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Synthesis and characterization of dinuclear pyrazolato bridged platinum(IV) complexes

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Abstract

Reactions of $[PtMe_3(OCMe_2)_3](BF_4)$ and $[(PtMe_3I)_4]$ with pyrazole (pzH) afforded mononuclear pyrazole platinum(IV) complexes $[PtMe_3(pzH)_3](BF_4)$ (**1**) and $[PtMe_3I(pzH)_2]$ (**2**), respectively. The formation of dinuclear pyrazolato bridged platinum(IV) complexes $(PPN)[(PtMe_3)_2(\mu\text{-}pz)_3]$ (**3**), $(PPN)[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]\cdot 1/2Et_2O$ (**4**) and $[K(18C6)][(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]$ (**5**) was achieved by the reaction of each **1** and **2** with $[PtMe_3(OCMe_2)_3](BF_4)$ in the presence of KOAc followed by reaction with (PPN)Cl (PPN^+ = bis(triphenylphosphine)iminium cation) and 18C6, respectively. The reaction of complex **4** with AgO_2CCF_3 followed by addition of RSR′ (R/R′ = Me/Me, Me/Ph) resulted in the formation of complexes $[(PtMe_3)_2(\mu\text{-}pz)_2(\mu\text{-}RSR')]$ (R/R′ = Me/Me, **6**; Me/Ph, **7**). All complexes were characterized unambiguously by microanalysis and NMR (^1H, ^{13}C) spectroscopic investigations. Additionally, crystal structures of complexes **3** and **4** as well as DFT calculation are presented. Furthermore, in vitro studies on the anti-proliferative activity of complexes **2** and **5** were carried out.

Keywords: Platinum complexes; Dinuclear complexes; Pyrazole ligands; Pyrazolato ligands; Crystal structures; DFT calculations; Antitumoral activity

1. Introduction

The synthesis of oligonuclear metal complexes may proceed in a self organizing process when the formation of the desired complex is thermodynamically favoured and the bond formation occurs reversibly [1,2]. An alternative way is a controlled synthesis in a stepwise reaction via structurally preformed mononuclear precursor complexes. In general, one of the coordination sites of the precursor complexes has to be protected either by classical protecting groups or by protons, inhibiting uncontrolled oligomerization at the beginning of the reaction. Pyrazole (pzH) is a ligand that can be monodentately coordinated to a metal (pzH-κ*N*) or can act after deprotonation as a bridging pyrazolato ligand (μ-pz-1κ*N*:2κ*N*′) [3–7].

The synthesis of oligonuclear platinum(IV) complexes is a challenging field in coordination chemistry. Their formation by ligand substitution reactions is often hampered due to the kinetic inertness of the low-spin d^6 electron configuration of Pt(IV). The tris(acetone) complex $[PtMe_3(OCMe_2)_3](BF_4)$ [8] was found to readily undergo ligand substitution reactions as acetone is a weakly bound ligand which has, additionally, a methyl ligand in the *trans* position exerting a large *trans* effect.

Mononuclear complexes of neutral pyrazole ligands (pzH-κ*N*) [9,10] as well as dinuclear complexes containing pyrazolato ligands (μ-pz-1κ*N*:2κ*N*′) [9,10] are well known in platinum(II) chemistry. In contrast to this no homonuclear complexes of Pt(IV) with bridging pyrazolato ligands have been reported in the literature to date. Here we

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describe the syntheses and characterization of dinuclear platinum(IV) complexes with bridging pyrazolato ligands starting from tris(acetone) complex $[PtMe_3(OCMe_2)_3]^+$ and the pyrazole complexes $[PtMe_3(pzH)_3]^+$ and $[PtMe_3I(pzH)_2]$, respectively, as precursor complexes. Due to the advantages of platinum(IV) complexes can have over platinum(II) complexes in chemotherapy, these complexes were investigated with respect to their antitumoral activity.

2. Experimental

2.1. General considerations

Syntheses of complexes were carried out under argon using standard Schlenk techniques whereas the work-up procedures were performed on air. Methylene chloride, acetone, *n*-pentane, benzene and diethyl ether were dried (CH_2Cl_2 over CaH_2, Me_2CO over molecular sieve 3A, *n*-pentane, benzene and Et_2O over Na-benzophenone) and distilled prior to use. $[(PtMe_3I)_4]$ and $[PtMe_3(OCMe_2)_3](BF_4)$ were obtained according to the literature [11,8]. Microanalyses (C, H, N, S) were performed by the microanalytical laboratory of the University of Halle using CHNS-932 (LECO) and Vario EL (elementar Analysensysteme) elemental analyzers. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200, VXR 400 and Unity 500 NMR spectrometers. Solvent signals and residual protons of solvent signals were used as internal standard.

2.1.1. Preparation of $[PtMe_3(pzH)_3](BF_4)$ (**1**)

A solution of $[PtMe_3(OCMe_2)_3](BF_4)$ (100 mg, 0.200 mmol) in acetone (10 ml) was added to a solution of pyrazole (40.9 mg, 0.600 mmol) in acetone (10 ml). The solution was evaporated to dryness under vacuum and the residue was extracted with CH_2Cl_2 (10 ml). The colourless product, which was precipitated within 12 h after adding of *n*-pentane (10 ml), was washed with *n*-pentane/CH_2Cl_2 (1:1, 3 × 2 ml) and dried under vacuum. Yield 96 mg, 90%.

Anal. Calc. for $C_{12}H_{21}BF_4N_6Pt$: C, 27.13; H, 3.98; N, 15.82. Found: C, 27.07; H, 4.85; N, 15.77%. ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 1.12 (s + d, $^2J_{Pt,H} = 70.1$ Hz, 9H, PtCH_3), 6.56 (m, 3H, *H*4), 7.70 (m, 3H, *H*5), 8.00 (m, 3H, *H*3), 12.35 (br, 3H, N*H*). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ −7.7 (s + d, $^1J_{Pt,C} = 695.8$ Hz, Pt*C*H_3), 107.4 (s + d, $^3J_{Pt,C} = 8.6$ Hz, *C*4), 132.9 (s + d, $^2J_{Pt,C} = 5.3$ Hz, *C*5), 140.4 (s + d, $^3J_{Pt,C} = 8.4$ Hz, *C*3).

2.1.2. Preparation of $[PtMe_3I(pzH)_2]$ (**2**)

A solution of pyrazole (37.7 mg, 0.554 mmol) in acetone (5 ml) was added to a suspension of $[(PtMe_3I)_4]$ (100 mg, 69.2 μmol) in acetone (10 ml). After dissolving the solid (4 h) the solution was evaporated to dryness under vacuum and the solid was extracted with CH_2Cl_2 (10 ml). The product was precipitated within 12 h on addition of *n*-pentane (10 ml) and filtered off. The solid was washed with *n*-pentane/CH_2Cl_2 (1/1, 3 × 2 ml) and dried under vacuum. Yield 41 mg, 90%.

Anal. Calc. for $C_9H_{17}IN_4Pt$: C, 21.48; H, 3.40; N, 11.13. Found: C, 22.00; H, 3.49; N, 11.14%. ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 1.29 (s + d, $^2J_{Pt,H} = 72.9$ Hz, 6H, PtCH_3 *trans* to pzH), 1.33 (s + d, $^2J_{Pt,H} = 71.6$ Hz, 3H, PtCH_3 *trans* to I), 6.43 (m, 2H, *H*4), 7.74 (m, 2H, *H*5), 7.88 (m, 2H, *H*3), 12.09 (br, 2H, N*H*); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ −10.5 (s + d, $^1J_{Pt,C} = 682.3$ Hz, Pt*C*H_3 *trans* to pzH), 8.4 (s + d, $^1J_{Pt,C} = 715.9$ Hz, Pt*C*H_3 *trans* to I), 106.4 (s + d, $^3J_{Pt,C} = 8.6$ Hz, *C*4), 131.1 (s + d, $^2J_{Pt,C} = 5.3$ Hz, *C*3), 138.5 (s + d, $^3J_{Pt,C} = 11.5$ Hz, *C*5).

2.1.3. Preparation of $(PPN)[(PtMe_3)_2(\mu\text{-}pz)_3]$ (**3**)

KOAc (118 mg, 1.20 mmol) was added to a solution of $[PtMe_3(OCMe_2)_3](BF_4)$ (100 mg, 0.200 mmol) in acetone (10 ml). A solution of $[PtMe_3(pzH)_3](BF_4)$ (**1**) (106 mg, 0.200 mmol) in acetone (10 ml) was added dropwise to this suspension. After 30 min the suspension was filtered and the filtrate evaporated to dryness under vacuum. The solid was extracted with CH_2Cl_2 (10 ml) and the extract was added to a solution of (PPN)Cl (115 mg, 0.200 mmol) in CH_2Cl_2 (10 ml). After evaporation to 10 ml the KCl was filtered off and the product was precipitated within 12 h by adding of Et_2O (10 ml). The resulting solid was filtered off, washed with *n*-pentane/CH_2Cl_2 (1/1, 3 × 2 ml) and dried under vacuum. Yield 146 mg, 60%.

Anal. Calc. for $C_{51}H_{57}N_7P_2Pt_2$: C, 50.20; H, 4.71; N, 8.04. Found: C, 49.67; H, 5.01; N, 7.77%. ^1H NMR (200 MHz, $(CD_3)_2CO$): δ 0.85 (s + d, $^2J_{Pt,H} = 66.2$ Hz, 18H, PtCH_3), 6.00 (m, 3H, *H*4), 7.31 (m, 6H, *H*3/*H*5), 7.50–7.77 (m, 30H, PPN^+); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ −6.7 (s + d, $^1J_{Pt,C} = 675.2$ Hz, Pt*C*H_3), 103.9 (s + d + t, $^3J_{Pt,C} = 15.4$ Hz, *C*4), 127.9/130.2/132.7/134.3 (PPN^+), 134.8 (s + d + d + d · d, $^{2/4}J_{Pt,C} = 25.9/10.6$ Hz, *C*3/*C*5).

2.1.4. Preparation of $(PPN)[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2] \cdot 1/2Et_2O$ (**4**)

The reaction was carried out according to the above procedure. Instead of $[PtMe_3(pzH)_3](BF_4)$ (**1**), $[PtMe_3I(pzH)_2]$ (**2**) (101 mg, 0.200 mmol) was used. Yield 163 mg, 60%.

Anal. Calc. for $C_{100}H_{118}I_2N_{10}OP_4Pt_4$: C, 45.60; H, 4.52; N, 5.32. Found: C, 45.89; H, 4.59; N, 5.75%. ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 1.08 (s + d, $^2J_{Pt,H} = 67.6$ Hz, 12H, PtCH_3 *trans* to pz), 1.10 (t, $^3J_{H,H} = 7.0$ Hz, 3H, OCH_2CH_3), 1.31 (s + d, $^2J_{Pt,H} = 75.7$ Hz, 6H, PtCH_3 *trans* to I), 3.39 (q, $^3J_{H,H} = 7.0$ Hz, 2H, OCH_2CH_3), 5.96 (m, 2H, *H*4), 7.27 (m, 4H, *H*3/*H*5), 7.50–7.77 (m, 30H, PPN); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ −11.1 (s + d, $^1J_{Pt,C} = 646.3$ Hz, Pt*C*H_3 *trans* to pz), 7.6 (s + d, $^1J_{Pt,C} = 740.4$ Hz, Pt*C*H_3 *trans* to I), 14.9 (s, OCH_2CH_3), 104.7 (s + d, $^3J_{Pt,C} = 13.6$ Hz, *C*4), 129.1/131.2/134.1/135.4 (PPN^+), 135.8 (s + d + d + d · d, $^{2/4}J_{Pt,C} = 28.2/11.8$ Hz, *C*3/*C*5).

2.1.5. Preparation of [K(18C6)][(PtMe$_3$)$_2$(μ-I)(μ-pz)$_2$] (5)

The reaction was carried out analogously to **4**, but instead of working with a solution of (PPN)Cl in CH_2Cl_2, a solution of 18C6 (52.9 mg, 0.200 mmol) in CH_2Cl_2 (10 ml) was used. Yield 105 mg, 50%.

Anal. Calc for $C_{24}H_{48}IKN_4O_6Pt_2$: C, 27.59; H, 4.63; N, 5.36. Found: C, 27.74; H, 5.08; N, 5.34%. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 1.08 (s + d, $^2J_{Pt,H} = 67.6$ Hz, 12H, PtC*H*$_3$ *trans* to pz), 1.31 (s + d, $^2J_{Pt,H} = 75.7$ Hz, 6H, PtC*H*$_3$ *trans* to I), 3.65 (s, 24H, C*H*$_2$O), 5.96 (m, 2H, *H*4), 7.27 (m, 4H, *H*3/*H*5).

2.1.6. Preparation of [(PtMe$_3$)$_2$(μ-pz)$_2$(μ-Me$_2$S)] (6)

AgO_2CCF_3 (15.5 mg, 70 μmol) was added to a solution of (PPN)[(PtMe$_3$)$_2$(μ-I)(μ-pz)$_2$] · 1/2Et$_2$O (**4**) (92.2 mg, 70 μmol) in acetone (10 ml). After complete precipitation of AgI (12 h) the reaction mixture was filtered. Me_2S (4.9 mg, 78 μmol) was added to the solution and the reaction mixture was evaporated to dryness under vacuum. The residue was extracted in benzene (10 ml) and washed with H_2O (10 ml). The combined organic phases were dried (Na_2SO_4) and concentrated to 5 ml. Then the product was precipitated by adding of *n*-pentane (10 ml), filtered of, washed with *n*-pentane (3 × 2 ml) and dried under vacuum. Yield 28.4 mg, 60%.

Anal. Calc. for $C_{14}H_{30}N_4Pt_2S$: C, 24.85; H, 4.47; N, 8.28; S, 4.74. Found: C, 25.37; H, 4.76; N, 8.38; S, 4.40%. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 0.76 (s + d, $^2J_{Pt,H} = 66.8$ Hz, 12H, PtC*H*$_3$ *trans* to pz), 1.40 (s + d, $^2J_{Pt,H} = 73.0$ Hz, 6H, PtC*H*$_3$ *trans* to S), 2.38 (s + d + t, $^3J_{Pt,H} = 8.7$ Hz, 6H, S(C*H*$_3$)$_2$), 6.18 (m, 2H, *H4*), 7.39 (m, 4H, *H3*/*H5*); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ −9.8 (s + d, $^1J_{Pt,C} = 642.1$ Hz, Pt*C*H$_3$ *trans* to pz), 5.2 (s + d, $^1J_{Pt,C} = 694.9$ Hz, Pt*C*H$_3$ *trans* to S), 15.2 (s, S*C*H$_3$, pz), 105.5 (s + d + t, $^3J_{Pt,C} = 14.9$ Hz, *C*4) 136.3 (s + d + d + d · d, $^{2/4}J_{Pt,C} = 27.7/10.3$ Hz, *C*3/*C*5).

2.1.7. Preparation of [(PtMe$_3$)$_2$(μ-pz)$_2$(μ-MeSPh)] (7)

The reaction was carried out according to the above procedure. Instead of Me_2S, MeSPh (9.7 mg, 78 μmol) was used. Yield 31.0 mg, 60%.

Anal. Calc. for $C_{19}H_{32}N_4Pt_2S$: C, 30.89; H, 4.37; N, 7.58; S, 4.34. Found: C, 31.42; H, 4.56; N, 7.65; S, 4.31%. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 0.43 (s + d, $^2J_{Pt,H} = 66.0$, 6H, PtC*H*$_3$ *trans* to pz), 0.74 (s + d, $^2J_{Pt,H} = 66.0$ Hz, 6H, PtC*H*′$_3$ *trans* to pz), 1.50 (s + d, $^2J_{Pt,H} = 74.7$ Hz, 6H, PtC*H*$_3$ *trans* to S), 2.69 (s + d + t, $^3J_{Pt,H} = 7.9$ Hz, 3H, SC*H*$_3$), 6.26 (m, 1H, pz *H*4′), 6.32 (m, 1H, pz *H*4), 6.66 (m, 2H, Ph *o*-*H*), 7.40 (m, 3H, *m*/*p*-*H*), 7.47 (m, 2H, pz *H*3′/*H*5′), 7.51 (m, 2H, pz *H*3/*H*5). ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ −9.0 (s + d, $^1J_{Pt,C} = 643.9$ Hz, Pt*C*H′$_3$ *trans* to pz), −7.1 (s + d, $^1J_{Pt,C} = 642.0$ Hz, Pt*C*H$_3$ *trans* to pz), 5.3 (s + d, $^1J_{Pt,C} = 704.4$ Hz, Pt*C*H$_3$ *trans* to S), 13.0 (s, S*C*H$_3$), 105.9 (s + d + t, $^3J_{Pt,C} = 14.9$ Hz, pz *C*4′), 106.3 (s + d + t, $^3J_{Pt,C} = 14.9$ Hz, pz *C*4), 122.5/128.4/130.0/130.4 (s, SPh), 136.7 (s + d + d + d · d, $^{2/4}J_{Pt,C} = 10.5/28.4$ Hz, pz *C*3/C3′/C5/C5′), 136.7 (s + d + d + d · d, $^{2/4}J_{Pt,C} = 9.8/24.1$ Hz, pz *C*3/C3′/C5/C5′).

Table 1
Crystal data and structure refinement data for **3** and **4**

	3	**4**
Empirical formula	$C_{51}H_{57}N_7P_2Pt_2$	$C_{50}H_{54}IN_5O_{0.5}P_2Pt_2$
Formula weight	1220.16	1312.00
Crystal system	monoclinic	triclinic
Space group	$P2_1/n$	$P\bar{1}$
a (Å)	17.041(3)	9.830(2)
b (Å)	11.555(2)	15.281(4)
c (Å)	25.675(5)	17.948(4)
α (Å)	90	78.22(3)
β (Å)	105.92(2)	74.32(3)
γ (Å)	90	78.77(3)
V (Å^3)	4862(2)	2513(1)
Z	4	2
D_{calc} (g/cm^3)	1.667	1.734
μ (mm^{-1})	5.856	6.277
F(000)	2392	1264
Independent reflections	9482	9068
Number of observed reflections [$I > 2\sigma(I)$]	6787	7690
Data/restraints/parameters	9482/0/722	9068/0/554
Goodness-of-fit	0.924	1.056
R_1 [$I > 2\sigma(I)$], R_1 (all data)	0.0364, 0.0621	0.0549, 0.0645
wR_2 [$I > 2\sigma(I)$], wR_2 (all data)	0.0723, 0.0790	0.1456, 0.1554

2.2. X-ray crystallography

Single-crystal X-ray diffraction analyses of suitable crystals of complexes **3** and **4** were performed at 220(2) K on a STOE-IPDS diffractometer using Mo Kα radiation (λ = 0.71073 Å, graphite monochromator). A summary of the crystallographic data, the data collection parameters and the refinement parameters is given in Table 1. Absorption correction for **3** was applied numerically ($T_{min}/T_{max} = 0.49/0.60$). The structures were solved by direct methods with SHELXS-97 [12]. The structure refinements were carried out by full-matrix least-square procedures against F^2 (SHELXL-97 [12]) for all reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were refined isotropically. In complex **3** all H atoms except those of the methyl ligands were found in the difference Fourier map. The H atoms of the methyl ligands and those of complex **4** were added to the models in their calculated positions using the "riding model". The thermal ellipsoids of the C atoms of the ether molecule in **4** point to a disorder, but refinement in split positions did not succeed.

2.3. Computational details

DFT calculations of compounds **3c**,[1] **4c**, **8c**, **8c′**, pz$^-$ and I$^-$ were carried out by the GAUSSIAN 03 program package [13] using the modified Perdew–Wang 1991 exchange functional

[1] The index "c" denotes calculated equilibrium structures.

by Adamo and Barone [14] plus the Perdew–Wang 1991 correlation functional [15] (MPWPW91). The 6-311G(d,p) [16] basis set as implemented in GAUSSIAN 03 was employed for C, H and N atoms, while the relativistic pseudopotentials of the Ahlrichs group and related basis functions of TZVPP quality [17] were employed for Pt and I atoms. All systems were fully optimized without any symmetry restrictions. The resulting geometries were characterized as equilibrium structures by the analysis of the force constants of normal vibrations. The interaction energies were corrected for basis set superposition errors (BSSE), that were estimated with counterpoise type calculations [18].

2.4. In vitro studies

Stock solutions of investigated platinum complexes and reference compound cisplatin were made in dimethyl sulfoxide (DMSO) at a concentration of 20 mM and diluted by nutrient medium to various working concentrations. Nutrient medium was RPMI-1640 (PAA Laboratories) supplemented with 10% fetal bovine serum (Biochrom AG) and penicillin/streptomycin (PAA Laboratories).

2.4.1. Cell cultures

The human tumor cell lines anaplastic thyroid cancer 8505C, head and neck tumors A253 and FaDu, cervical cancer A431, lung carcinoma A549, ovarian cancer A2780, colon carcinoma DLD-1, HCT-8 and HT-29 were cultivated in the Biocentrum, Martin Luther University Halle-Wittenberg. All cells were maintained as monolayers in nutrient medium in a humidified atmosphere with 5% CO_2.

2.4.2. Cytotoxicity assay

The cytotoxic activity of the platinum compounds was measured by the sulforhodamine-B (SRB) assay [19]. In brief, exponentially growing cells were seeded into 96-well plates and 24 h later, after the cell adherence, nine different concentrations of investigated compounds were added to the wells. The final concentrations were in the range from 0.1 to 100 μM. All experiments were done in triplicate. Nutrient medium with corresponding concentrations of compounds, but void of cells was used as blank. Five days after seeding the cells were fixed with 10% trichloroacetic acid and processed according to the published SRB assay protocol. Absorbance was measured at 570 nm using a 96-well plate reader (SpectraFluor Plus Tecan, Germany) and the percentages of surviving cells relative to untreated controls were determined. The concentration IC_{50}, was defined as the concentration of a drug that inhibited cell survival by 50%, compared with vehicle-treated control.

3. Results and discussion

3.1. Syntheses

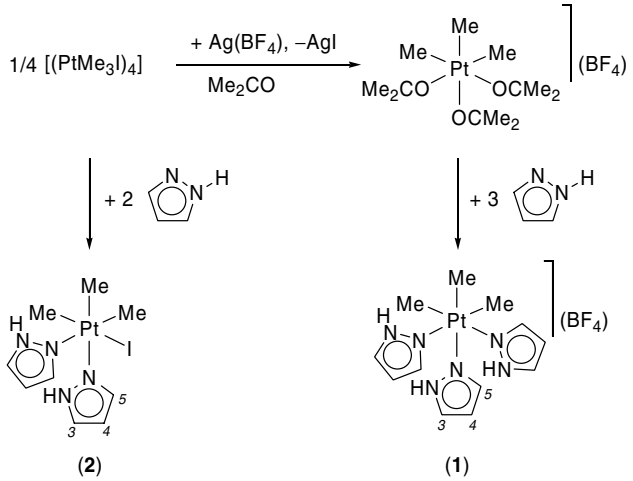
The complex $[PtMe_3(OCMe_2)_3](BF_4)$, obtained by the reaction of $[(PtMe_3I)_4]$ with $Ag(BF_4)$ in acetone [8], was found to react rapidly in acetone with three equivalents of pyrazole yielding the cationic tris(pyrazole) complex **1** (Scheme 1). Furthermore, the tetranuclear platinum complex $[(PtMe_3I)_4]$ was also found to react with pyrazole yielding the neutral bis(pyrazole) complex **2**, but this reaction took one day at room temperature (Scheme 1). Both mononuclear complexes were isolated as airstable colourless (**1**) and pale yellow (**2**) crystals in high yields (ca. 90%). The constitution of both complexes was determined unambiguously by microanalysis and NMR spectroscopy (^1H, ^{13}C).

Deprotonation of the coordinated pyrazole ligand in **1** and **2** afforded μ-pyrazolato complexes. Thus, complexes **1** and **2** reacted with $[PtMe_3(OCMe_2)_3](BF_4)$ in the presence of KOAc yielding dinuclear tris(μ-pyrazolato) and (μ-iodo)bis(μ-pyrazolato) complexes, respectively (Scheme 2). To yield crystalline complexes, the primarily obtained potassium salts were converted in a methatetical reaction to the PPN salts **3** and **4**, respectively. Addition of the crown ether 18C6 to the potassium salt of the (μ-iodo)-bis(μ-pyrazolato) complex resulted in the formation of the [K(18C6)] salt **5**. The colourless, airstable complexes (**3**, **4**, **5**) were obtained in moderate yields (ca. 50–60%) and characterized by microanalysis, NMR spectroscopy (^1H, ^{13}C) and single-crystal X-ray diffraction analyses.

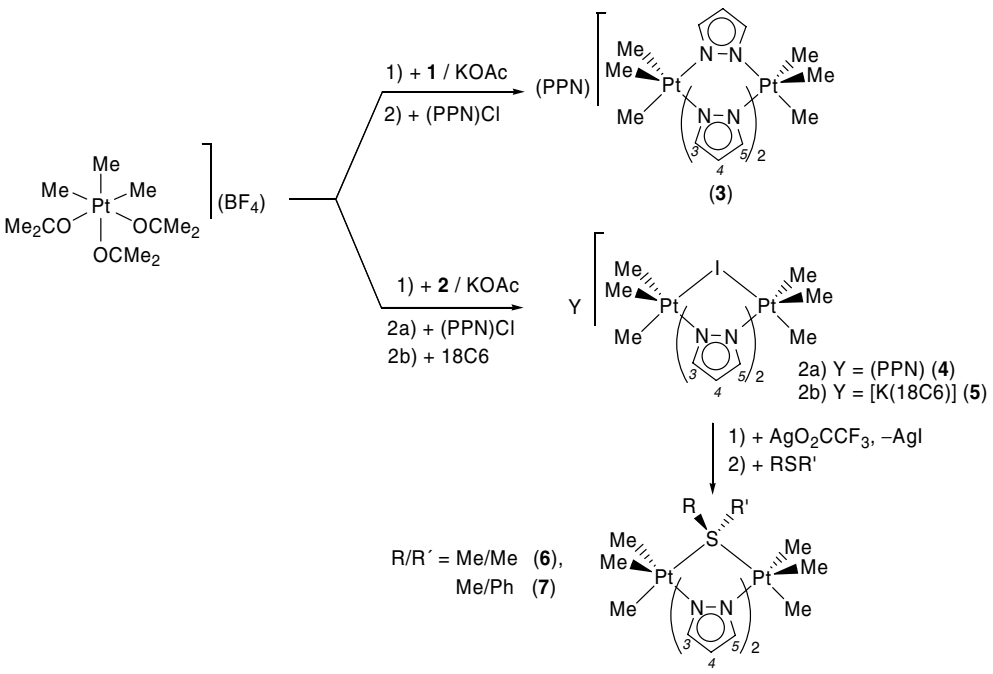
Substitution of the μ-iodo ligand in complex **4** could be achieved by reaction with silver trifluoroacetate followed by addition of thioethers (Scheme 2). Thus, the thioether bridged complexes **6** and **7** were obtained as colourless, airstable crystals in moderate yields (ca. 60%). Their identities have been confirmed by microanalysis and NMR spectroscopy (^1H, ^{13}C).

3.2. Spectral properties

^1H and ^{13}C NMR spectra gave proof that complexes **1** and **2** exhibit (mean) C_{3v} and C_s symmetry, respectively. Thus, in complex **1** all three pyrazole and methyl ligands are chemically equivalent. In complex **2** the two pyrazole



Scheme 1.



Scheme 2.

ligands were found to be equivalent, whereas two different methyl signals were observed. ^{1}H and ^{13}C NMR spectroscopic measurements established the identities of complexes **3**–**7**. In all these complexes the chemical equivalence $\delta(C^3) = \delta(C^5)$ and $\delta(H^3) = \delta(H^5)$[2] indicated a mirror plane perpendicular to the pyrazolato ligands. Furthermore, in accordance with a (mean) D_{3h} symmetry, the anion in **3** showed six and three chemically equivalent methyl and pyrazolato ligands, respectively. In accordance with a (mean) C_{2v} symmetry, in complexes **4**, **5** and **6** two equivalent pyrazolato ligands and two groups of chemically inequivalent methyl ligands (*trans* to pz^- and *trans* to I^-/Me_2S) were observed. On the other hand, in complex **7** (mean C_s symmetry) two inequivalent pyrazolato ligands and three inequivalent methyl ligands were found.

In *fac*-trimethylplatinum(IV) complexes the $^{1}J_{Pt,C}$ and $^{2}J_{Pt,H}$ coupling constants are indicative of the *trans* influence of ligands *trans* to the methyl ligands [20]. The values for dinuclear complexes **3**, **4**, **6** and **7** are given in Table 2. On the basis of the $^{1}J_{Pt,C}$ coupling constants the expected sequence of the *trans* influence was found: 642.0–675.2 Hz (pz^- in **3**–**7**) >694.9 Hz (Me_2S in **6**) ≈ 704.4 Hz (MeSPh in **7**) >740.4 Hz (I^- in **4**). The unusually low *trans* influence of the pyrazolato ligand in complex **3** compared with that in complexes **4**–**7** (675.2 Hz versus 642.0–646.3 Hz) might be reasoned to be due to a different angle strain in the tris- and bis(μ-pyrazolato) complexes as well as a different *cis* influence of the pz^- ligand compared to I^-/MeSR ligands. Principally, the same order of the *trans* influence can be derived from the $^{2}J_{Pt,H}$ coupling constants

Table 2
Selected coupling constants (in Hz) of complexes (PPN)[$(PtMe_3)_2$(μ-pz)$_2$(μ-X)] (**3**, **4**) and [$(PtMe_3)_2$(μ-pz)$_2$(μ-L)] (**6**, **7**)

Compound	X/ L = ligand	$^{1}J_{Pt,C}$ (*trans* N)	$^{1}J_{Pt,C}$ (*trans* X/L)	$^{2}J_{Pt,H}$ (*trans* N)	$^{2}J_{Pt,H}$ (*trans* X/L)
3	$X = pz^-$	675.2		66.2	
4	$X = I^-$	646.3	740.4	67.6	75.7
6	$L = Me_2S$	642.1	694.9	66.8	73.0
7	L = MeSPh	643.9/642.0	704.4	66.0/66.0	74.7

but, as known [21], these are not so sensitive as the $^{1}J_{Pt,C}$ coupling constants are.

In the neutral mononuclear complex [$PtMe_3I(pzH)_2$] (**2**) the magnitude of the $^{1}J_{Pt,C}$ coupling constant *trans* to N (682.3 Hz) demonstrated that, in comparison with the requisite coupling constants in **3**–**7** (642.0–675.2 Hz), pyrazole has a smaller *trans* influence than that of the μ-pyrazolato ligand. Furthermore, the comparison to the $^{1}J_{Pt,C}$ coupling constants in complexes **2** and **4** *trans* to the iodo ligand (715.9 versus 740.4 Hz) showed a *trans* influence $I_{terminal} > I_{bridging}$ as expected.

3.3. Structures

Crystals of complexes **3** and **4** suitable for X-ray diffraction analyses were obtained by recrystallization from CH_2Cl_2/Et_2O. The complexes crystallized as isolated cations and anions without unusual intermolecular interactions. The shortest distances of non-hydrogen atoms between cations and anions are 3.52 Å (C13···C12, **3**) and 3.43 Å (C1···C18, **4**). At distances <3.8 Å from the anion, in complex **3** seven PPN cations are found whereas

[2] Numbering scheme of pzH/pz^- ligands see Schemes 1 and 2.

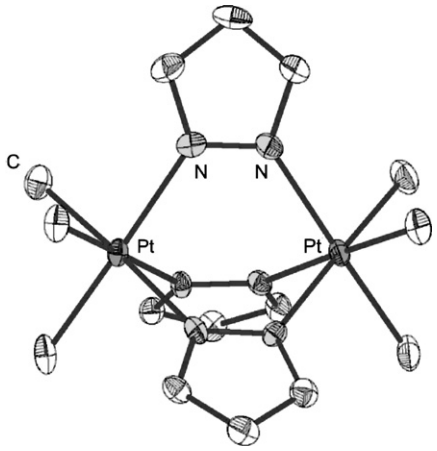


Fig. 1. Molecular structure of $[(PtMe_3)_2(\mu\text{-}pz)_3]^-$ in crystals of **3** (H atoms are omitted for clarity, 30% probability ellipsoids).

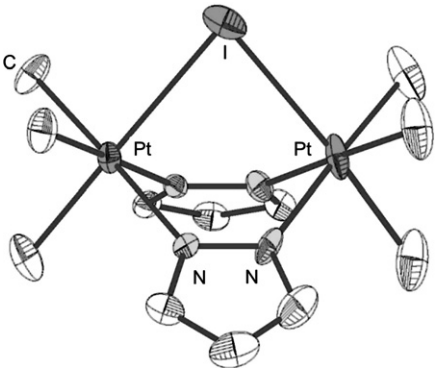


Fig. 2. Molecular structure of $[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]^-$ in crystals **4** (H atoms are omitted for clarity, 30% probability ellipsoids).

in complex **4** six PPN cations and another anion are found. The molecular structures of the anions are shown in Figs. 1 and 2, selected geometrical parameters are given in Table 3.

The structure of the tris(μ-pyrazolato) bridged dinuclear anion in crystals of **3** is approximately of D_{3h} symmetry (Fig. 1). The platinum atoms exhibit an octahedral coordination (angles between neighbouring ligands: 88.1(3)–91.8(3)°). The Pt···Pt distance amounts to 3.7827(8) Å excluding any direct interaction. The structure of the (μ-iodo)bis(μ-pyrazolato) bridged dinuclear anion $[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]^-$ in crystals of **4** is very nearly of C_{2v} symmetry (Fig. 2). The platinum atoms are octahedrally coordinated exhibiting a PtC_3N_2I coordination (angles between neighbouring ligands: 87.3(6)–91.4(4)°). The Pt–C bond lengths did not prove to be dependent on the ligand in the *trans* position (Pt–C (*trans* to N): 2.05(2)–2.08(1) Å; Pt–C (*trans* to I): 2.06(2)/2.07(1) Å). The Pt···Pt distance in **4** is significantly shorter than in **3** (3.706(1) versus 3.7827(8) Å).

3.4. DFT calculations

To gain further insight into the strength of the platinum–μ-ligand bonds in the dinuclear platinum(IV) complexes **3** and **4**, quantum chemical calculations were performed on the DFT level. The calculated equilibrium structures of the dinuclear anions $[(PtMe_3)_2(\mu\text{-}pz)_3]^-$ (**3c**) and $[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]^-$ (**4c**) contained in complexes **3** and **4/5** are illustrated in Fig. 3. Two different diastereoisomers of fragments $[(PtMe_3)_2(\mu\text{-}pz)_2]$ (**8c/8c′**, Fig. 3), with similar energies, were observed in these calculations. Only fragment **8c** is discussed here, because it exhibits a structure close to complexes **3c** and **4c**. Thus, **8c** is expected to be an intermediate in the substitution processes of complex **4**. Selected structural parameters of the equilibrium structures of **3c**, **4c** and **8c** are listed in Table 4. The calculated structures **3c** and **4c** show a good agreement with the experimentally found values. Interestingly, both in the calculated and experimental structures the Pt···Pt distance of the (μ-iodo)-bis(μ-pyrazolato) complex (**4c/4**) was found to be shorter than in the tris(μ-pyrazolato) complex (**3c/3**). An even shorter Pt···Pt distance was found in the complex fragment **8c**. Thus, addition of the μ-pyrazolato (**8c→3c**) and μ-iodo ligand (**8c→4c**) results in a lengthening of the Pt···Pt distance, indicating that the "coordination pocket" of this fragment is too small for both the μ-iodo and the μ-pyrazolato ligand.

Table 3
Selected interatomic distances (in Å) and angles (in °) of complexes $(PPN)[(PtMe_3)_2(\mu\text{-}pz)_3]$ (**3**) and $(PPN)[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]\cdot 1/2Et_2O$ (**4**)

3		**4**	
Pt–C	2.045(8)–2.085(7)	$Pt–C_{trans\,N}$	2.05(2)–2.08(1)
		$Pt–C_{trans\,I}$	2.06(2)/2.07(1)
Pt–N	2.138(5)–2.157(5)	Pt–N	2.123(8)–2.15(1)
N–N	1.328(8)–1.352(8)	N–N	1.35(1)/1.37(1)
		Pt–I	2.826(1)/2.833(1)
Pt···Pt	3.7827(8)	Pt···Pt	3.706(1)
C–Pt–C	88.1(3)–89.5(3)	$C_{trans\,N}$-Pt-$C_{trans\,N}$	87.3(6)/89.0(5)
		$C_{trans\,N}$-Pt-$C_{trans\,I}$	87.3(5)–89.9(6)
C–Pt–N_{cis}	89.3(3)–91.8(3)	$C_{trans\,I}$–Pt–N_{cis}	88.6(6)–91.4(4)
		$C_{trans\,N}$–Pt–N_{cis}	89.7(4)–91.3(6)
C–Pt–N_{trans}	176.8(2)–179.3(2)	$C_{trans\,N}$ –Pt–N_{trans}	177.4(4)–178.4(4)
		$C_{trans\,I}$–Pt–I	175.9(4)/179.1(4)
N–Pt–N	90.1(2)–91.7(2)	N–Pt–N	90.5(3)/91.0(3)
		Pt–I–Pt	81.83(4)
Pt–N–N	123.9(4)–125.5(4)	Pt–N–N	123.2(5)–123.4(6)
P–N–P	133.7(4)	P–N–P	139.6(6)
Pt–N–N–Pt	2.7(7)–5.9(7)	Pt–N–N–Pt	–1(1)/1(1)
C–C–N–N	–0.3(8)–1.3(8)	N–N–C–C	0(1)–1(1)

On the basis of an energetic approach the strength of metal–ligand interactions can be expressed either as the dissociation energy E_{diss} of the complex into the free fragments in their equilibrium structures or as the interaction energy E_{int} of the "prepared" fragments (isolated fragments having the same geometry as in the complex). For an explanation of these fundamental steps, see Ref. [22]. Thus, the equation

$$-E_{diss} = E_{int} + E_{prep}$$

holds whereas the preparation energy E_{prep} of a bond formation A + B→AB is the energy which is necessary to promote fragments A and B from their equilibrium geometries

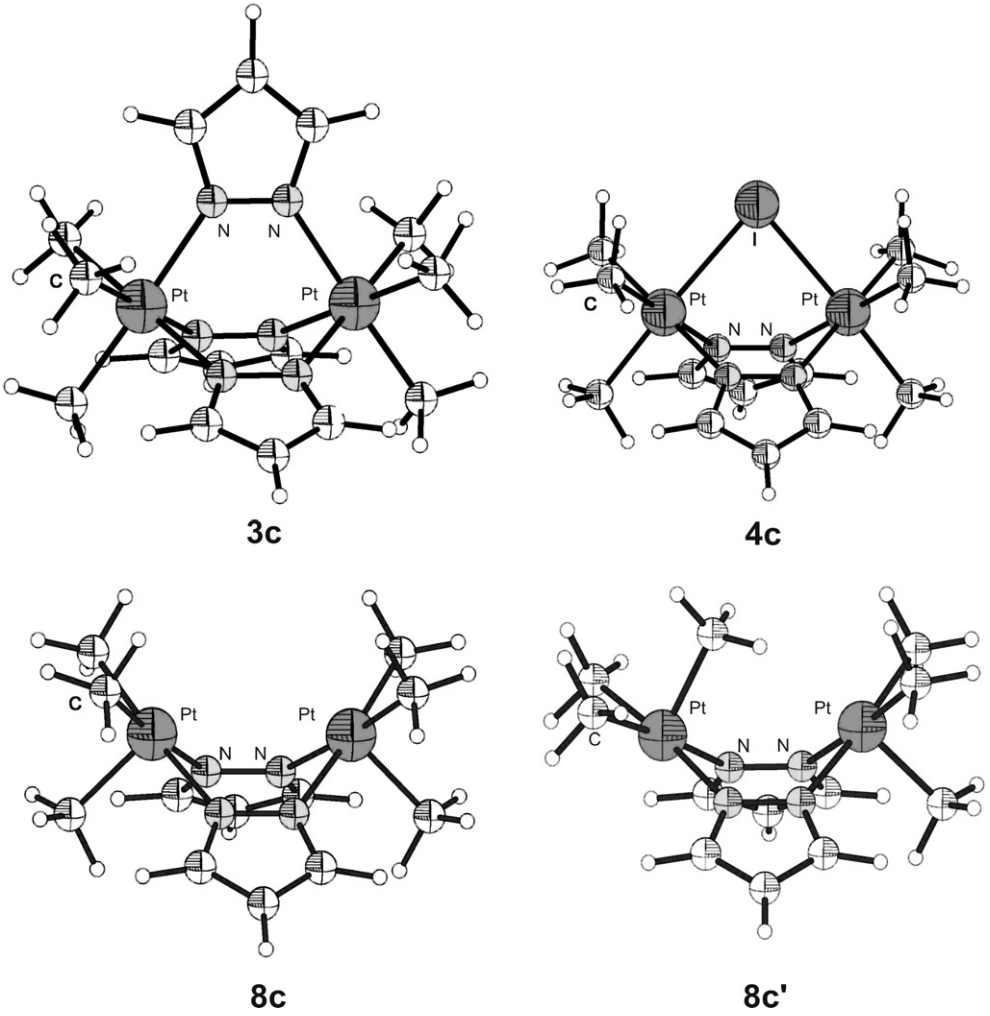


Fig. 3. Calculated equilibrium structures of $[(PtMe_3)_2(\mu\text{-}pz)_3]^-$ (**3c**), $[(PtMe_3)_2(\mu\text{-}I)(\mu\text{-}pz)_2]^-$ (**4c**) and $[(PtMe_3)_2(\mu\text{-}pz)_2]$ (**8c**/**8c′**).

Table 4
Selected interatomic distances (in Å) and angles (in °) of calculated equilibrium structures $[(PtMe_3)_2(\mu\text{-}X)(\mu\text{-}pz)_2]^-$ (μ-X = pz^-, **3c**; I^-, **4c**) and $[(PtMe_3)_2(\mu\text{-}pz)_2]$ (**8c**)

	3c	4c	8c
Pt–$C_{trans\,L}$		2.071	2.043[a]
Pt–$C_{trans\,N}$	2.068–2.070	2.071	2.054
Pt–N	2.168–2.172	2.174	2.161
N–N	1.357–1.358	1.358–1.359	1.363
Pt···Pt	3.830	3.780	3.636
C–Pt–C	88.4–96.2	86.8–89.7	88.7–91.5
C–Pt–N_{cis}	88.9–91.3	89.9–92.5	90.6–92.6
C–Pt–N_{trans}	178.1–179.3	178.9–179.8	175.8–179.8

[a] *trans* to the free coordination site.

to the geometries which they acquire in the complex AB. As shown in Fig. 4, for both processes the μ-pyrazolato ligand in **3c** is more strongly bound ($E_{int} = -80.5$ kcal/mol, $-E_{diss} = -73.7$ kcal/mol) than the μ-iodo ligand in **4c** ($E_{int} = -50.8$ kcal/mol, $-E_{diss} = -46.2$ kcal/mol), which is in accord with the differences in the *trans* influence of the bridging ligands measured by the $^1J_{Pt,C}$ coupling constants. The preparation energy of the platinum fragment in **3c** was found to be larger than that in **4c** (6.3 versus 4.6 kcal/mol) as expected by inspection of the Pt···Pt distances (3.636 Å (**8c**) <3.780 Å (**4c**) <3.830 Å (**3c**)).

3.5. Antitumoral activities

Since the discovery of cisplatin (*cis*-$[PtCl_2(NH_3)_2]$) by Rosenberg [23] the anticancer activity of platinum complexes is well known. In contrast to the large number of platinum(II) complexes, substantially fewer platinum(IV) complexes have been investigated with respect to their cancerostatic properties [24,25]. However, a number of platinum(IV) complexes have been tested in clinical trials. These include iproplatin (*cis*, *trans*, *cis*-$[PtCl_2(OH)_2(NH_2iPr)_2]$) [24] tetraplatin ($[PtCl_4$(D,L-dach)]; dach = 1,2-diaminocyclohexane) [24] and satraplatin (*cis*, *trans*-$[PtCl_2(OAc)_2(NH_3)(NH_2cy)]$) [24,26]. As reported in the literature [27], dinuclear platinum(II) complexes should be able to coordination to DNA in a fashion differing from that observed for mononuclear complexes and thus might show activity against tumor cell lines resistant to cisplatin.

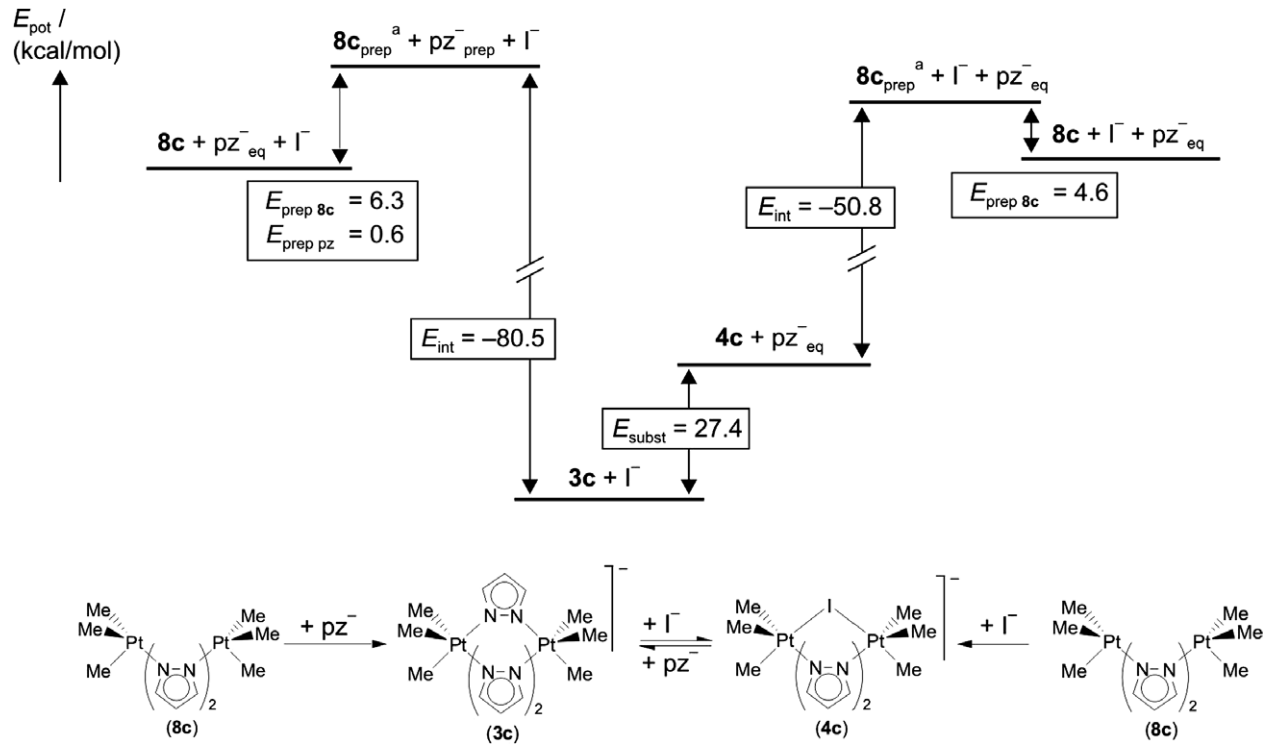


Fig. 4. Energy decomposition analyses of bond formation between fragment **8c** and pz^- and I^-, respectively. Interaction energies include BSSE corrections. (a) $\mathbf{8c}_{prep}$ denotes the fragment **8c** having the geometry as in complex **3c** and **4c**, respectively.

In contrast to the investigation of the anticancer activities of dinuclear platinum(II) complexes, investigations with dinuclear platinum(IV) complexes are lacking. To study the activity of the synthesized trimethylplatinum(IV) complexes two different compounds were chosen (**2**, **5**), exhibiting mono- and dinuclear arrangement, but containing similar (iodo, pyrazole/pyrazolato) ligands.

To investigate the activities of complexes **2** and **5** against various human tumor cell lines, in vitro experiments were carried out. The antitumoral activities of compounds **2** and **5** in comparison to the respective activity of cisplatin are presented in Table 5. The anti-proliferative activity of complex **2** was found to be about one order of magnitude lower than that of cisplatin (IC_{50}(**2**)/IC_{50}(cisplatin) = 7.0–58.4). In contrast, the activity of complex **5** proved to be in the same order than the corresponding activity of cisplatin (IC_{50}(**5**)/IC_{50}(cisplatin) = 0.4–2.7). Two cell lines (8505C, DLD-1), which exhibit low sensitivities against cisplatin, were included in these investigations. On these particular cell lines, complex **5** was found to be more active than cisplatin (IC_{50}(**5**)/IC_{50}(cisplatin) = 0.4–0.5). However, taking into consideration that **5** is a dinuclear complex, roughly the same anti-proliferative activity per Pt atom was observed. The reason for the significantly higher anti-proliferative activity of the dinuclear complex **5** in comparison with the mononuclear complex **2** is not yet clear. It can be speculated that the dinuclear fragment [$(PtMe_3)_2(\mu\text{-pz})_2$] allows a bridging coordination of the nucleobases.

Table 5
IC_{50} values of complexes **2** and **5** against different human tumor cell lines

Cell line	IC_{50} [μM]		
	Complex **2**[a]	Complex **5**[a]	Cisplatin[b]
8505C	35.03 ± 0.86	1.96 ± 0.15	5
A253	20.95 ± 0.94	1.13 ± 0.03	0.8
A431	19.29 ± 0.35	0.95 ± 0.01	0.65
A549	36.22 ± 0.75	2.30 ± 0.03	1.5
A2780	4.82 ± 0.31	1.49 ± 0.07	0.55
DLD-1	37.04 ± 0.56	2.51 ± 0.14	5
FaDu	36.42 ± 0.85	2.32 ± 0.06	1.2
HCT-8	44.97 ± 3.20	3.76 ± 0.13	1.5
HT-29	35.03 ± 1.19	2.18 ± 0.08	0.6

[a] Mean value ± SD from experiments.
[b] Mean value without SD.

To summarize, the investigations showed that dinuclear pyrazolato bridged platinum(IV) complexes can be built up by the synthesis of mononuclear pyrazole precursor complexes followed by controlled deprotonation of the pyrazole ligands. Due to the highly stable *fac*-$PtMe_3$ moiety, threefold bridged dinuclear platinum(IV) complexes were obtained. The substitution lability of the μ-iodo ligand in complex **4**/**5** opened up a way to synthesize and to characterize further complexes having a relatively rigid $Me_3Pt(\mu\text{-pz})_2PtMe_3$ fragment in which to metal centers in high oxidation state are in the vicinity of one another. Furthermore it could be demonstrated that the investigated dinuclear complex **5** exhibited a quite high proliferative activities against a series of human tumor cell lines.

Acknowledgements

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Appendix A. Supplementary material

CCDC 663385 and 663386 contain the supplementary crystallographic data for **3** and **4**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Energies and Cartesian coordinates of atom positions of the calculated structures **3c**, **4c**, **8c**, **8c′**, pz_{eq}^{-} and I^{-} are available from the authors. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2007.11.020.

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