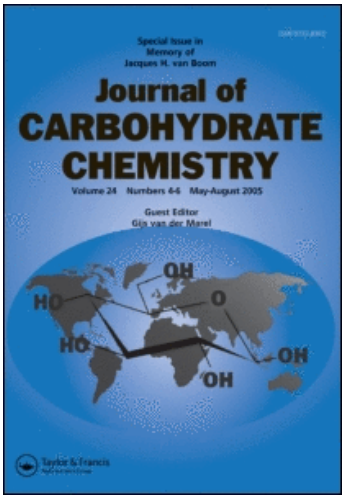

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SYNTHESIS OF PLATINUM COMPLEXES FROM SUGAR DERIVATIVES

Mauro Vieira De Almeida,[a*] Eloi Teixeira Cesar,[b,c] Ana Paula Soares Fontes,[a]
Emanoel de Castro Antunes Felício[a]

a-Departamento de Química-UFJF-36036-330-Juiz de Fora-MG-Brazil
b-Departamento de Química-UFMG-Belo Horizonte-MG-Brazil
c-Colégio de Aplicação João XXIII-Juiz de Fora-MG-Brazil
*email: mvieira@quimica.ufjf.br

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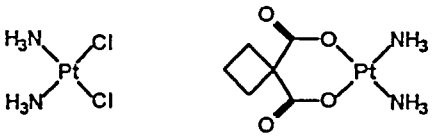
ABSTRACT

Six new platinum(II) complexes containing a diamino sugar, analogs of cisplatin and carboplatin, have been prepared and characterized. The new ligands were obtained by reaction of D-galactose and D-ribose derivatives with ethylenediamine.

INTRODUCTION

More than 2000 cisplatin analogs have been prepared[1] since the discovery of the anticancer activity of cisplatin by Rosenberg *et al.*[2] Several works has been devoted to decreasing their side effects, such as nephrotoxicity and neurotoxicity, and increasing their solubility. The quest for platinum complexes with improved therapeutic properties led to the second generation drugs such as carboplatin (Figure). The latter compound shows the same level of activity as cisplatin in treating some kinds of cancers, such as ovarian cancer and small-cell lung cancer and is much less nephrotoxic and emetic than cisplatin.[3] Since antitumour activities for complexes containing a platinum center are known[4,5] and since some monosaccharides[6,7] or ethylenediamine[8,9] complexes have shown cytotoxicity, we sought to synthesize complexes containing platinum center bound to ethylenediamine group with galactose or ribose derivatives.



Cisplatin Carboplatin

Figure

RESULTS AND DISCUSSION

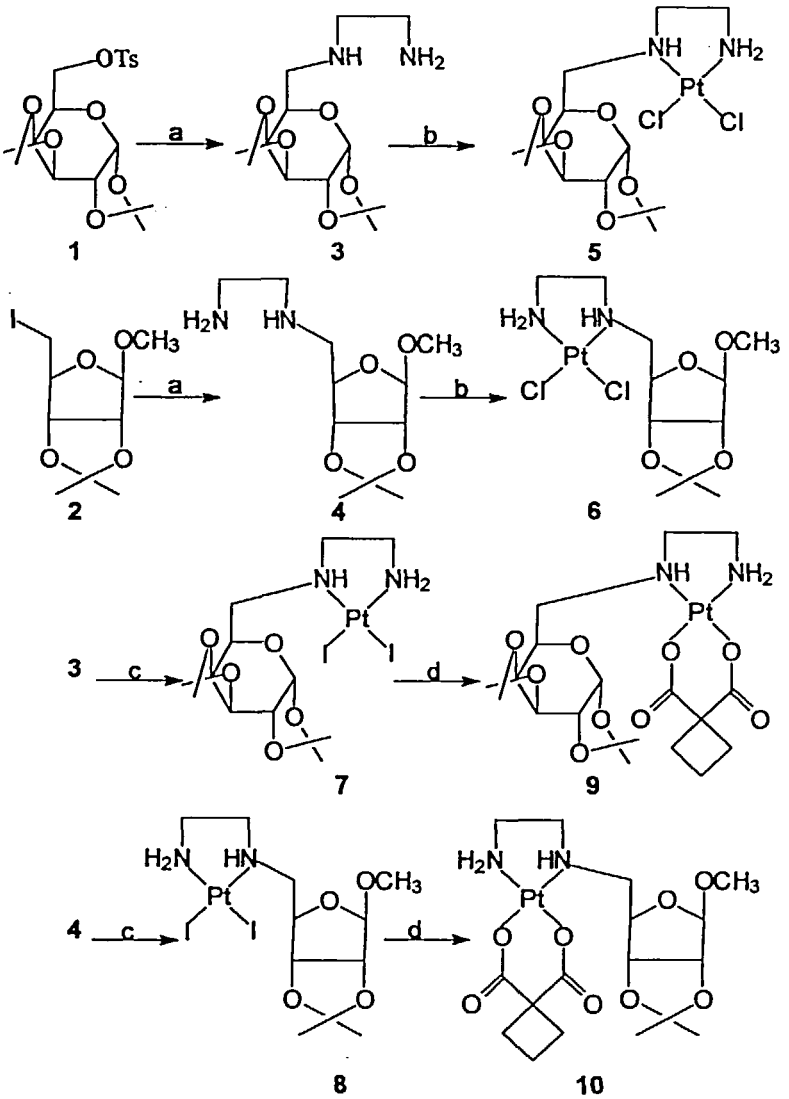
The new ligands **3** and **4** were prepared in satisfactory yields (90% and 82%, respectively) by the reaction of ethylenediamine with either 1,2:3,4 di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose **1**[10] or methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside **2**[11] in ethanol at reflux for 24 h (Scheme). In the ^{1}H NMR of these ligands, signals were observed between δ 2.38 and 3.10, corresponding to the $\underline{C}H_2NH_2$ and $\underline{C}H_2NH$. In the ^{13}C NMR, signals between δ 42.3 and 54.7 were observed, corresponding to the methylenic carbons.

The dichloro platinum(II) complexes **5** (90% yield) and **6** (80% yield) were synthesized by the reaction of these ligands with $K_2[PtCl_4]$ in water at room temperature for 12 h and isolated by simple filtration. For the complexes, one can see in their IR spectra absorptions corresponding to γ Pt-N and γ Pt-Cl at 514 and 316 cm^{-1}, respectively. The ^{195}Pt NMR spectra, as expected, showed only one signal at δ -2351 and -2365 for compounds **5** and **6** respectively.

Compounds **3** and **4** were reacted with an equimolar amount of *in situ* generated potassium tetraiodoplatinate(II) to produce the diiodo platinum(II) complexes **7** and **8** in 70-80% yields. The ^{195}Pt NMR spectra for these complexes showed one signal at δ -3467, supporting the proposed structure. Reaction of **7** and **8** with an aqueous silver 1,1-cyclobutanedicarboxylate solution afforded the corresponding carboplatin analogs **9** and **10** in 50 and 40% yields, respectively (Scheme). The IR spectra of these complexes showed absorptions at 3222 cm^{-1} (γ NH), 2987 cm^{-1} (γ CH aliphatic) and 1634 cm^{-1} (γ C=O), as well as the γ Pt-N and γ Pt-O at 559 cm^{-1} and 513 cm^{-1}, respectively. In the ^{1}H NMR spectrum of compound **9**, signals at δ 1.66 and 2.34 corresponding to the CH_2 groups of the cyclobutane ring were evident. In the ^{13}C NMR spectrum signals at δ 14.9,

30.0, 30.4 and 54.5 showed the presence of the cyclobutane ring. ^{195}Pt NMR spectra for **9**, as expected, showed only one signal at δ -1975.

The cytotoxicity and the preparation of the corresponding deprotected sugars complexes are currently under investigation in our laboratory.



a: $H_2NCH_2CH_2NH_2$; ethanol; reflux; 24 h; b: $K_2[PtCl_4]$; H_2O; rt; 12 h; c: $K_2[PtI_4]$; H_2O; rt; 12 h; d: Ag_2CBDCA; H_2O; rt; 24 h

Scheme

EXPERIMENTAL

General methods. IR spectra were obtained on a Bomem FT IR MB-102 spectrometer in KBr pellets. ^{1}H NMR (200 and 400 MHz), ^{13}C NMR (50 and 100 MHz) and ^{195}Pt NMR (86 MHz) spectra were recorded on Bruker Avance DRX 200 and DRX 400 spectrometers at the Federal University of Minas Gerais. Mass spectra (*m/z*) were recorded on Atlas CH_4 or AEI MS9 spectrometers. Column chromatography was performed using silica gel 60G (0.063-0.200 mm, E. Merck). Elemental analyses were carried at "Laboratoire Central de Microanalyse du C.N.R.S., I.C.S.N, Gif sur Yvette, France".

Synthesis of ligands 3 and 4. To a solution of ethylenediamine (6.7 mL, 100 mmol) in ethanol (20 mL), were slowly added the corresponding compounds **1** or **2** (20 mmols) during 4 h. The reaction mixture was stirred at reflux for 48 h, after which, the volume was reduced. The products were purified on silica gel (eluent: dichlomethane/methanol 9/1). Yields: 80% for compound **3** and 90 % for compound **4**.

3: $[\alpha]_D$ -46 (*c* 1, DMSO); IR (KBr) 3390 (NH) cm^{-1}; ^{1}H NMR (C_5D_5N) δ 1.31, 1.33, 1.51, 1.54 (4s, 12 H, 4 CH_3), 2.80 (m, 2 H, CH_2NH_2), 3.10 (m, 4 H, CH_2NH, H6, H6'), 4.17 (m, 1H, H5), 4.36 (dd, 1H, H4, J_{4-5}= 2.4Hz), 4.48 (dd, 1H, H2, J_{2-1}= 5.2 Hz; J_{2-3}= 2.4 Hz), 4.74 (dd, 1H, H3, J_{3-4}= 8 Hz), 5.74 (d, 1H, H-1); ^{13}C NMR (C_5D_5N) δ 24.5, 25.1, 26.2, 26.3 (CH_3), 42.3, 50.0, 54.0 (C_6, $\underline{C}H_2NH$, $\underline{C}H_2NH_2$), 67.6, 71.2, 71.3, 72.3 (C2, C3, C4, C5), 97.0 (C1), 108.4, 109.0 [($C(\underline{C}H_3)_2$]); MS: *m/z*=303 (M^++ 1).

4: IR (KBr) 3360 and 3292 (NH) cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.07 (bs, 3H, NH, NH_2), 1.18, 1.52 (2s, 6H, 2 CH_3), 2.38 (t, 2H, CH_2NH_2), 2.51 (t, 2H, CH_2NH), 2.58 (ddd, 2H, H5, H5', J_{5-4}= 6.8 Hz, $J_{5-5'}$= 12 Hz), 3.08 (s, 3H, OCH_3), 4.32 (t,1H, H3, J_{2-3}=J_{3-4}= 6.8 Hz), 4.62 (m, 2H, H2, H4), 5.07 (s, 1H, H1); ^{13}C NMR (C_6D_6) δ 25.1, 26.8 (CH_3 isoprop.), 42.1(OCH_3), 52.8, 53.5, 54.7 (C-5, CH_2NH; CH_2NH_2), 83.3, 85.9, 86.9 (C2, C3, C4), 110.1 (C1), 112.2 [$C(CH_3)_2$]; : MS: *m/z*= 247 (M^+ + 1).

Preparation of complexes 5 and 6. To a solution of K_2PtCl_4 (0.415 g, 1 mmol) in water (10 mL), the appropriate ligand was slowly added (1 mmol) and dissolved in water (5 mL), while stirring. After 24 h in the dark at room temperature, the yellow solid that formed was filtered off, washed with water, and dried. Yields: 94% for compound **5** and 64% for compound **6**.

5: $[\alpha]_D$ + 21 (*c* 1, DMSO); IR (KBr) 3306, 3190 (NH) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.28, 1.30, 1.33, 1.71 (4s, 12H, CH_3), 2.40 (m, 4H, CH_2NH, CH_2NH_2), 2.86 (dd, 1H, H6, J_{6-5}= 8.0 Hz), 3.10 (dd, 1H, H6', $J_{6'-6}$= 12.4 Hz), 4.23 (d, 1H, H5), 4.37 (dd, 1H, H2, J_{2-3}= 2.0 Hz), 4.41 (d, 1H, H4, J_{4-3}= 8.0 Hz), 5.48 (d, 1H, H1, J_{1-2}= 4.8 Hz); ^{13}C NMR (DMSO d_6) δ 24.2, 24.9, 25.8, 25.9, (CH_3), 46.4, 52.0, 55.6 (C6, CH_2NH, CH_2NH_2), 65.6, 69.5, 70.2, 71.5 (C2, C3, C4, C5), 95.7 (C1), 108.2, 108.3 [$C(\underline{C}H_3)_2$]; ^{195}Pt NMR (DMSO d_6) δ -2351.

Anal. Calcd for $C_{14}H_{26}Cl_2N_2O_5Pt$: C, 29.59; H, 4.61; N, 4.93. Found: C, 29.19; H, 4.58; N, 4.81.

6: $[\alpha]_D$ +8 (*c* 0.8, DMSO); IR (KBr) 3311, 3188 (NH) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.18, 1.33 (2 s, 6H, 2 CH_3), 2.02 (bs, 2H, $C\underline{H}_2NH_2$), 2.30 (m, 2H, CH_2NH), 2.80 (t, 1H, H5), 3.04 (t, 1H, H5'), 3.28 (s, 3H, OCH_3), 4.47 (d, 1H, H3, J_{3-2}= 6.0Hz), 4.64 (d, 1H, H2), 4.72 (d, 1H, H4, J_{4-5}= 8.0 Hz), 4.85 (s, 1H, H1), 5.25 (bs, 2H, NH_2), 6.20 (bs, 1H, NH); ^{13}C NMR (DMSO d_6) δ 24.6, 26.3 (CH_3 isoprop.), 46.5 (OCH_3), 55.0, 55.1, 55.6 (C5, $\underline{C}H_2NH_2$, $\underline{C}H_2NH$), 82.8, 84.3, 84.6 (C2, C3, C4), 109.3 (C1), 111.4 [$C(CH_3)_2$]; ^{195}Pt NMR (DMSO d_6) δ -2365.

Anal. Calcd for $C_{11}H_{22}Cl_2N_2O_4Pt$: C, 25.79; H, 4.33; N, 5.47; Cl, 13.84. Found: C, 25.39; H, 4.31; N, 5.41; Cl, 13.95.

Synthesis of compounds 7 and 8. A solution of K_2PtCl_4 (0.415 g, 1 mmol) and KI (0.664 g, 4 mmol) in water (10 mL) was stirred in the dark at room temperature for 30 minutes, after which the appropriate ligand (1 mmol), dissolved in water (5 mL) was added slowly. After stirring 24 h in the dark at room temperature, the product was isolated by filtration and recrystallized from acetone/water. Yields: 86% for compound **7** and 75% for compound **8**.

7: IR (KBr) 3212, 3174 (NH) cm^{-1}; ^1H NMR (acetone d_6) δ 1.33, 1.35, 1.40, 1.74 (4 s, 12H, 4 CH_3), 2.90 (m, 2H, $C\underline{H}_2NH_2$), 3.10 (m, 2H, $C\underline{H}_2NH$), 3.55 (ddd, 1H, H6, $J_{6-6'}$= 14 Hz, J_{6-5}= 9.1 Hz), 3.75 (ddd, 1H, H6'), 4.37 (dd, 1H, H4, J_{4-3}= 7.8 Hz, J_{4-5}= 2.1 Hz), 4.41 (dd, 1H, H2, J_{2-3}= 2.6 Hz, J_{2-1}= 5.1 Hz), 4.62 (dt, 1H, H5),4.67 (dd, 1H, H3), 5.54 (d, 1H, H1); ^{13}C NMR (acetone d_6) δ 24.9, 25.2, 26.5, 27.0 (CH_3), 49.0, 53.9, 56.0 (C6, CH_2NH_2, Ch_2NH), 67.1, 71.1, 71.8, 72.8 (C2, C3, C4, C5), 97.4 (C1), 109.6, 110.1 [$C(CH_3)_2$]; ^{195}Pt NMR (DMSO d_6) δ -3467.

Anal. Calcd for $C_{14}H_{26}I_2N_2O_5Pt$: C, 22.38; H, 3.49; N, 3.73, Found: C, 22.52; H, 3.41; N, 3.58.

8: $[\alpha]_D$ -5 (*c* 1, DMSO); IR (KBr) 3197 (NH) cm^{-1}; ^1H NMR (acetone d_6) δ 1.29, 1.40 (2 s, 6H, 2 CH_3), 2.90 (m, 2H, CH_2NH_2), 3.05 (m, 2H, CH_2NH), 3.43 (s, 3H, OCH_3), 3.50 (ddd, 2H, H5, H5', $J_{5\text{-}5'}$= 10.5 Hz, $J_{5\text{-}4}$= 2.8 Hz), 4.60 (d, 1H, H3), 4.80 (m, 2H, H2, H4), 4.95 (s, 1H, H1); ^{13}C NMR (acetone d_6) δ 25.0, 26.7 (CH_3), 48.4, 55.1, 56.4 (C5, CH_2NH_2, CH_2NH), 56.8 (OCH_3), 83.6, 84.6, 85.9 (C2, C3, C4), 111.3 (C1), 112.8 [$C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{22}I_2N_2O_4Pt$: C, 19.00; H, 3.19; N, 4.03, Found: C, 19.47; H, 3.23; N, 4.13.

Preparation of complexes 9 and 10. To a solution of the appropriate iodide complexes (compounds **7** and **8**) in 5 mL of acetone, was added 1 mmol of silver 1,1 cyclobutanedicarboxylate previously prepared by reaction of 1,1-cyclobutanedicarboxylic acid with silver nitrate in water. After stirring for 48 h at room temperature in the dark, the silver iodide formed was filtered off. The volume of the filtrate was reduced and, after 24 h in the freezer, a white powder was isolated. Yields: 38% for compound **9** and 49% for compound **10**.

9: $[\alpha]_D$ +37 (*c* 1, $CHCl_3$); IR (KBr) 3222 (NH) cm^{-1}, 1634 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.30, 1.36 (2s, 12H, 4 CH_3), 1.66 (m, 2H, CH_2), 2.34 (t, 4H, 2 CH_2), 2.69 (m, 6H, H6, H6', $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 3.94 (d, 1H, H5), 4.21 (t, 1H, H4), 4.38 (d, 1H, H2), 4.60 (d, 1H, H3, $J_{3\text{-}2}$= 8 Hz), 5.36, 5.69 (2bs, 2H, NH_2), 5.51 (d, 1H, H_1, $J_{1\text{-}2}$= 4.8 Hz); ^{13}C NMR (DMSO d_6) δ 14.9 (CH_2 cyclobutane), 24.1, 24.7, 25.8, 25.9 (CH_3), 30.0, 30.4 (CH_2 cyclobutane), 46.0, 51.6, 54.5 (C6, CH_2NH, CH_2NH_2), 55.3 [$\underline{C}(CH_2)_2$] , 64.0, 69.6, 70.2, 71.2 (C2, C3, C4, C5), 95.8 (C1), 108.1, 108.5 [$\underline{C}(CH_3)_2$], 177.1, 177.5 (C=O); ^{195}Pt NMR (DMSO d_6) δ -1975.

Anal. Calcd for $C_{20}H_{32}N_2O_9Pt$. 4 H_2O: C, 33.76; H, 5.67; N, 3.94; Found: C, 33.18; H, 5.61; N, 3.75.

10: $[\alpha]_D$ +40 (*c* 1, DMSO); IR (KBr) 3256 (NH), 1631 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.23, 1.36 (2s, 6H, 2 CH_3), 1.80 (m, 2H, CH_2 cyclobutane), 1.91 (m, 4H, 2 CH_2 cyclobutane), 2.61 (m, 6H, CH_2N), 3.31 (m, 3H, OCH_3), 4.5 (m, 3H, H2, H3, H4), 4.8 (m, 1H, H1), 5.24 (bs, 2H, NH_2), 6.93 (bs, 1H, NH).

Anal. Calcd for $C_{17}H_{28}N_2O_8Pt$: C, 34.99; H, 4.84; N, 4.80; found: C, 34.77; H, 4.91; N, 4.68.

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