J. Braz. Chem. Soc., Vol. 11, No. 2, 154-158, 2000.
Printed in Brazil

0103 - 5053 $6.00+0.00

Article

Synthesis of Platinum Complexes from N-Benzyl Ethylenediamine Derivatives

Mauro V. de Almeida[a,*], Eloi T. Cesar[b,c], Emanoel de C. A. Felício[a], Ana Paula S. Fontes[a] and Malka Robert-Gero[d]

[a]*Departamento de Química, Universidade Federal de Juiz de Fora, 36036-330, Juiz de Fora - MG, Brazil*

[b]*Colégio de Aplicação João XXIII, Universidade Federal de Juiz de Fora, 36036-330, Juiz de Fora - MG, Brazil*

[c]*Departamento de Química, Universidade Federal de Minas Gerais, 31270-901, Belo Horizonte - MG, Brazil*

[d]*ICSN - CNRS - 91190 - Gif/Yvette - France*

O ligante N-benziletilenodiamina e derivados foram preparados em bons rendimentos utilizando-se metodologia diferente da descrita na literatura. Espectros de RMN de ^{1}H e de ^{13}C foram empregados para a caracterização destes compostos. Nove novos complexos de platina(II) com estes ligantes, análogos da cisplatina e da carboplatina, foram preparados e caracterizados. Testes preliminares *in vitro* em linhagens celulares de carcinoma bucal humano (células KB) indicam que estes complexos são citotóxicos.

N-benzylethylenediamine derivatives have been prepared in good yields using methodology diferent than that described in the literature. ^{1}H and ^{13}C NMR spectra were used to characterize those compounds. Nine new platinum(II) complexes, analogs of cisplatin and carboplatin, containing these ligands have been prepared and characterized. Preliminary *in vitro* tests against buccal human carcinoma cell lines (KB cells) showed that the complexes are cytotoxic.

Keywords: platinum(II) complexes, N-benzylethylenediamine, anticancer agents, substitution reactions

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin)[1] is one of the most widely used and effective oncological agents against cancers of the testicles, ovaries, bladder, head and neck[2-4]. It is also an important adjunct for cancers of the lung, cervix and breast[2]. Its most spectacular success has been in the treatment of testicular cancer, a form of cancer previously resistant to any therapy, but now considered to be curable in most cases. However, its clinical usefulness has frequently been limited by severe side effects[5-7], such as nephrotoxicity, ototoxicity and neurotoxicity, and by the emergence of cancer cells resistant to cisplatin.

cis-Diammine(1,1-cyclobutanedicarboxylato) platinum(II) (carboplatin)[8-10] is the only clinically successful second-generation platinum complex, being less nephrotoxic and emetogenic than cisplatin. These properties have been attributed to the greater pharmacokinetic stability of its 1,1-cyclobutanedicarboxylate ligand in solution[11,12]. Nonetheless, carboplatin still has drawbacks. Like cisplatin, it only exhibits a relatively narrow spectrum of antitumor activity, and it is not effective in the treatment of cancer cells resistant to cisplatin.

In recent years, extensive efforts have been made to develop third-generation platinum complexes with a broader spectrum of activity, improved clinical effectiveness, lack of cross-resistance to cisplatin, and enhanced water solubility[13]. Since some substituted ethylenediamine platinum complexes have shown antitumor activity against a variety of cell tumors[14,15], and since aromatic compounds have shown the possibility of intercalation between DNA bases[16], we sought to synthesize several complexes containing N-benzylethylenediamine and derivatives as ligands, which are analogs of cisplatin and carboplatin.

Experimental

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 a Bruker Avance DRX 200 and DRX 400 spectrometers at the Federal University of Minas Gerais. Elemental analyses were done at the Microanalyses Laboratory at ICSN/CNRS, Gif/Yvette, France. The cytotoxicity studies were done at ICSN/CNRS, Gif/Yvette, France.

Reagents:

All chemicals were reagent grade and were used without further purification.

*Synthesis of ligands $PhCH_2NH(CH_2)_2NH_2$ **(a)**, $ClPhCH_2NH(CH_2)_2NH_2$ **(b)** and $CH_3OPhCH_2NH(CH_2)_2NH_2$ **(c)***

To ethylenediamine (6.7 mL, 100 mmol) in ethanol (30 mL), the corresponding benzyl chloride (20 mmols) was slowly added during 4 h. The reaction mixture was stirred for 24 h. at room temperature, after which time, it was evaporated under reduced pressure, and the residue purified on silica gel 60 G (0.2-0.5 mm), using dichloromethane/methanol 9/1 as eluent. Yields: 2.70 g, 90 % for compound **a**; 3.14 g, 85 % for compound **b** and 2.95 g, 82 % for compound **c**.

a: IR ν_{max} KBr (cm^{-1}): 3294, 3027, 2934, 2850, 1568, 1453, 1312, 740, 699; ^{1}H NMR (200 MHz DMSO-d_6) δ 2.19 (s, 3H, NH, NH_2), 2.45 (m, 2H, $C\underline{H}_2NH_2$), 2.60 (m, 2H, $C\underline{H}_2NH$), 3.68 (s, 2H, $C\underline{H}_2Ar$), 7.28 (m, 5H, Ar); ^{13}C NMR (50 MHz DMSO-d_6) δ 41.4, 51.9, 52.9 (CH_2), 126.4, 127.8, 128.0, 141.1 (Ar); MS (*m/z*, %): 151(100); 134(12); 120(16); 106(2); 91(20).

b: IR ν_{max} KBr (cm^{-1}): 3287, 2934, 2830, 1595, 1489, 1089, 1016, 803; ^{1}H NMR (200 MHz DMSO-d_6) δ 2.28 (s, 3H, NH, NH_2), 2.54 (m, 2H, $C\underline{H}_2NH_2$), 2.62 (m, 2H, $C\underline{H}_2NH$), 3.67 (s, 2H,$C\underline{H}_2Ar$), 7.35 (m, 4H, Ar); ^{13}C NMR (50 MHz DMSO-d_6) δ 41.4, 51.8, 52.0 (CH_2), 127.9, 129.6, 130.8, 140.2 (Ar); MS (*m/z*, %): 185(100); 168(6); 154(28); 140(3); 125(99).

c: IR ν_{max} KBr (cm^{-1}): 3290, 3001, 2936, 2837, 1613, 1513, 1461, 1245, 1178, 1036, 820; ^{1}H NMR (200 MHz DMSO-d_6) δ 2.30 (s, 3H, NH, NH_2), 2.50 (m, 2H, $C\underline{H}_2NH_2$), 2.60 (m, 2H,$C\underline{H}_2NH$), 3.63 (s, 2H, $C\underline{H}_2Ar$), 3.72 (s, 3H, OCH_3), 6.85 (d, 2H, H3, H3', $J_{3\text{-}2}$ 8.6Hz), 7.22 (d, 2H, H2, H2'); ^{13}C NMR (50 MHz DMSO-d_6) δ 51.7, 52.3, 54.9 (CH_2), 113.4, 129.4, 133.0, 157.9 (Ar); MS (*m/z*, %): 181(92); 163(3); 150(4); 136(4); 121(100).

*Synthesis of complexes $[PtCl_2(PhCH_2NH(CH_2)_2NH_2)]$ **(1)**, $[PtCl_2(ClPhCH_2NH(CH_2)_2NH_2)]$ **(2)** and $[PtCl_2(CH_3OPhCH_2NH(CH_2)_2NH_2)]$ **(3)***

To a solution of K_2PtCl_4 (0.415 g, 1 mmol) in water (10 mL), the appropriate ligand (1 mmol) was dissolved in water (5 mL), and added slowly with stirring. After 24 h in the dark at room temperature, the yellow solid that formed was filtered off, washed with water, and dried. Yields: 0.37 g, 90% for compound **1**; 0.36 g, 80 % for compound **2** and 0.35 g, 80% for compound **3**.

1: IR ν_{max} KBr (cm^{-1}): 3294, 3180, 3119, 3027, 2951, 2889, 2863, 1579, 1453, 1282, 1191, 1062, 1017, 760; ^{1}H NMR (400 MHz DMSO-d_6) δ 2.01, 2.22 (2 s, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 3.86, 4.20 (2 dd, 2H, CH_2Ar), 5.30 (2 s, 2H, NH_2), 6.60 (s, 1H, NH), 7.40 (m, 5H, Ar); ^{13}C NMR (100 MHz DMSO-d_6) δ 46.3, 54.3, 55.3 (CH_2), 127.9, 128.4, 130.0, 135.1 (Ar); ^{195}Pt NMR (DMSO-d_6) δ - 2357; Anal. Calcd. for $C_9H_{14}Cl_2N_2Pt$: C, 25.97; N, 6.73; H, 3.39; Cl, 17.04; found: C, 25.76; N, 6.91; H, 3.43; Cl, 16.94.

2: IR ν_{max} KBr (cm^{-1}): 3299, 3188, 3108, 2949, 2889, 1597, 1575, 1493, 1188, 1153, 1093, 1066, 1018, 840, 796, 753, 602, 496; ^{1}H NMR (400 MHz DMSO-d_6) δ 2.05, 2.21 (2 s, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 4.01 (dd, 2H, $C\underline{H}_2Ar$), 5.27 (2 s, 2H, $N\underline{H}_2$), 6.65 (s, 1H, NH); 7.37 (d,2H, H3, H3'), 7.57 (d, 2H, H2, H2', $J_{2\text{-}3}$ 7.6 Hz); ^{13}C NMR (100 MHz DMSO-d_6) δ 46.4, 54.1, 54.3 (CH_2), 128.3, 132.03, 132.7, 134.1 (Ar); ^{195} Pt NMR (DMSO-d_6) δ - 2361; Anal. Calcd. for $C_9H_{13}Cl_3N_2Pt$: C, 23.99; N, 6.22; H, 2.91; found: C, 24.21; N, 6.19; H, 2.97.

3: IR ν_{max} KBr (cm^{-1}): 3280, 3193, 3135, 2970, 2932, 2837, 1612, 1513, 1452, 1245, 1180, 1113, 1010, 835, 762, 629, 513; ^{1}H NMR (400 MHz DMSO-d_6) δ 1.88, 2.10 (2 s, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$); 3.70 (s, 3H, OCH_3), 3.90 (dd, 1H, H7'), 5.26, 5.34 (2 s, 2H, $N\underline{H}_2$), 6.53 (s, 1H, NH), 6.93 (d, 2H, H3, H3a, $J_{3\text{-}2}$= 8,0 Hz), 7.46 (d, 2H, H2, H2a); ^{13}C NMR (100 MHz DMSO-d_6) δ 46.1, 54.1, 54.5 (CH_2), 55.0 (OCH_3), 113.7, 127.0, 131.4, 158.9 (Ar); ^{195}Pt NMR (DMSO-d_6) δ -2359; Anal. Calcd. for $C_{10}H_{16}Cl_2N_2OPt$: C, 26.92; H, 3.61; N, 6.28; found: C, 27.25; H, 3.71; N, 6.25.

*Synthesis of compounds $[PtI_2(PhCH_2NH(CH_2)_2NH_2)]$ **(4)**, $[PtI_2(ClPhCH_2NH(CH_2)_2NH_2)]$ **(5)** and $[PtI_2(CH_3OPhCH_2NH(CH_2)_2NH_2)]$ **(6)***

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 min, 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 brown product was isolated by filtration and recrystalized from acetone/water. Yields: 0.50g, 83% for compound **4**; 0.62 g, 95% for compound **5** and 0.57 g, 91% for **6**.

4: IR ν_{max} KBr (cm^{-1}): 3253, 3180, 3025, 2945, 2923, 1567, 1455, 1148, 1057, 1112, 1007, 748, 702; ^{1}H NMR (400 MHz acetone-d_6) δ 2.70 (m, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 4.09 (dd, 1H, H7, $J_{7\text{-}7'}$ 13.8 Hz, $J_{7\text{-}NH}$ 10.3 Hz), 4.80 (s, 2H, NH_2), 4.90 (dd, 1H, H7', $J_{7'\text{-}NH}$ 2.3Hz), 5.50 (s, 1H, NH), 7.50 (m, 5H, Ar); ^{13}C NMR (100 MHz acetone-d_6) δ 48.3, 54.5, 57.0 (CH_2), 129.2, 129.6, 130.8, 131.0 (Ar); Anal. Calcd. for $C_9H_{14}I_2N_2Pt$: C, 18.04; H, 2.36; N, 4.68; found: C, 18.44; H, 2.37; N, 4.67.

5: IR ν_{max} KBr (cm^{-1}): 3250, 3189, 3145, 2950, 2885, 1599, 1567, 1494, 1447, 1141, 1090, 1066, 1009, 841, 796, 491; ^1H NMR (400 MHz DMSO-d_6) δ 2.50 (m, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 4.05 (dd, 1H, H7, $J_{7\text{-}7'}$ 13.2 Hz, $J_{7\text{-}NH}$ 9.2 Hz), 4.52 (dd, 1H, H7', $J_{7'\text{-}NH}$ 4.8Hz), 6.06 (s, 2H, NH_2), 7.04 (s, 1H, NH), 7.55 (m, 4H, Ar); ^{13}C NMR (100 MHz DMSO-d_6) δ 46.7, 53.9, 54.6 (CH_2), 128.6, 131.8, 132.0, 133.7 (Ar); ^{195}Pt NMR (DMSO-d_6) δ - 3313; Anal. Calcd. for $C_9H_{13}ClI_2N_2Pt.H_2O$: C, 16.57; N, 4.29; H, 2.30; found: C, 16.16; N, 3.98; H, 1.96.

6: IR ν_{max} KBr (cm^{-1}): 3238, 3185, 3000, 2951, 2827, 1609, 1512, 1458, 1254, 1176, 1030, 835, 804, 571; ^1H NMR (400 MHz DMSO-d_6) δ 2.50 (m, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 3.75 (s, 3H, OCH_3), 3.95 (d, 1H, H7, $J_{7\text{-}7'}$ 13.2 Hz), 4.50 (d, 1H, H7'), 6.01, 6.05 (2 s, 2H, NH_2), 6.27 (s, 1H, NH), 6.95 (d, 2H, H_3, $H_{3'}$, $J_{3\text{-}2}$ 8.4Hz), 7.42 (d, 2H, H_2, $H_{2'}$); ^{13}C NMR (100 MHz DMSO-d_6) δ 46.5, 53.6, 54.9 (CH_2), 55.1 (OCH_3), 113.9, 126.5, 131.2, 159.3 (Ar); ^{195} Pt NMR (DMSO-d_6) δ - 3313; Anal. Calcd. for $C_{10}H_{16}I_2N_2OPt$: C, 19.09; N, 4.45; H, 2.56; found: C, 19.52; N, 4.26; H, 2.57.

Synthesis of compounds [Pt(CBDCA)($PhCH_2NH(CH_2)_2NH_2$)].H_2O ***(7)****, [Pt(CBDCA)($ClPhCH_2NH(CH_2)_2NH_2$)].$2H_2O$* ***(8)*** *and [Pt(CBDCA)($CH_3OPhCH_2NH(CH_2)_2NH_2$)].$3H_2O$* ***(9)****, (CBDCA = 1,1-cyclobutanedicarboxylate)*

To a solution of 1 mmol of the appropriate iodide complex (compounds **4, 5** and **6**) 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: 0.16 g, 33 % for compound **7**; 0.17 g, 31 % for compound **8** and 0.18 g, 31 % for compound **9**.

7: IR ν_{max} KBr (cm^{-1}): 3204, 3170, 3105, 2991, 2954, 2883, 1652, 1364, 1115, 755, 708, 472; ^1H NMR (400 MHz CD_3OD) δ 1.69 (m, 2H, $C\underline{H}_2$ cyclobutane), 2.25 (m, 4H, 2 $C\underline{H}_2$ cyclobutane), 2.73 (m, 4H, $C\underline{H}_2NH$, $C\underline{H}_2NH_2$), 3.80 (dd, 1H, H7, $J_{7\text{-}7'}$ 10.8 Hz; $J_{7\text{-}NH}$ 8.4 Hz), 3.93 (dd, 1H, H7', $J_{7'\text{-}NH}$ 2.8 Hz), 5.47, 5.72 (2 s, 2H, NH_2), 6.81 (s, 1H, NH), 7.45 (m, 5H, Ar); ^{13}C NMR (100 MHz DMSO-d_6) δ15.0, 30.2, 30.3 (CH_2 cyclobutane), 45.8, 54.4, 55.3, 55.4 [CH_2N, $\underline{C}(CH_2)_2$], 128.1, 128.5, 130.1, 134.3 (Ar), 177.2, 177.4 (C=O); Anal. Calcd. for $C_{15}H_{20}N_2O_4Pt$. 1 H_2O: C, 35.65; H, 4.39; N, 5.54, found: C, 35.66; H, 4.48; N, 5.43.

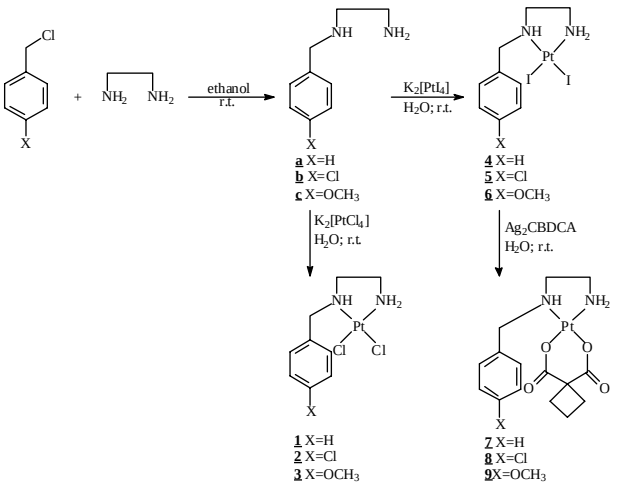
8: IR ν_{max} KBr (cm^{-1}): 3268, 3144, 3013, 2995, 1658, 1548, 1377, 1305, 1098; ^1H NMR (200 MHz DMSO-d_6) δ 1.67, 2.20 (2 m, 6H, $3CH_2$ cyclobutane), 2.70 (m, 4H, $C\underline{H}_2NH$, $C\underline{H}_2NH_2$), 3.83 (m, 2H, CH_2Ar), 5.44, 5.68 (2 s, 2H, NH_2), 6.85 (s, 1H, NH), 7.45 (d, 2H, H3, H3', $J_{3\text{-}2}$ 8.4 Hz), 7.60 (d, 2H, H2, H2'); ^{13}C NMR (50 MHz DMSO-d_6) δ 15.0, 30.0, 30,4 (CH_2 cyclobutane), 45.0, 54.2, 55.4 [CH_2N, $\underline{C}(CH_2)_2$], 128.4, 132.2, 133.0, 133.3 (Ar), 177.1, 177.3 (C=O); Anal. Calcd. for $C_{15}H_{19}ClN_2O_4Pt.2H_2O$: C, 32.26; N, 5.01; H, 4.12; found: C, 32.36; N, 4.51; H, 4.51.

9: IR ν_{max} KBr (cm^{-1}): 3252, 3109, 3001, 2946, 1651, 1612, 1515, 1253, 1181, 1115, 1025, 842, 469l; ^1H NMR (400 MHz DMSO-d_6) δ 1.64 (s, 2H, CH_2 cyclobutane), 2.15 (m, 4H, 2 CH_2 cyclobutane), 2.66 (m, 4H, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$), 3.70 (s, 3H, OCH_3), 3.75 (m, 2H, CH_2Ar), 5.40, 5.63 (2 s, 2H, $N\underline{H}_2$), 6.67 (s, 1H, NH), 6.87 (d, 2H, H3, H3', $J_{3\text{-}2}$ 8 Hz), 7.40 (d, 2H, H2, H2'); ^{13}C NMR (100 MHz DMSO-d_6) δ 15.0, 30.2, 30.3 (CH_2 cyclobutane), 45.8, 54.2, 54.7, 55.1, 55.4 [CH_2N, $\underline{C}(CH_2)_2$, OCH_3], 113.8, 126.2, 131.6, 159.1 (Ar), 177.3, 177.5 (C=O); ^{195}Pt NMR (DMSO-d_6) δ -1996; Anal. Calcd. for $C_{16}H_{22}N_2O_5Pt.3H_2O$: C, 33.62; N, 4.89; H, 4.93; found: C, 33.77; N, 4.92; H, 4.83.

Results and Discussion

The syntheses of ligands $PhCH_2NH(CH_2)_2NH_2$ **(a)**, $ClPhCH_2NH(CH_2)_2NH_2$ **(b)** and $CH_3OPhCH_2NH(CH_2)_2NH_2$ **(c)** are described in the literature[17-19] from the reactions of the corresponding benzaldehyde with ethylenediamine, followed by reduction of the resulting Schiff bases with formic acid. We found that these ligands can be prepared in satisfactory yields by treatment of ethylenediamine with the corresponding benzyl chloride in ethanol at room temperature for 24 h (Scheme 1). The IR spectra of all the ligands showed the characteristic absorptions at $\nu_{N\text{-}H}$ at 3294 cm^{-1}, $\nu_{C\text{-}H(aromatic)}$ at 3027 cm^{-1} and $\nu_{C\text{-}H(aliphatic)}$ at 2934 cm^{-1} for compound **a**, for instance. In addition to these absorptions, the IR spectrum of compound **b** showed $\nu_{Cl\text{-}C(aromatic)}$ at 1089 cm^{-1} and for compound **c** one can observe $\nu_{C\text{-}O\text{-}C}$ at 1036 cm^{-1}. These ligands were also characterized using ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum, signals were observed at δ 2.19, 2.45, 2.60, 3.68 and 7.28, corresponding to the NH, $C\underline{H}_2NH_2$, $C\underline{H}_2NH$, $C\underline{H}_2Ar$ and aromatic hydrogens. For compound **c**, a signal at δ 3.72 attributable to the OCH_3 was also observed. In the ^{13}C NMR spectrum, signals at δ 41.4, 51.9, 52.9 corresponding to the methylenic carbons and signals in the δ 113 to 160 region, due to the aromatic carbons were observed. For compound **c**, the OCH_3 was observed at δ 54.9. The mass spectra showed the following principal fragments. For compound **a**, *m/z*: 151 $(M+H)^+$; 134 ($ArNHCH_2CH_2$); 120 ($ArNHCH_2$); 106 ($ArCH_2NH$) and 91 ($ArCH_2$). For compound **b**, *m/z*: 185 $(M+H)^+$; 168 ($ClArNHCH_2CH_2$); 154 ($ClArCH_2NHCH_2$); 140 ($ClArCH_2NH$) and 125 ($ClArCH_2$).

For compound **c**, *m/z*: 181$(M+H)^+$; 163 ($OCH_3ArCH_2NCH_2CH_2$); 150 ($CH_3OArCH_2NHCH_2$); 136 (CH_3OArCH_2NH) and 121 (CH_3OArCH_2).



Scheme 1

The dichloro platinum(II) complexes [$PtCl_2(PhCH_2NH(CH_2)_2NH_2)$] **(1)**, [$PtCl_2(ClPhCH_2NH(CH_2)_2NH_2)$] **(2)** and [$PtCl_2(CH_3OPhCH_2NH(CH_2)_2NH_2)$] **(3)** were synthesized by reaction of the corresponding ligands with $K_2[PtCl_4]$ in water at room temperature for 12 h, and isolated by simple filtration. For these complexes, one can see in the IR spectra the absorptions corresponding to ν_{Pt-N} and ν_{Pt-Cl} at 495 and 322 cm^{-1}, respectively, in addition to the absorptions observed for the ligand. In the ^1H NMR spectra one observes that there is a marked downfield shift for the NH and NH_2 signals compared to those for the ligands. The ^{195}Pt NMR spectra showed only one signal at δ -2357, -2361 and -2359 for compounds **1**, **2** and **3**, respectively. These chemical shift values can be expected based on data for similar compounds described in the literature. For instance, the spectrum of [$Pt(DACH)Cl_2$] shows a signal at δ - 2287 (DACH= 1,2-diaminocyclohexane)[20].

Compounds **a**, **b** and **c** were reacted with an equimolar amount of potassium tetraiodoplatinate(II), generated *in situ*, to produce the diiodo platinum(II) complexes [$PtI_2(PhCH_2NH(CH_2)_2NH_2)$] **(4)**, [$PtI_2(ClPhCH_2NH(CH_2)_2NH_2)$] **(5)** and [$PtI_2(CH_3OPhCH_2NH(CH_2)_2NH_2)$] **(6)**. Besides the absorptions observed in the spectra of the ligands, the IR spectra of the iodide complexes showed one absorption due to ν_{Pt-N} at 491 cm^{-1}. The ^1H and ^{13}C NMR spectra are analogous to those of compounds **1, 2** and **3**. The ^{195}Pt NMR spectra of these complexes showed one signal at δ -3313, supporting the proposed structure. Compared to compounds **1**, **2** and **3**, the replacement of chloride by iodide causes an upfield shift of the signal in the ^{195}Pt NMR spectrum, as expected[21,22].

Reactions of **4**, **5** and **6** with an aqueous silver 1,1-cyclobutanedicarboxylate (Ag_2CBDCA) suspension afforded the corresponding carboplatin analogs [$Pt(CBDCA)(PhCH_2NH(CH_2)_2NH_2)$].$H_2O$ **(7)**, [$Pt(CBDCA)(ClPhCH_2NH(CH_2)_2NH_2)$].2 H_2O **(8)** and [$Pt(CBDCA)(CH_3OPhCH_2NH(CH_2)_2NH_2)$].3$H_2O$ **(9)**, (Scheme 1). The IR spectra showed absorptions at 3204 cm^{-1} (ν_{NH}), 3064 cm^{-1} ($\nu_{CH\ aromatic}$), 2954 cm^{-1} ($\nu_{CH\ aliphatic}$) and 1652 cm^{-1} ($\nu_{C=O}$), as well as the ν_{Pt-N} and ν_{Pt-O} at 472 cm^{-1} and 535 cm^{-1}, respectively. In the ^1H NMR spectrum, multiplets at δ 1.69 and 2.25 corresponding to the CH_2 groups of the cyclobutane ring were evident. The downfield shift of the NH and NH_2 signals was also evident, as mentioned previously for compounds **1**, **2** and **3**. In the ^{13}C NMR spectrum the signals corresponding to the CH_2 groups of the cyclobutane ring appear at δ 15.0, 30.2 and 30.3. The quaternary carbon exhibits a resonance at δ 55.4, and the carbonyl carbons at δ 177.2 and 177.4. The ^{195}Pt NMR spectra, as expected, showed only one signal at δ - 1996. Compared to compounds **1**, **2** and **3**, the coordination of the oxygen atoms in these complexes causes a downfield shift of the signal in the ^{195}Pt NMR spectra, as expected. For instance, the spectrum of [Pt(DACH)(ox)] shows a signal at δ - 1857 (DACH= 1,2-diaminocyclohexane and ox= oxalate anion)[23]. Figure 1 shows the ^{195}Pt NMR spectra of compounds **3**, **6** and **9**. One can see the upfield and downfield shifts of the signal when chloride **3** is replaced for iodide **6** or carboxylate **9**.

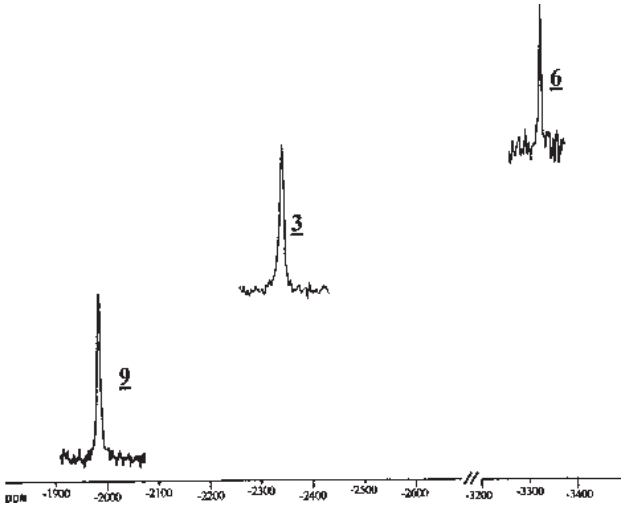


Figure 1. ^{195}Pt NMR spectra of complexes **3**, **6** and **9**.

The results of elemental analysis for all the complexes prepared are in agreement with the calculated values.

Preliminary cytotoxicity tests for complexes **1**, **2** and **3** were undertaken to verify their potencial as anticancer agents. A standard test using buccal human carcinoma cell

lines (KB cells)[24,25] was performed *in vitro* along with cisplatin, as the reference drug, using a colorimetric method. These compounds are not cytotoxic at 1 and 10mg mL^{-1} concentrations. Complexes **1** and **2** show 30% and 65% cytotoxicity, respectively, at a concentration of 50mg mL^{-1}.

Conclusion

This work describes the synthesis and characterization of three N-benzylethylenediamine analogs used as ligands for the preparation of nine new platinum(II) complexes. These complexes were fully characterized and have potential for acting as cytotoxic agents, which was demonstrated by a preliminary test done using KB cells. Further investigation of the biological properties of the new compounds is desirable to determine their possible utility as anticancer agents.

Acknowledgments

E. T. C. gratefully acknowledges CAPES (Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) for a fellowship. The authors are grateful to Dr. Richard Grazul for his review of this paper.

References

1. Rosenberg, B.; VanCamp, L.; Trosko, J. F.; Mansour, V. H. *Nature* (London) **1969**, *222*, 385.
2. Krakoff, I. H. *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy: Clinical Aplications of Platinum Complexes*; Nicoline, M., ED.; Martinus Nijhoff Publishing: Boston, MA, **1988**, p. 351.
3. Loehrer, P. J., Williams, S. D.; Einhorn, L. H. *J. Natl. Cancer Inst.* **1988**, *80*, 1373.
4. Loehrer, P. J.; Einhorn, L. H. *Ann. Intern. Med.* **1984**, *100*, 704.
5. Krakoff, I. H. *Cancer Treat. Resp.* **1979**, *63*, 1623.
6. Vermorken, J. B.; Pinedos, H. M. *Neth. J. Med.* **1982**, *25*, 270.
7. Vonhoff, D. D.; Schilky, R.; Reichert, C. M. *Cancer Treat. Resp.* **1979**, *63*, 1527.
8. Calvert, A. H.; Harland, S. J.; Newell, D. R.; Siddik, Z. H.; Jones, A. C.; McElwain, T. J.; Raju, S.; Wiltshaw, E.; Smith, I. E.; Baker, J. M.; Peckham, M. J.; Harrap, K. R. *Cancer Chemother. Pharmaco.* **1982**, *9*, 140.
9. Harland, S. J.; Smith, I. E.; Smith, N.; Alison, D. L. *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds; Martinus Nihoff Publishing: Boston, MA, **1984**, 352.
10. Egorin, M. J.; Van Echo, D. A.; Olman, E. A.; Whitacre, M. Y.; Forrest, A. Aisner *J. Cancer Res.* **1985**, *45*, 6502.
11. Harland, S. J.; Newell, D. R.; Siddik, Z. H.; Chadwick, R.; Calvert, A. H.; Harrap, K. R. *Cancer Res.* **1984**, *44*, 1693.
12. Mauldin, S. K.; Husain, I.; Sancar, A.; Chaney, S. G. *Cancer Res.* **1986**, *46*, 2876.
13. Fontes, A. P. S.; Almeida, S. G.; Nader, L. A . *Quím. Nova*, **1997**, *20*, 398.
14. Beaumont, K. P.; McAuliffe, C. A.; Cleare, M. J. *Chem. Biol. Interact.* **1976**, *14*, 179.
15. Paul, A. K.; Srivastava, T. S.; Chavan, S. J.; Chitnis, M. P.; Desai, S.; Rao, K. K. *J. Inorg. Biochem.* 1**996**, *61*, 179.
16. Farrell, N. P. *Transition Metal Complexes as Drugs and Chemotherapeutic Agents;* Kluwer Academic Publishers; Dordrecht, **1989,** p. 18.
17. Eckstein, Z.; Lukasiewicz, A. *Bull. Acad. Polon. Sci. Sér. Sci. Chim. Géol. Et Géograph*. **1959**, *7*, 789.
18. Eckstein, Z.; Lukasiewicz, A. *Bull. Acad. Polon. Sci. Sér. Sci. Chim. Géol. Et Géograph.* **1959**, *7*, 797.
19. Bonet, D.; Funke, A. *Compt. Rend. Soc. Biol.* **1947**, *141*, 325.
20. Vollano, J. F.; Al-Baker, S.; Dabrowiak, J. C.; Schurig, J. E. *J. Med. Chem.* **1987,** *30*, 716.
21. Pesek, J.; Mason, W. R. *J. Magn. Reser.* **1977**, *25*, 519.
22. Pregosin, P. S. *Coord. Chem. Rev.* **1982,** *44*, 247.
23. Hoeschele, J. D.; Farrell, N.; Turner, W. R.; Rithner, C. D. *Inorg. Chem.* **1988**, *27*, 4106.
24. Sachinvala, N. D.; Chen, H.; Niemezura, W. P.; Furusawa, E.; Cramer, R. E.; Rupp, J. J.; Ganjian, I. *J. Med. Chem.* **1993**, *36*, 1791.
25. Ichikawa, M.; Yoshimura, A.; Furukawa, T.; Sumizawa, T.; Nakazima, Y.; Akiyama, S. I. *Biochim. Biophys. Acta* **1991**, *1073(2)*, 309.

Received: May 31, 1999