mp 202–204 °C dec (melts); mp 196 °C (shrinks), 212–213 °C dec (melts); ^1H NMR ($\text{DMF-}d_7/\text{TMS}$) δ 0.95 (t, 4 H, $J = 6$ Hz), 1.4, 1.6 [(1.08–1.8), m, 6 H], 2.3 (tt, 4 H, $J = 6$ Hz, $J = 27$ Hz), 4.83 (br t, NH_2 , $J = 36$ Hz); IR (KBr) 3267, 3221, 3135, 2908, 2846, 1595, 1438, 1293, 1187, 1156, 908 cm^{-1} . Anal. ($\text{C}_7\text{H}_{18}\text{N}_2\text{Cl}_2\text{PtSi}$) C, H, N.

[Bis(aminomethyl)pentamethylenesilane]tetrachloroplatinum(IV) (11b). Chlorine gas was bubbled through a stirred suspension of pure [bis(aminomethyl)pentamethylenesilane]dichloroplatinum(II) (**11a**; 0.37 g, 0.87 mmol) in 0.5 N HCl (60 mL) at 50 °C for 20 min. The mixture was cooled to room temperature, and the excess chlorine was removed by bubbling air through the reaction mixture for 30 min. The yellow solid was filtered, washed with water and ether, and then dissolved in acetonitrile (all dissolved, no insoluble polymeric material left). The acetonitrile solution was evaporated to dryness in vacuo to give yellow prisms (0.289 g, 67%); mp 191–196 °C (sintered), 202–203 °C dec (melted). The aqueous filtrate and water washings were combined and concentrated in vacuo at 40 °C to yield a yellow solid (0.124 g). The combined yellow solid (0.413 g, 96%) was dissolved in acetonitrile, ether was added, and the precipitate was collected to yield [bis(aminomethyl)pentamethylenesilane]tetrachloroplatinum(IV) (**11b**; 0.34 g, 79%); mp 198–200 °C (sintered), 201–202 °C dec (melted); ^1H NMR ($\text{DMF-}d_7/\text{TMS}$) δ 0.9 (br s, 4 H), 1.5, 1.63 [(0.18–1.9), m, 6 H], 2.47 (t br t, 4 H, $J = 19$ Hz, $J = 4.8$ Hz), 6.77 (br t, 4 H, NH_2 , $J = 20.3$ Hz); IR (KBr) 3207, 3114, 2912, 2853, 1569, 1411, 1149, 769 cm^{-1} . Anal. ($\text{C}_7\text{H}_{18}\text{N}_2\text{Cl}_4\text{SiPt}$) C, H, N.

2,2-Dimethyl-1,3-diaminopropane. A solution of 2,2-dimethylmalonic acid (25 g, 189.4 mmol) in thionyl chloride (60 mL) was heated under an argon atmosphere at gentle reflux for 20 h. The mixture was cooled and distilled (Vigreux column) to give the diacid chloride as a colorless liquid (22.8

g, 71%); bp 58–60 °C (18 mmHg); IR (neat) 1775 cm^{-1} ; ^1H NMR (CDCl_3/TMS) δ 1.63. The diacid chloride (10 g, 59.17 mmol) was slowly added to an ice-cooled, mechanically stirred 28% ammonia solution (60 mL). The white precipitated solid was collected, washed with water (10 mL portions), and dried in vacuo to give the amide (6.3 g, 82%); mp 263–265 °C; ^1H NMR ($\text{CF}_3\text{CO}_2\text{D}/\text{TMS}$) δ 1.15; IR (Nujol) 3400, 3200, 1650, 1610 cm^{-1} .

Borane–dimethyl sulfide¹⁸ (22.04 g, 0.29 mol) was added over a period of 20 min to a solution, heated at reflux under a nitrogen atmosphere, of amide (13.0 g, 0.1 mol) in anhydrous THF (80 mL). The mixture was heated at reflux for 2 h after the addition was completed (dimethyl sulfide was liberated), and then the reaction mixture was cooled to 25 °C and treated with 6 N HCl (33 mL). Sodium hydroxide was added to make the solution basic, ether was added, and the organic phase was separated. The aqueous layer was extracted with chloroform (3 \times 50 mL), and the combined organic phase was dried (sodium sulfate) and concentrated in vacuo. Calcium hydride was added to the residual liquid, and the mixture was distilled to give 2,2-dimethyl-1,3-diaminopropane as a pale yellow liquid (7.6 g, 75%); bp 150–153 °C; ^1H NMR (CDCl_3/TMS) δ 0.85 (s, 6 H), 1.04 (s, 4 H, exchangeable with D_2O), 1.51 (s, 4 H).

cis-(2,2-Dimethyl-1,3-diaminopropane)dichloroplatinum(II) (12). A solution of 2,2-dimethyl-1,3-diaminopropane (1.02 g, 0.01 mol) in argon-degassed water (5 mL) was rapidly added to a solution of potassium tetrachloroplatinate (4.15 g, 0.01 mol) in argon-degassed water (45 mL) that was maintained under an argon atmosphere. The mixture was protected from light and stirred at 20 °C for 20 h. The precipitated solid was collected on a medium sintered glass funnel and washed with water, 1 N HCl, cold ethanol, and ether. The product was air-dried to give **12** (2.93 g, 80%) as an off-white solid. Slow (1 week) crystallization from DMF gave **12** as pale yellow crystals (2.05 g, 56%); IR (KBr) 3220, 3180, 3115, 3940, 3905, 3860, 1545, 1425, 1272, 1228, 1204, 1266, 1254, 1050, 1030, 1014, 1007, 951, 932, 911, 900, 835, 762, 711, 562, 520 cm^{-1} .

cis-Bis(2,2-dimethylaminopropane)dichloroplatinum(II) (13). A solution of 2,2-dimethylaminopropane (2.34 g, 0.02 mol) in argon-degassed methanol (5 mL) was added rapidly to a stirred solution of potassium tetrachloroplatinate (4.15 g, 0.01 mol) in argon-degassed water (45 mL) that was maintained under an argon atmosphere. The mixture was protected from the light and stirred at 20 °C for 26 h. The precipitated solid was collected on a medium sintered glass funnel and washed with water, 1 N HCl, cold ethanol, and ether. The product was air-dried to give **13** as an off-white solid (3.73 g, 85%) that was crystallized slowly (ca. 1 week) from DMF to give **13** as a yellow crystalline solid (1.64 g, 37%); ^1H NMR ($\text{DMF-}d_7/\text{TMS}$) δ 0.57 (s, 18 H), 2.4 (s, 4 H), 2.57 (s, 4 H); IR (KBr) 3240, 3130, 2950, 2875, 1640, 1590, 1470, 1425, 1375, 1355, 1293, 1264, 1242, 1208, 1148, 1104, 1038, 1005, 938, 904, 811, 750, 734, 658 cm^{-1} .

Hydrolysis Studies. A sample of the platinum complex (ca. 5 mg) was added to HPLC grade water (5 mL); the mixture was sonicated for 1 min and filtered. The filtrate was analyzed by HPLC every 15 min (for **12**) or 30 min (for **2a**). The samples were analyzed on an Alltech C-8, 10 μm , 600 RP8 column (25 cm \times 4.6 mm) with a mobile phase of water–acetonitrile (95.5) at a flow rate of 1.5 mL/min. The eluant was monitored by UV at 203 nm (4 nm bandwidth).

Acknowledgment. This research was supported in part by contracts NO1-CM-17569 and NO1-CM-67698 from the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

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