Communications to the Editor

Synthesis, Characterization, and Anticancer Activities of the First Platinum Complexes from Sucrose†,‡

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Despite the fact that more than 2000 cisplatin analogs have been produced[1] since the discovery of the anticancer activity of cisplatin by Rosenberg,[2] there is still an urgent need for new platinum complexes that will combat intrinsic and acquired drug resistance and that will reduce the toxic side effects and morbidity of cisplatin and carboplatin chemotherapy.[3] We have succeeded in creating an unprecedented class of water-soluble multi(platinum) complexes from sucrose-based ligands with marked in vivo anticancer activities. Since anticancer activities for complexes containing one and two platinum centers are known,[4,5] and since some monosaccharide complexes have shown anticancer activities,[6] we sought to prepare complexes containing one, two, and three platinum centers bound to sucrose-derived ligands and explore their biological activities. We prepared mono(platinum) complexes **3** from 6,6′-diamino-6,6′-dideoxy-1′,2,3,3′,4,4′-hexa-*O*-methylsucrose (**2**),[7] bis(platinum) complex **5** from the rigid 6,6′-diamino-6,6′-dideoxy-1′,2-anhydrosucrose (**4**), and tris(platinum) complexes **7** from 1′,6,6′-triamino-1′,6,6′-trideoxy-2,3,3′,4,4′-penta-*O*-methylsucrose (**6**) (see Scheme I). Our intent was to create sucrose-based cisplatin analogs that may have greater water solubility and less general systemic toxicity than cisplatin, be able to transport more than one platinum complex per molecule of sucrose to the tumor cell, and be able to bind both strands of DNA, so that replication of tumor cells resistant to cisplatin and carboplatin may be effectively arrested.[3,4] Herein we report the syntheses, spectroscopic characterizations, and anticancer activities of these first platinum complexes from sucrose.

The diamine **2**[7] (4.41 mmol in 10 mL of water) was converted to the mono(platinum) complex **3a** (90% yield) upon addition to potassium tetraiodoplatinate[8] in water (4.64 mmol, 30 mL). Although **3a** precipitates from an aqueous solution within 30 min, the final one-third of the product was recovered by extraction with ethyl acetate. Conversion of the key intermediate **3a** to the oxalate **3b** (42% yield), malonate **3c** (65% yield), and cyclopropyl-

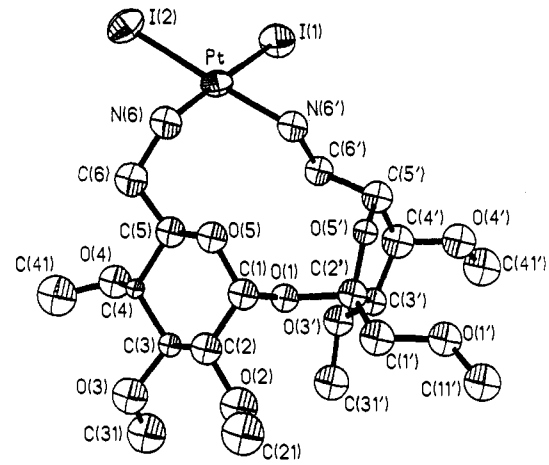
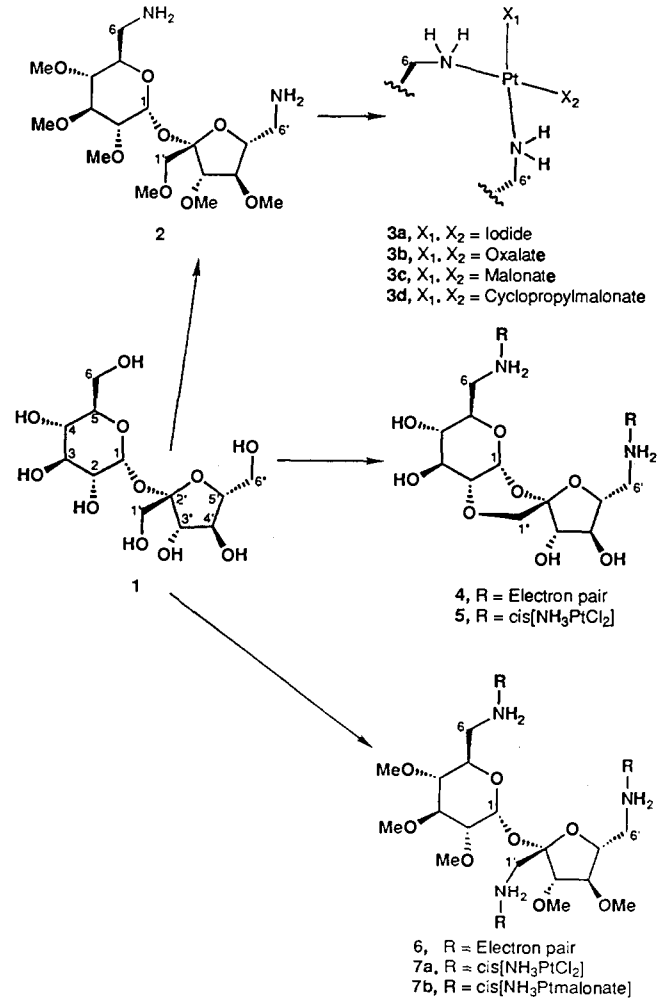


Figure 1. Structure of **3a**·H_2O·$(CH_3)_2C{=}O$. Selected bond distances (Å) and angles (deg) are as follows: Pt–I(1), 2.607(3); Pt–I(2), 2.604(3); Pt–N(6), 2.05(2); Pt–N(6′), 2.08(2); N(6)–C(6), 1.51(4); C(6′)–N(6′), 1.50(4); C(1)–O(1)–C(2′), 118(2); Pt–N(6)–C(6), 120(2); Pt–N(6′)–C(6′), 117(2).

Scheme I



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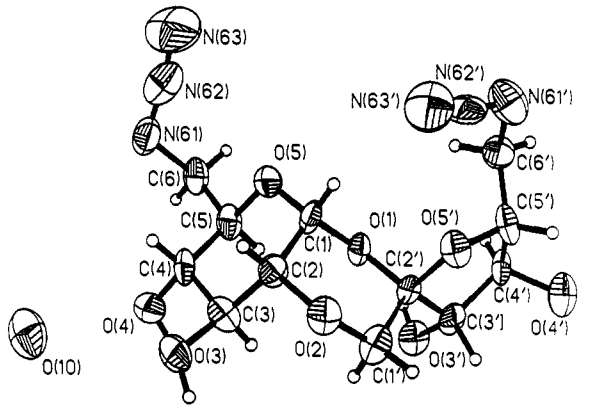
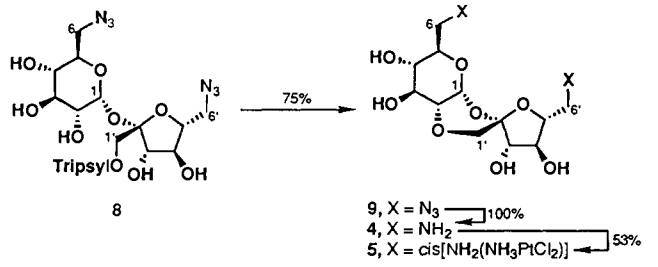
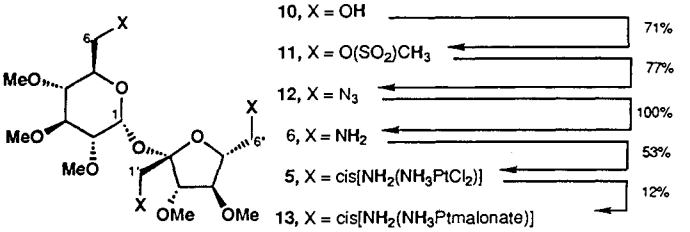


Figure 2. Structure of diazidoanhydrosucrose hydrate. Selected bond distances (Å) and angles (deg) are as follows: C(6)–N(61), 1.521(17); C(6')–N(61'), 1.488(17); C(2)–O(2), 1.446(13); C(1')–O(2), 1.447(14); C(1)–O(1), 1.462(14); O(1)–C(2'), 1.427(12); C(1)–C(2)–O(2), 109.5(7); C(2)–O(2)–C(1'), 111.9(9); O(2)–C(1')–C(2'), 113.0(8); C(2)–C(1)–O(1), 111.6(8); C(1)–O(1)–C(2'), 111.2(9); O(1)–C(2')–C(1'), 110.7(7).

Scheme II



Scheme III



malonate **3d** (26% yield) required preparation of the diaquo complex ($AgNO_3$ 2 equiv, $NaNO_3$ 1 M, in water–acetone, 8:2 mL), followed by addition of an aqueous solution of the disodium salt of the diacid (5 equiv, 10 mL of water) at pH 7.6.[9] Figure 1 shows the X-ray crystal structure of compound **3a**.[10] The bis(platinum) complex **5** was prepared in three steps from 6,6'-diazido-6,6'-dideoxy-1'-*O*-((triisopropylphenyl)sulfonyl)sucrose (**8**).[11] Treatment of **8** (7.6 mmol) with sodium ethoxide in ethanol (0.75 M, 80 °C, 24 h), followed by neutralization, concentration, and countercurrent chromatography (silica gel GF plate, 0.40-cm thickness, 10% methanol in methylene chloride) afforded the anhydro diazide **9** in 75% yield (see Figure 2 for X-ray crystal structure).[12] Compound **9** was quantitatively reduced (10% Pd/C, H_2, 60 psi, methanol, 48 h) to ligand **4**. Complexation of **4** (3.5 mmol) was achieved (in 53% yield) by reaction with tetraethylammonium amminetrichloroplatinate[13] (2 equiv, 48 h) in the presence of triethylamine (2 mL) in methanol (50 mL)[5b] (see Scheme II). The tris(platinum) complex **7a** was prepared in four steps from 2,3,3',4,4'-penta-*O*-methylsucrose (**10**)[7b] (see Scheme III). Mesylation of **10** was

Table I. 500-MHz ^1H NMR and 125-MHz ^{13}C NMR Data (*N,N'*-Dimethylformamide-d_7) for **3a**, **5**, and **7b**

3a[a]				**5**[b]				**7b**[c]			
^{13}C		^1H		^{13}C		^1H		^{13}C		^1H	
C_1	97.957	H_1	5.797	C_1	91.269	H_1	5.485	C_1	90.679	H_1	5.648
C_2	82.493	H_2	3.125	C_2	74.989	H_2	3.480	C_2	81.993	H_2	3.247
C_3	82.492	H_3	3.575	C_3	67.349	H_3	4.144	C_3	83.884	H_3	3.446
C_4	83.182	H_4	2.956	C_4	72.368	H_4	3.240	C_4	80.251	H_4	3.233
C_5	70.853	H_5	4.229	C_5	73.018	H_5	4.426	C_5	69.813	H_5	3.878
C_6	50.428	H_{6a}	2.805	C_6	48.487	H_{6a}	3.293	C_6	47.655	H_{6a}	3.109
		H_{6b}	3.516			H_{6b}	2.601			H_{6b}	3.031
$C_{1'}$	76.163	$H_{1'a}$	3.579	$C_{1'}$	62.048	$H_{1'a}$	4.000	$C_{1'}$	51.398	$H_{1'a}$	3.122
		$H_{1'b}$	3.654			$H_{1'b}$	3.461			$H_{1'b}$	3.098
$C_{2'}$	107.985			$C_{2'}$	104.044			$C_{2'}$	104.220		
$C_{3'}$	87.133	$H_{3'}$	3.848	$C_{3'}$	78.988	$H_{3'}$	3.762	$C_{3'}$	86.426	$H_{3'}$	4.197
$C_{4'}$	88.259	$H_{4'}$	3.699	$C_{4'}$	81.367	$H_{4'}$	4.161	$C_{4'}$	85.475	$H_{4'}$	3.916
$C_{5'}$	83.629	$H_{5'}$	4.206	$C_{5'}$	77.047	$H_{5'}$	4.169	$C_{5'}$	80.471	$H_{5'}$	4.587
$C_{6'}$	51.108	$H_{6'a}$	3.460	$C_{6'}$	51.103	$H_{6'a}$	3.106	$C_{6'}$	50.437	$H_{6'a}$	3.012
		$H_{6'b}$	3.145			$H_{6'b}$	2.921			$H_{6'b}$	2.986
OMe_2	59.456	OMe_2	3.503					OMe_2	59.795	OMe_2	3.636
OMe_3	60.408	OMe_3	3.553					OMe_3	60.205	OMe_3	3.568
OMe_4	60.311	OMe_4	3.516					OMe_4	60.105	OMe_4	3.562
$OMe_{1'}$	59.456	$OMe_{1'}$	3.380					$OMe_{3'}$	58.554	$OMe_{3'}$	3.543
$OMe_{3'}$	58.942	$OMe_{3'}$	3.516					$OMe_{4'}$	58.194	$OMe_{4'}$	3.489
$OMe_{4'}$	56.923	$OMe_{4'}$	3.354					Mal_A CH_2	50.638	Mal_A H_a	3.458
										Mal_A H_b	3.464
								Mal_B CH_2	50.437	Mal_B H_a	3.383
										Mal_B H_b	3.430
								Mal_C CH_2	50.327	Mal_C H_a	3.387
										Mal_C H_b	3.432
								Mal_A C=O	176.658, 176.317		
								Mal_B C=O	175.577, 175.016		
								Mal_C C=O	175.176, 174.836		

[a] Proton coupling constants for compound **3a** (Hz): $^3J_{1,2}$ = 3.14, $^3J_{2,3}$ = 9.76, $^3J_{3,4}$ = 9.60, $^3J_{4,5}$ = 9.10, $^3J_{5,6a}$ = 2.10, $^3J_{5,6b}$ = 7.10, $^2J_{6a,6b}$ = −11.21, $^2J_{1'a,1'b}$ = −10.85, $^3J_{3',4'}$ = 2.11, $^3J_{4',5'}$ = 1.90, $^3J_{5',6'a}$ = 6.8, $^3J_{5',6'b}$ = 4.10, $^3J_{6'a,6'b}$ = −11.62. [b] Proton coupling constants for compound **5** (Hz): $^3J_{1,2}$ = 3.79, $^3J_{2,3}$ = 9.24, $^3J_{3,4}$ = 9.72, $^3J_{4,5}$ = 9.51, $^3J_{5,6a}$ = 3.81, $^3J_{5,6b}$ = 7.11, $^2J_{6a,6b}$ = −13.12, $^2J_{1'a,1'b}$ = −12.21, $^3J_{3',4'}$ = 6.97, $^3J_{4',5'}$ = 6.71, $^3J_{5',6'a}$ = 3.61, $^3J_{5',6'b}$ = 6.93, $^3J_{6'a,6'b}$ = −12.89. [c] Proton coupling constants for compound **7b** (Hz): $^3J_{1,2}$ = 3.3, $^3J_{2,3}$ = 9.8, $^3J_{3,4}$ = 10.2, $^3J_{4,5}$ = 9.7, $^3J_{5,6a}$ = 4.4, $^3J_{5,6b}$ = 7.8, $^2J_{6a,6b}$ = −11.7, $^2J_{1'a,1'b}$ = −10.5, $^3J_{3',4'}$ = 6.9, $^3J_{4',5'}$ = 6.8, $^3J_{5',6'a}$ = 6.0, $^3J_{5',6'b}$ = 3.9, $^3J_{6'a,6'b}$ = −11.4, Mal_A CH_2 $^2J_{a,b}$ = −13.78, Mal_B CH_2 $^2J_{a,b}$ = −14.06, Mal_C CH_2 $^2J_{a,b}$ = −14.71.

achieved in 71% yield (15 mmol of **10**, methanesulfonyl chloride 15 equiv, in pyridine 0–25 °C, 24 h), and the trimesylate **11** was converted to the triazide **12** (sodium azide 30 equiv, HMPA, 120 °C, 2 days, 77% yield). Reduction of the triazide **12** followed by direct isolation of **6** without resorting to amidation proved arduous. Phosphorus,[14] sulfur,[15] and tin reagents[16] produced mixtures from which the desired triamine **6** was difficult to separate. Catalytic hydrogenation[17] was accompanied by epimerization at C-1. Serendipitously, it was discovered that the triamine **6** which was produced upon lithium aluminum hydride[18] (15 equiv, in dry THF) reduction of **12** could be quantitatively freed from the reaction mixture by concentrating the neutralized filtrate after workup[18] and triturating the wet residue with DMF. Finally the tris(platinum) complex **7a** was prepared by reaction of **6** (1 mmol) with tetraethylammonium amminetrichloroplatinate[13,5b] (3 equiv, triethylamine 2 mL, methanol 50 mL, 48 h, 50% yield). Compound **7a** could not be completely characterized by NMR methods owing to excessive overlapping of broadened proton resonances. Exchange of the chloride ligands to the tris(malonate) chelates **7b** enabled unambiguous assignments of the carbohydrate portion of this molecule.

NMR assignments of compounds **3a**, **5**, and **7b**[19] (see Table I) were accomplished using a combination of spectroscopic techniques. The COSY spectrum was used to establish the interproton connectivities of the glucopyranoside and fructofuranoside rings.[20] Cross peaks established the chemical shifts of H-1, H-2, H-3, H-4, H-5, H-6a, and H-6b of the pyran and H-3′, H-4′, H-5′, H-6′a, and H-6′b of the furan. H-1′a and H-1′b proton resonances were identified as an isolated AB quartet. Carbon chemical shifts were determined through the direct correlations observed in the HMQC experiment,[21] thereby establishing the assignments of the corresponding sugar ring carbon atoms. Assignments of the *O*-methyl groups in the mono- (**3a–d**) and tris(platinum) complexes (**7a–b**) were determined by (a) the correlations between the sugar ring carbons and the methyl protons in the HMBC spectrum[22] via $^3J_{C,H}$ long-range coupling constants and (b) reverse correlation of the sugar ring protons to the methyl carbon resonances in the latter spectrum. Proton–proton coupling constants were determined by measuring the observed splitting and then refined by comparing the experimental spectrum with a calculated spectrum using initial parameters.

Biological studies on our complexes show that compounds **3a–d** are noncytotoxic and possess no anticancer activity.[23–25] On the other hand, the bis(platinum)complex **5** is water soluble (≥10 mg/mL) and is comparable to cisplatin in terms of its cytotoxicity to human KB cells in culture (3+, 10 μg/mL, 11.3 μM)[23] and its anticancer activity against both implanted Lewis lung carcinoma in mice (T/C ≥ 310%)[24,25] and P388 leukemia (T/C ≥ 291%).[26] However, unlike cisplatin, compound **5** in mice showed no severe toxic side effects other than recoverable weight loss for the 50-day observation period. Compound **7a** represents the first example of a tris(*cis*-platinum) complex. It is sparingly soluble in water (≈1.5 mg/mL) and shows marked in vitro cytotoxicity and in vivo anticancer activity against human KB cells in culture (3+, 10 μg/mL, 7.9 μM) and implanted Lewis lung carcinoma (T/C ≥ 355%), respectively.[23–25] Our immediate goals hereafter are (a) to complete a preclinical picture of the efficacies of these new complexes against a wide range of solid tumors, (b) to generate more water-soluble multi(platinum) complexes from sucrose and other mono-, di-, and oligosaccharides, and (c) to understand the mode with which these complexes can bind DNA by isolating and characterizing their DNA adducts.

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Supplementary Material Available: X-ray data for compounds **3a** and **9** as well as full details of cytotoxicity and anticancer activity experiments on compounds **3a–d**, **5**, and **7a** (24 pages). Ordering information is given on any current masthead page.

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(24) (a) Control group (C): Mean survival time of mice (days) in which tumor cells were implanted intraperitoneally and were not subjected to chemotherapy. Treated group (T): Mean survival time of mice (days) in which tumor cells were implanted intraperitoneally but were subjected to treatment with chemotherapeutic agent. (b) T/C (%): ratio between the mean survival time of mice treated with chemotherapeutic agent and untreated (control) mice × 100. (c) Percent increase in life span (ILS, %) = [(T − C)/C] × 100.

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(26) For in vivo activity against P388 leukemia, the following method was used: A 0.1-mL aliquot of a 10-fold dilution of P388 ascites (ca. 10^6 cells) was injected intraperitoneally (ip) into syngeneic DBA/2 mice (ca. 20 g body weight). The ip administration was done on day 1 only by a single 2-mg dose or by 1-mg dose administered days 1–4. Results: Complex **5** (1.0 mg/0.1 mL of distilled water) at single dose 2 mg, or daily dose 1 mg showed significant antitumor activity (T/C > 211% and > 291%, respectively). At dose 0.1 mg, this complex showed no antitumor activity. Complex **5** at high doses is not toxic systemically. This activity is strong enough to compare with the activity of cisplatin against P388 leukemia. See refs 4c, 24, and 25 for direct comparison with cisplatin and carboplatin. See Table 13 in supplementary material for details.