Hydrocarbon-bridged Metal Complexes, LIII [1]. Trinuclear (*cis*-Dichloro-ethylenediamine) Platinum(II) Complexes from Amides of Tricarboxylic Acids and 1,2,4-Triaminobutane

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Dedicated to Professor Helmut Werner on the occation of his 75th birthday

The coupling of the tricarboxylic acids, 1,3,5-benzene-tricarboxylic acid, *cis*,*cis*-1,3,5-cyclohexane-tricarboxylic acid and of citric acid, with *rac*-N^1,N^2-di-Boc-1,2,4-triaminobutane affords the corresponding triamides which were deprotected. From the novel tris(bidendate) ligands with three terminal ethylenediamine donors the tris(*cis*-dichloro platinum) complexes were obtained.

Key words: Tris(dichloroplatinum) Complexes, Tricarboxylic Acid, Tris(ethylenediamine) Ligands, 1,2,4-Triaminobutane, Platinum(II)

Introduction

At present, multinuclear platinum complexes find much interest as "non-classical" platinum antitumor compounds with a high potential of activity which may overcome cisplatin resistance [2, 3]. Among others, Farrell and coworkers [2] are pioneers in the field and have – besides a series of bis(platinum) complexes – designed and synthesized also tris(platinum) complexes with polyamine linkers [4] of which the highly potent compound $[(H_3N)_2(Cl)PtNH_2(CH_2)_6NH_2Pt(NH_3)_2NH_2(CH_2)_6NH_2Pt(Cl)(NH_3)_2]^{4+}$ (BBR 3464) was particularly well studied [5, 6]. Its mechanism of action to DNA differs from that of cisplatin [2, 6]. Other early examples of antitumor active tris(platinum) complexes were obtained by Navarro-Ranninger [7a] from spermidine ($H_2N(CH_2)_3NH(CH_2)_4NH_2$), *e. g.* $[(Cl_2Pt)_3(spermidine)_2]$ and by Mandal [7b] from thiopyridyltriazine. Several other trinuclear platinum complexes with various bridging ligands and with cytotoxic properties have been reported [8].

In our group, the coupling of α,ω dicarboxylic acids $HO_2C(CH_2)_nCO_2H$ [9], pyrrole-dicarboxylic acids [10], pyridine-2,6-dicarboxylic acid, phenylene-1,4-diacetic acid, terephtalic acid dichloride, and benzene-1,2,4,5-tetracarboxylic acid [1] with the selectively protected N^1,N^2-di-Boc-1,2,4-triaminobutane [9, 11 – 13] has led to the corresponding amides from which after removal of the Boc groups novel ligands with two terminal ethylenediamine donor units could be obtained. Dinuclear bis(dichloroplatinum) complexes were synthesized from these bis(bidendate) ligands. The interaction of the complexes $[Cl_2Pt(NH_2CH_2CH(NH_2)(CH_2)_2NHC(O)(CH_2)_nC(O)NH(CH_2)_2CH(NH_2)CH_2NH_2)PtCl_2]$ with DNA was studied [14].

In continuation of these studies we report in the following the coupling of various tricarboxylic acids with the useful reagent 1,2,4-triaminobutane [9, 11] to give tris(bidendate) ligands for the synthesis of trinuclear metal complexes.

Results and Discussion

Exemplarily, tricarboxylic acids with an aromatic, an alicyclic and an open aliphatic backbone have been chosen.

1,3,5-Benzene-tricarboxylic acid trichloride, *cis,cis*-1,3,5-cyclohexane-tricarboxylic acid and citric acid were coupled with N^1,N^2-di-Boc-1,2,4-triaminobutane and afforded the corresponding triamides **1** – **3**. Deprotection with a solution of hydrogen chloride in acetic ethyl ester yielded the free ligands **4** – **6** as hydrochlorides from which, using K_2PtCl_4, the tris(*cis*-dichloroplatinum) complexes **7** – **9** were obtained (Scheme 1).

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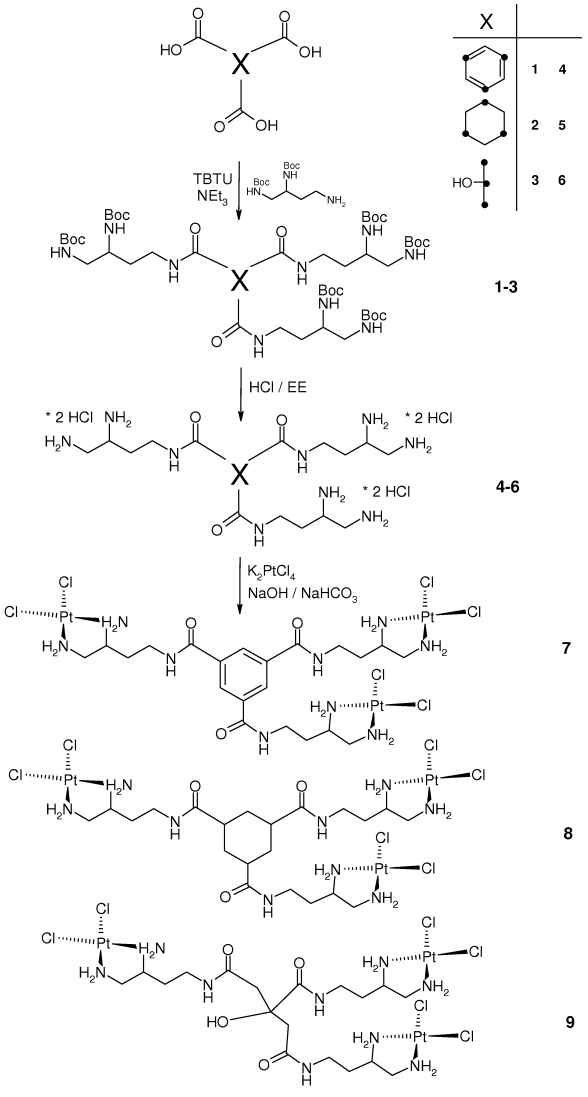

Scheme 1.

The high symmetry of the compounds **1** – **9** renders the NMR spectra easy to survey. The ^{1}H and ^{13}C signals correspond to those of comparable compounds [9, 11]. The exchange of the chloro ligands by DMSO in [D$_6$]DMSO of **9** – **12** can also be observed [9 – 11] after a few hours. In the IR spectra of the complexes **9** – **12** characteristic absorptions appear at 320 cm^{-1} (Pt–Cl), 565 cm^{-1} (Pt–N), 1660 cm^{-1} (amide), and 1530, 3200 cm^{-1} (N–H).

The evaluation of the cytotoxic properties of **9** – **12** was hindered by the low solubility in water. Attempts to dilute solutions of **9** – **12** in DMSO by water resulted in the partial precipitation of the complexes [15].

Experimental Section

rac-4-Amino-1,2-di(*tert*-butoxycarbonylamino)butane was synthesized from trifluor-acetylhistidine [9, 11]. *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and the tricarboxylic acids were purchased.

General method for the preparation of ***1*** *–* ***3***

To a solution of the tricarboxylic acid (1 equiv.) in acetonitrile (5 mL) *rac*-4-amino-1,2-di(*tert*-butoxycarbonylamino)butane (2 equiv.), NEt$_3$ (4 equiv.) and TBTU (2 equiv.) were added at 0 °C. After 2 h, the mixture was warmed to r. t. and stirred for 12 h (DC control: SiO$_2$, CHCl$_3$ / MeOH, 10 : 1 v/v, blue fluorescence). The mixture was heated under reflux for 1 h, stirred for 30 min and concentrated *in vacuo*. The residue was dissolved in EtOAc, and the solution was shaken with 1.1 M aqueous KHSO$_4$ (3×), saturated aqueous NaHCO$_3$ (3×) and saturated aqueous NaCl (1×). The organic phase was dried with MgSO$_4$, and the solvent was removed *in vacuo*. The brown products were purified by chromatography [SiO$_2$, Merck Kieselgel 60 (0.063 – 0.200 mm), CHCl$_3$ / MeOH 10 : 1 v/v] and recrystallized from EtOAc / *n*-hexane to give **1** – **3** as colorless compounds.

Compound ***1***: From 1,3,5-benzenetricarboxylic acid (trimesic acid) (250 mg, 1.2 mmol), 1,2-di-Boc-amino-4-aminobutane (1.20 g, 3.96 mmol), NEt$_3$ (1.17 mL, 0.85 g, 8.4 mmol) and TBTU (1.3 g, 4.06 mmol). – Yield 815 mg (63%). – M. p. > 60 °C (dec.). – IR (KBr): ν = 3348 (s, ν NH), 3070 (w), 2976 (s), 2932 (s), 2882 (sh), 1695 (s, br, COO), 1668 (s, CON), 1597 (w), 1524 (s, δ NH), 1480 (sh), 1455 (m), 1441 (sh), 1392 (s), 1367 (s), 1280 (s), 1251 (s), 1172 (s), 1065 (m), 1035 (sh), 999 (w), 905 (w), 866 (w, ρ NH), 781 (w), 745 (w), 708 (w), 687 (w), 642 (w), 463 (w), 351 (sh), 330 (w) cm^{-1}. – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.40 (s, 3 H, CH), 8.25 (s, 3 H, N4-H), 6.28 (m, 3 H, N2-H), 6.22 (m, 3 H, N1-H), 3.77 (s, 3 H, C4-H), 3.63 (s, 3 H, C4-H), 3.36 (m, 3 H, C2-H), 3.22 (s, 6 H, C1-H), 1.88 (m, 3 H, C3-H), 1.73 (m, 3 H, C3-H), 1.39 (s, 54 H, CH$_3$). – ^{13}C NMR (101 MHz, [D$_6$]acetone): δ = 165.90 (3 C, CON), 156.59 (2 C, COO), 156.43 (COO), 135.51 (3 C, qC), 128.47 (3 C, CH), 78.28 (3 C, qC), 78.12 (3 C, qC), 49.54 (3 C, C2), 44.37 (3 C, C1), 37.04 (3 C, C4), 32.31 (3 C, C3), 28.00 (18 C, CH$_3$). – EI MS (710 °C): *m/z* (%) = 1066 (< 1) [M$^+$], 663, 648, 531, 99, 59, 57. – C$_{51}$H$_{87}$N$_9$O$_{15}$ (1066.29): calcd. C 56.49, H 8.27, N 11.62; found C 56.63, H 8.32, N 11.49.

Compound ***2***: From *cis,cis*-1,3,5-cyclohexane-tricarboxylic acid (338 mg, 1.56 mmol), 1,2-di(*tert*-butoxycarbonylamino)-4-aminobutane (1.58 g, 5.21 mmol), NEt$_3$ (2.2 mL, 15.6 mmol) and TBTU (2.01 g, 6.25 mmol). – Yield 510 mg (31 %). – M. p. > 65 °C (dec.). – IR (KBr): ν = 3344 (s, br, ν

NH), 3071 (m), 2977 (s), 2933 (s), 2875 (sh), 1692 (s, COO), 1663 (sh, CON), 1650 (s), 1527 (s, br, δ NH), 1480 (sh), 1455 (s), 1393 (s), 1367 (s), 1267 (sh), 1253 (s), 1172 (s), 1065 (m), 1041 (sh), 1003 (m), 942 (w), 921 (w), 901 (w), 865 (m, ρ NH), 780 (m), 760 (m), 649 (m, br), 464 (w), 435 (w), 332 (w) cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.77 (s, 3 H, N4-H), 6.72 (t, 6 H, N2-H, ^3J = 5.1 Hz), 6.56 (d, 6 H, N1-H, ^3J = 8.8 Hz), 3.43 (s, 3 H, C2-H), 3.04 (s, 3 H, C1-H), 2.89 (m, 9 H, C1-H, C4-H), 2.08 (t, 3 H, CH, ^3J = 11.7 Hz), 1.66 (m, 3 H, C3-H), 1.51 (m, 3 H, C3-H), 1.36 (s, 54 H, CH_3), 1.15 (m, 6 H, CH_2). – ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 174.51 (3 C, CON), 156.32 (2 C, COO), 155.98 (COO), 78.11 (6 C, qC), 48.92 (3 C, C2), 44.47 (3 C, C1), 43.48 (3 C, CH), 36.46 (3 C, C4), 32.44 (3 C, C3), 32.01 (3 C, CH_2), 28.82 (18 C, CH_3). – $C_{51}H_{93}N_9O_{15} \cdot 1/2\ H_2O$ (1081.31): calcd. C 56.65, H 8.76, N 11.65; found C 56.59, H 8.74, N 11.75.

Compound ***3***: From citric acid (298 mg, 1.55 mmol), 1,2-di(*tert*-butoxycarbonylamino)-4-aminobutane (1.49 g, 4.90 mmol), NEt_3 (1.30 mL, 9.31 mmol) and TBTU (1.20 g, 3.72 mmol). – Yield 835 mg (51 %). – M. p. > 60 °C (dec.). – IR (KBr): ν = 3344 (s, ν NH), 3086 (w), 3002 (sh), 2977 (s), 2933 (m), 2886 (sh), 1701 (s, COO), 1664 (s, CON), 1526 (s, CON), 1479 (w), 1454 (m), 1440 (sh), 1392 (s), 1367 (s), 1324 (w), 1272 (m), 1251 (s), 1173 (s), 1065 (m), 998 (w), 913 (w), 901 (w), 868 (m, ρ NH), 783 (m), 759 (w), 638 (w), 580 (w), 662 (w), 462 (w), 435 (w), 356 (w), 332 (w) cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]acetone): = 7.79 (s, NH), 7.59 (br, 2 H, NH), 6.57 – 6.55 (m, NH), 6.25 (br, NH), 6.14 (br, 2 H, NH), 5.99 (br, 2 H, NH), 3.69 – 3.33 (m, 6 H, C2-H, C1-H), 3.16 (m, 3 H, C1-H), 2.66 – 2.53 (m, 6 H, C4-H), 1.95 (s, 2 H, CH_2), 1.86 (s, 2 H, CH_2), 1.72 (m, 6 H, C3-H), 1.40 (s, 54 H, CH_3). – ^{13}C NMR (101 MHz, [D$_6$]acetone): δ = 165.17 (3 C, CON), 156.49 (2 C, COO), 156.24 (4 C, COO), 78.05 (6 C, qC, COH), 49.23 (2 C, C2), 44.38 (3 C, C1), 38.02 (2 C, CH_2), 36.08 (3 C, C4), 32.28 (3 C, C3), 27.96 (18 C, CH_3). – $C_{48}H_{89}N_9O_{10}$ (1048.29): calcd. C 55.00, H 8.56, N 12.03; found C 54.46, H 8.72, N 12.32.

General method for the synthesis of the hydrochlorides ***4 – 6***

To a solution of **1 – 3** in EtOAc (3 mL), EtOAc saturated with HCl (10 mL), was added. Gas evolution occurred, and after 2 h a colorless precipitate was formed which was washed with EtOAc (3×) and dry Et_2O (1×) and dried *in vacuo*.

Compound ***4***: From **1** (400 mg, 375 μmol). – Yield 249 mg (94 %). – IR (KBr): ν = 3385 (s, ν NH), 3281 (s, ν NH), 2949 (s), 2004 (w), 1651 (s, CO), 1598 (s), 1540 (s, δ NH), 1502 (s), 1452 (m), 1375 (w), 1330 (m), 1296 (s), 1274 (sh), 1205 (w), 1159 (m), 1052 (m), 975 (w), 914 (w), 835 (w, ρ NH), 814 (w), 781 (w), 735 (w), 705 (w), 684 (w), 599 (w), 475 (w), 454 (w) cm^{-1}. – ^1H NMR (400 MHz, D_2O): δ = 8.36 (s, 3 H, CH), 3.76 (s, 3 H, C2-H), 3.63 (s, 6 H, C4-H), 3.43 (s, 6 H, C1-H), 2.11 (m, 6 H, C3-H). – ^{13}C NMR (101 MHz, D_2O): δ = 169.42 (3 C, CON), 134.55 (3 C, qC), 129.63 (3 C, CH), 47.53 (3 C, C2), 41.07 (3 C, C1), 35.85 (3 C, C4), 30.46 (3 C, C3). – $C_{21}H_{45}Cl_6N_9O_3 \cdot 3\ H_2O$ (738.36): calcd. C 34.16, H 6.96, N 17.06; found C 34.29, H 7.34, N 17.05.

Compound ***5***: From **2** (215 mg, 203 μmol). – Yield 125 mg (95 %). – IR (KBr): ν = 3429 (s, br, ν NH), 3290 (sh), 2945 (s), 2059 (w), 2001 (w), 1638 (s, CON), 1546 (s, δ NH), 1462 (m), 1450 (m), 1384 (m), 1311 (m), 1266 (m), 1204 (s), 1185 (sh), 1158 (m), 1143 (m), 1055 (m, br), 983 (w), 834 (w), 799 (w), 723 (w), 667 (w), 597 (w), 533 (w), 519 (w), 474 (w), 450 (w), 422 (w), 382 (w) cm^{-1}. – ^1H NMR (400 MHz, D_2O): δ = 3.65 (s, 3 H, C2-H), 3.41 (s, 12 H, C1-H, C4-H), 2.09 (m, 9 H, CH, C3-H), 1.53 (m, 3 H, CH_2), 1.27 – 1.18 (m, 3 H, CH_2). – ^{13}C NMR (101 MHz, D_2O): δ = 178.52 (3 C, CON), 47.42 (3 C, C2), 42.91 (3 C, C1), 41.14 (3 C, CH), 35.13 (3 C, C4), 31.17 (3 C, C3), 30.50 (3 C, CH_2). – $C_{21}H_{51}Cl_6N_9O_3 \cdot H_2O$ (708.36): calcd. C 35.61, H 7.54, N 17.79; found C 35.83, H 7.34, N 18.20.

Compound ***6***: From **3** (260 mg, 248 μmol). – Yield 152 mg (92 %). – IR (KBr): ν = 3341 (sh, ν NH), 3229 (sh), 2949 (br), 2669 (sh), 2578 (sh), 2008 (w), 1777 (w), 1741 (m), 1703 (m), 1646 (s, CON), 1539 (s, CON), 1501 (sh), 1448 (m), 1407 (m), 1396 (m), 1375 (m), 1340 (sh), 1245 (m), 1204 (w), 1158 (m), 1047 (m), 980 (w), 945 (w), 915 (w), 892 (w), 845 (w), 813 (w), 766 (w), 742 (w), 693 (w), 634 (w), 605 (w), 587 (w), 476 (w), 455 (w), 426 (w) cm^{-1}. – ^1H NMR (400 MHz, D_2O): δ = 8.42 – 8.17 (m, 3 H, N4-H), 3.79 – 3.63 (m, 3 H, C2-H), 3.46 – 3.36 (m, 7 H, C1-H), 2.87 – 3.19 (m, 6 H, C4-H), 2.72 (2 H, CH_2), 2.68 (2 H, CH_2), 2.21 – 1.91 (m, 6 H, C3-H). – ^{13}C NMR (101 MHz, D_2O): δ = 176.40 (3 C, CON), 72.86 (COH), 47.21 (3 C, C2), 41.00 (3 C, C1), 38.45 (3 C, C4), 35.14 (3 C, C3), 30.22 (2 C, CH_2). – $C_{18}H_{47}Cl_6N_9O_4 \cdot 2\ H_2O$ (702.34): calcd. C 31.78, H 7.31, N 17.94; found C 31.14, H 7.67, N 17.00.

General method for the synthesis of the platinum complexes ***7 – 9***

To a solution of **4 – 6** in water (2 mL), the stochiometric amount of K_2PtCl_4 (dissolved in a very small amount of water) was added, and the solution was heated to 65 °C. After cooling, about 90 % of the hydrochloride was neutralized with 1 M NaOH, and finally the resulting solution was adjusted to pH = 5.5 with 1 M $NaHCO_3$ under potentiometric control. During the neutralization the products were obtained as pale-beige precipitates which were centrifuged off, washed with ice cold water (3×) and ice cold EtOH (1×) and dried *in vacuo*.

Compound ***7***: From **4** (150 mg, 219 μmol), K_2PtCl_4 (273 mg, 658 μmol) and 1 M NaOH (1.32 mL, 1.32 mmol). – Yield 191 mg (69 %). – M. p. > 200 °C (dec.). – IR (KBr):

ν = 3462 (s), 3357 (s), 3201 (s), 3116 (s, ν NH), 2944 (s), 2387 (w), 1648 (s, CO), 1591 (s, δ NH), 1534 (s), 1448 (m), 1374 (w), 1323 (sh), 1289 (s), 1188 (m), 1132 (m), 1090 (m), 1026 (w), 1002 (w), 911 (w), 778 (w), 741 (w), 708 (w), 681 (w), 569 (w, Pt-N), 469 (w), 439 (w), 321 (m, Pt-Cl) cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.12 (s, 3 H, CH), 8.62 (m, 3 H, NH), 6.43 (m, 6 H, NH), 6.19 (m, 6 H, NH), 3.40 (s, 3 H, C2-H), 3.00 (s, 6 H, C4-H), 2.73 (m, br, 6 H, C1-H), 1.92 (m, 6 H, C3-H). – ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 166.00 (2 C, CON), 165.94 (CON), 135.05 (3 C, qC), 129.17 (3 C, CH), 57.92 (3 C, C2), 51.66 (3 C, C1), 42.97 (3 C, C4), 30.72 (3 C, C3). – $C_{21}H_{39}Cl_6N_9O_3Pt_3 \cdot H_2O$ (1281.61): calcd. C 19.68, H 3.22, N 9.53; found C 19.33, H 3.21, N 9.68.

Compound ***8***: From **5** (50 mg, 72 μmol), K_2PtCl_4 (90 mg, 217 μmol) and 0.1 M NaOH (4.43 mL, 434 μmol). – Yield 58 mg (63 %). – IR (KBr): ν = 3441 (s, br, NH), 3207 (s, NH), 3111 (s), 2945 (m), 2873 (w), 2365 (s), 1642 (s, CO), 1592 (m), 1539 (s), 1455 (sh), 1446 (m), 1384 (w), 1308 (w), 1308 (m), 1263 (m), 1206 (m), 1139 (w), 1099 (w), 1033 (w), 799 (w), 787 (w), 602 (m), 563 (m, Pt-N), 466 (w), 436 (w), 319 (s, Pt-Cl) cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.14 (br, N4-H), 6.45 – 5.35 (m, N1-H, N2-H), 3.08 (s, C4-H), 2.83 (s, C2-H), 2.73 – 2.55 (s, C1-H), 2.08 (m, CH), 1.88 – 1.38 (m, CH_2, C3-H). – $C_{21}H_{45}Cl_6N_9O_3Pt_3 \cdot H_2O$ (1287.55): calcd. C 19.59, H 3.68, N 9.78; found C 19.81, H 4.01, N 9.76.

Compound ***9***: From **6** (109 mg, 164 μmol), K_2PtCl_4 (204 mg, 491 μmol) and 1 M NaOH (838 μL, 838 μmol). – Yield 112 mg (55 %). – IR (KBr): ν = 3414 (br, OH), 3367 (br, ν NH), 3204 (s, ν NH), 3118 (m), 2945 (m), 2371 (w), 1780 (w), 1700 (sh), 1646 (s, CON), 1582 (m), 1535 (s, δ NH), 1439 (m), 1399 (w), 1371 (w), 1308 (w), 1228 (w), 1216 (w), 1188 (m), 1147 (w), 1094 (m), 1030 (w), 1000 (w), 895 (w), 865 (m), 798 (w), 654 (w), 596 (w), 567 (m, Pt-N), 467 (w), 441 (w), 320 (m, Pt-Cl) cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.40 (m, 3 H, N4-H), 6.30 (m, 4 H, NH), 5.92 (m, 4 H, NH), 5.62 (m, 4 H, NH), 3.11 – 2.92 (m, 3 H, C2-H), 2.67 (m, 6 H, C1-H), 2.40 (m, 6 H, C4-H), 1.66 (m, 10 H, CH_2, C3-H). – $C_{18}H_{41}Cl_6N_9O_4Pt_3 \cdot 2\ H_2O$ (1281.48): calcd. C 16.87, H 3.53, N 9.83; found C 16.99, H 3.52, N 9.65.

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[1] Part 52: B. Miller, J. Altman, W. Beck, *Z. Naturforsch.* **2009**, *64b*, 153.

[2] N. P. Farrell, S. G. De Almeida, K. A. Skov, *J. Am. Chem. Soc.* **1988**, *110*, 5018; E. I. Montero, B. T. Benedetti, J. P. Mangrum, M. J. Oehlsen, Y. Qu, N. P. Farrell, *Dalton Trans.* **2007**, 4938, and refs. therein; N. F. Farrell, in *Metal Ions in Biological Systems*, Vol. 41, *Metal Ions and Their Complexes in Medication* (Eds.: A. Sigel, H. Sigel) Marcel Dekker, New York, NY: **2004**, p. 252; Q. Liu, Y. Qu, R. Van Antwerpen, N. Farrell, *Biochem.* **2006**, *45*, 4248, and refs. therein; Y. Qu, A. Harris, A. Hegmans, A. Petz, P. Kabolizadeh, H. Penazova, N. Farrell, *J. Inorg. Biochem.* **2004**, *98*, 1581; N. F. Farrell in *Platinum Based Drugs in Cancer Therapy* (Eds.: L. R. Kelland, N. Farrell), Humana Press, Totowa, NJ, **2000**, p. 321; N. Farrell, Y. Qu, U. Bierbach, M. Valsecchi, E. Menta, in *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug* (Ed.: B. Lippert), VHCA, Zürich, Wiley-VCH, Weinheim, **1999**, p. 479; N. Farrell, *Cancer investigation* **1993**, *11*, 578; S. Komeda, M. Lutz, A. L. Spek, M. Chikuma, J. Reedijk, *Inorg. Chem.* **2000**, *39*, 4230; G. V. Kalayda, S. Fakih, H. Bertram, T. Ludwig, H. Oberleithner, B. Krebs, J. Reedijk, *J. Inorg. Biochem.* **2006**, *100*, 1332; S. Fakih, W. C. Tung, D. Eierhoff, C. Mock, B. Krebs, *Z. Anorg. Allg. Chem.* **2005**, *631*, 1397, and refs. therein.

[3] Reviews: E. Wong, C. M. Giandominico, *Chem. Rev.* **1999**, *99*, 2451; N. J. Wheate, J. G. Collins, *Coord. Chem. Rev.* **2003**, *241*, 133; M. A. Fuertes, J. Castilla, P. A. Nguewa, C. Alonso, J. M. Perez, *Med. Chem. Rev.* **2004**, *I*, 187; A. S. Abu-Surrah, *Rev. Med. Chem.* **2007**, *7*, 203.

[4] Y. Qu, T. G. Appleton, J. D. Hoeschele, N. Farrell, *Inorg. Chem.* **1993**, *32*, 2591.

[5] M. S. Davies, D. S. Thomas, A. Hegmans, S. J. Berners-Price, N. Farrell, *Inorg. Chem.* **2002**, *41*, 1101, and refs. therein.

[6] C. Manzotti, G. Pratesi, E. Menta, R. Di Domenico, E. Cavalletti, H. B. Fiebig, L. R. Kelland, N. Farrell, D. Polizzi, R. Supino, G. Pezzoni, F. Zunino, *Clinical Cancer Research* **2000**, *6*, 2626; J. Kasparkova, J. Zehnulova, N. Farrell, V. Brabec, *J. Biol. Chem.* **2002**, 48076; M. E. Oehlsen, Y. Qu, N. Farrell, *Inorg. Chem.* **2003**, *42*, 5498, and refs. therein; A. Hegmans, S. J. Berners-Price, M. S. Davies, D. S. Thomas, A. S. Humphreys, N. Farrell, *J. Am. Chem. Soc.* **2004**, *126*, 2166; A. L. Harris, J. J. Ryan, N. Farrell, *Mol. Pharmacol.* **2006**, *69*, 666.

[7] a) C. Navarro-Ranninger, P. A. Ochoa, J. M. Pérez, V. M. González, J. R. Masaguer, C. Alonso, *J. Inorg. Biochem.* **1994**, *53*, 177; b) S. Ray, F. R. Smith, J. N. Bridson, Q. Hong, V. J. Richardson, S. K. Mandal, *Inorg. Chim. Acta* **1994**, *227*, 175.

[8] M. R. C. Couri, M. V. de Almeida, A. P. S. Fontes, J. D'Arc S. Chaves, E. T. Cesar, R. J. Alves, E. C. Pereira-Maia, A. Garnier-Suillerot, *Eur. J. Inorg. Chem.* **2006**, 1868, and refs. therein; Y. Zhao, W. He, P. Shi, J. Zhu, L. Qiu, L. Lin, Z. Guo, *Dalton Trans*. **2006**, 2617; S. Rubino, P. Portanova, A. Albanese, G. Calvaruso, S. Orecchio, G. Fontana, G. C. Stocco, *J. Inorg. Biochem*. **2007**, *101*, 1473; S. L. Woodhouse, L. M. Rendina, *Dalton Trans*. **2004**, 3669.

[9] E. Schuhmann, J. Altman, K. Karaghiosoff, W. Beck, *Inorg. Chem*. **1995**, *34*, 2316.

[10] B. Miller, A. Terpin, W. Steglich, W. Beck, *Z. Naturforsch*. **2009**, *64b*, 159.

[11] J. Altman, E. Schuhmann, K. Karaghiosoff, E. Eichin-Karaghiosoff, W. Beck, *Z. Naturforsch*. **1991**, *46b*, 1473.

[12] J. Altman, W. Beck, *Tetrahedron* **1995**, *48*, 13309; J. Altman, D. Ben-Ishai, W. Beck, *Tetrahedron: Assymmetry* **1994**, *5*, 887.

[13] Recently another method for the synthesis of N^1,N^2-di-Boc-1,2,4-triaminobuane (in optically pure form) starting from L-glutamic acid has been reported: A. P. Treder, A. Walkowiak, W. Zgoda, R. Andruszkiewicz, *Synthesis* **2005**, 2281.

[14] H. Büning, J. Altman, H. Zorbas, W. Beck, *J. Inorg. Biochem*. **1999**, *75*, 269; H. Büning, J. Altman, W. Beck, H. Zorbas, *Biochemistry* **1997**, *36*, 11408; H. Büning, J. Altman, W. Beck, H. Zorbas, *Bioinorganic Chemistry, Transition Metals in Biology and their Coordination Chemistry* (Ed.: A. X. Trautwein), Deutsche Forschungsgemeinschaft, Research Report, Wiley-VCH, Weinheim, **1997**, p. 167.

[15] H. Zorbas, S. Wild, LMU München, private communication.