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Synthesis and structure of new trichloroplatinum π-complexes: Reactivity of nitrogen lone-pair versus C–C double bond π-electrons in ligands, effect of steric hindrance

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Abstract

Two trichloroplatinum π-complexes and a diammonium tetrachloroplatinate (II) salt have been unexpectedly isolated during the attempt to synthesize the corresponding cisplatinum square-planar complexes of tertiary cyclohexane 1,4-diamines. All three compounds have been physically and spectroscopically characterized, including X-ray diffraction analysis in two of the three compounds. The formation of the π-complexes instead of the diamino *cis*-platinum complexes could be explained as due to the steric hindrance exerted by methyl groups on the tertiary amines. So, the π-electrons of the C=C double bond are more available than the electron lone pair of nitrogen atom from the amino groups. When the π-electrons of the C=C from the molecule of ligand were made unavailable by transforming the cyclohexene subunit into a benzene aromatic ring, no *cis*-diamino dichloro platinum(II) complex nor trichloroplatinum-complexes were isolated but the corresponding tetrachloroplatinate(II) diammonium salt of the 1,4-diamino ligand.

Keywords: Platinum; π-Complexes; Steric hindrance; X-ray structures

1. Introduction

In the development of our research project on the rational design, synthesis and evaluation of anticancer activity of square-planar *cis*-platinum complexes, we have prepared a library of diamino ligands with a basic skeleton of 1,2-bis(aminomethyl)-cyclohexane (Fig. 1), with the purpose of preparing seven membered diaminoplatinocycles with a 1,4-diamino subunit. In this library of diamines we have included primary, secondary and tertiary amines in order to evaluate their different coordination ability towards platinum and also to know by structure-activity relationship studies (SAR) [1], the influence of the bulkiness and steric hindrance of the diamino groups of the chelating arms of ligands on the cytotoxic activity. Here, we describe the reactivity of tertiary amines (Fig. 1) and the ability of these ligands to chelate Pt(II).

The aforementioned series of diamino ligands has been designed in order to perform a comparative cytoregulatory study versus cisplatin [2] and oxaliplatin [3] (Fig. 2).

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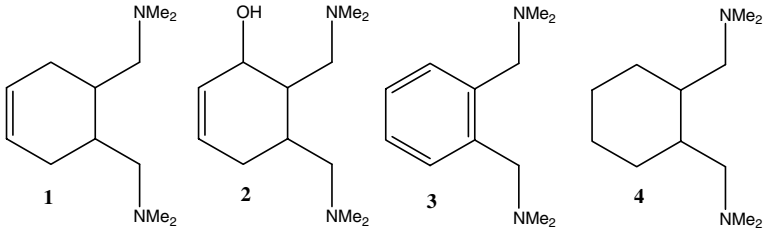
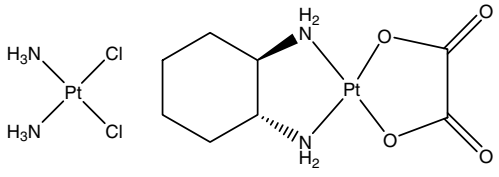


Fig. 1. Studied ligands having tertiary amino groups as chelating entities.



Cisplatin Oxaliplatin

Fig. 2. Structures of cisplatin and oxaliplatin used actually in oncological therapeutics.

cis-[(*R*,*R*)-cyclohexane-1,2-diamine]oxalatoplatinum(II), which represents a third generation of platinum drugs that has been approved in many countries of Asia, Latin America and Europe for clinical use in oncology [1,4,5].

Oxaliplatin has shown a wider spectrum of activity than cisplatin, and it was found to be active in several tumour cell lines with acquired or intrinsic resistance to cisplatin or carboplatin. This different behaviour is not only due to a different degree of interaction with DNA. Oxaliplatin acts as an alkylating agent, inducing mainly the formation of platinated intra-strand adducts between two adjacent guanine bases or two adjacent guanine adenine bases of DNA [6]. Moreover, the wider spectrum of activity of oxaliplatin compared to that of parent compound may be attributed to differences in mechanisms of resistance, because of their different interaction with the proteins that recognize damages and lesions in DNA [7].

2. Results and discussion

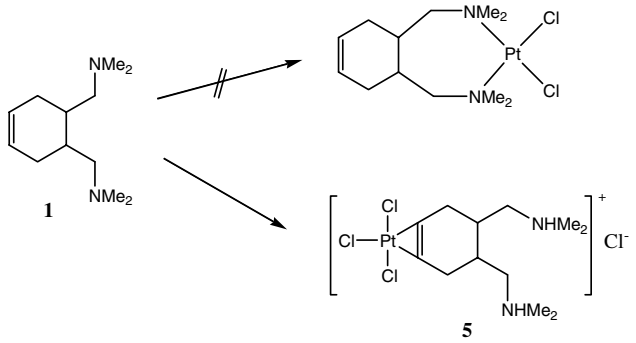
In this context, series of primary, secondary and tertiary amines from our library of ligands were reacted, under several conditions [8], with $PtCl_2$, K_2PtCl_4, PtI_2, etc., in order to obtain the corresponding seven-membered cisplatinum 1,4-diaminometallacycles. In the case of ligands having primary and secondary amino groups, we obtained the cisplatinum complexes as expected, with moderate to good yields [9], but when using tertiary amines as starting materials no cisplatinum coordination complexes were formed. Instead of the expected complexes, depending on both the structure of ligand and the reaction conditions, π-coordination products were isolated, resulting from unusual rearrangements (which involved hydride migration) [10] or organoplatinum complexes as **5** and **6**, which are described here. We think that this behaviour could be due to the steric hindrance exerted by the methyl groups on the electron lone pair of the nitrogen atom in the amino groups of ligands, so the bulky platinum atom cannot reach it. For this last reason, platinum atom coordinates the ligand by the π-electrons of the carbon-carbon double bond of the cyclohexene system, forming trichloroplatinum complexes [11] of the type of Zeise's salt (see Scheme 1) [12].

Complexation reactions were carried out starting from ligand **2** in order to evaluate the possibility to form platinum stable six-membered platinocycles involving the OH group and one of the NMe_2 groups (see Scheme 2), or otherwise seven-membered 1,4-diamino metallacycles but, instead of these expected compounds, the formation of a π-complex **6** was observed.

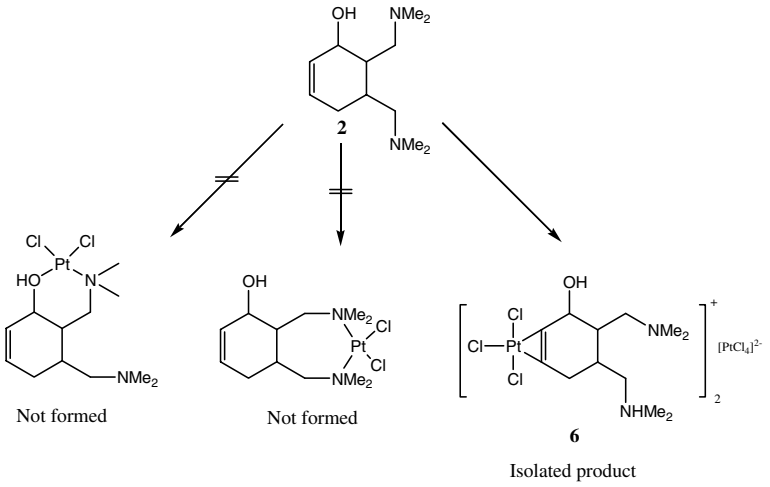
Finally, in order to force the complexation by the dimethylamino groups, the aromatic ligand **3** was synthesized and, on the other hand, the cyclohexene ring of ligand **1** was transformed into the saturated cyclohexane ring of ligand **4** by catalytic hydrogenation.

When working with the aromatic diamino ligand **3** we did not obtain a diamino cisplatinum complex nor an organoplatinum π-complex but the diammonium tetrachloroplatinate salt **7** (Scheme 3), clearly identified by X-ray diffraction analysis.

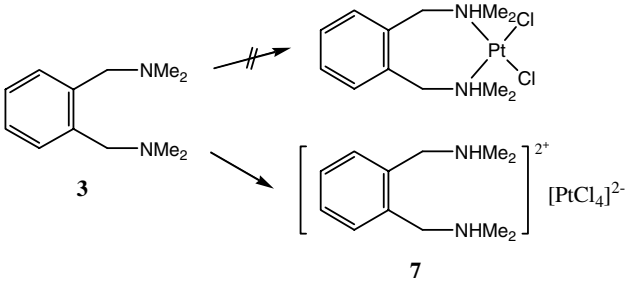
On the other hand, when reacting the saturated compound **4**, the expected cisplatinum complex was not obtained but a π-coordinated product **8** was formed,



Scheme 1. Formation of the trichloroplatinum π-complex **5** from ligand **1**.



Scheme 2. Chimioselective formation of the complex **6** from ligand **2**.



Scheme 3. Structure of the reaction product of the aromatic diamino ligand **3**.

resulting from an unusual molecular rearrangement (involving NMe_2 elimination followed by hydride migration) [10] (see Scheme 4).

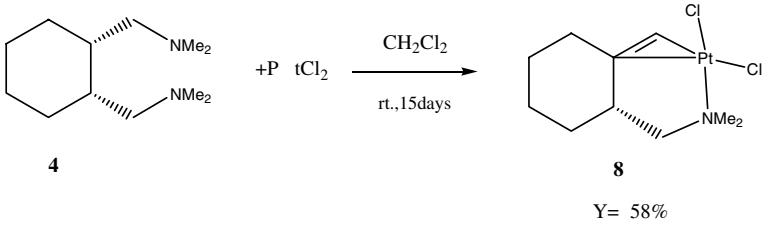
Studies to evaluate the biological activity of the compounds described here are in progress at the present moment in our laboratories. These studies are being carried out at two levels. A first level includes the studies of interaction of complexes with DNA (normally by an alkylation mechanism of DNA bases) by using several techniques: (a) circular dichroism (in order to study the modification of the secondary structure of DNA); (b) electrophoresis on agarose gel (in order to evaluate the modification of the tertiary structure of DNA); and (c) atomic forces microscopy (AFM) to observe DNA incubated with the complexes in order to evaluate de degree or intensity of the interaction complex–DNA, by counting the statistical frequency of formation of nodules, supercoiled forms and scissions of DNA chains. The second level of biological evaluation of the isolated compounds is the in vitro evaluation of their cytotoxic activity against cancer cell lines of several types, resistant and non-resistant to cisplatin (the standard platinum drug used in oncological therapeutics).

2.1. Synthesis of diamines

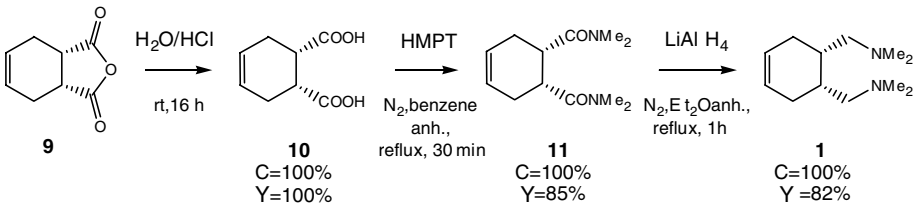
Synthesis of ligand **1** was carried out starting from commercially available *cis*-3,3,6,6-tetrahydrophthalic anhydride [13]. Hydrolysis of anhydride **9** led to *cis*-3,3,6,6-tetrahydrophtalic acid (**10**), whose amidation was easily accomplished by refluxing it with HMPT in benzene. Diamine **1** was obtained by reduction of diamide **11** with $LiAlH_4$. The synthetic pathway used to prepare ligand **1** and the yields of every step are shown in Scheme 5.

Ligand **3** was obtained by the same synthetic methodology used to prepare ligand **1**, but starting from commercially available phthalic acid **12**, as it is illustrated on Scheme 6.

Ligand **2** was obtained following a different synthetic pathway (see Scheme 7). First, a Diels–Alder reaction



Scheme 4. Formation of organoplatinum complex **8** via NMe_2 elimination and hydride shift of the parent ligand **4**.



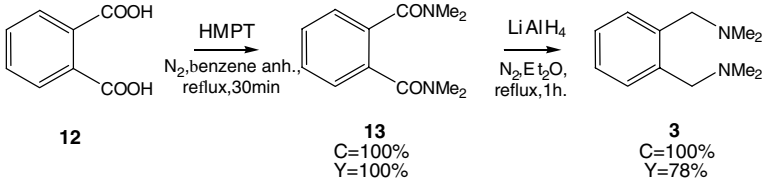
Scheme 5. Synthetic pathway of ligand **1**.

between 1-acetoxy-1,3-butadiene and fumaryl chloride was carried out at room temperature to obtain, in good yield, cycloadduct **16** as a major diastereoisomer, which was isolated and purified by column chromatography. Next, the reaction with dimethylamine led to diamide **17**. Finally, the desired ligand **2** was synthesized by reduction of diamide **17** with $LiAlH_4$. The characterization of each intermediate, as well as the final ligands, was performed by ^1H NMR, ^{13}C NMR, IR, MS and elemental analysis.

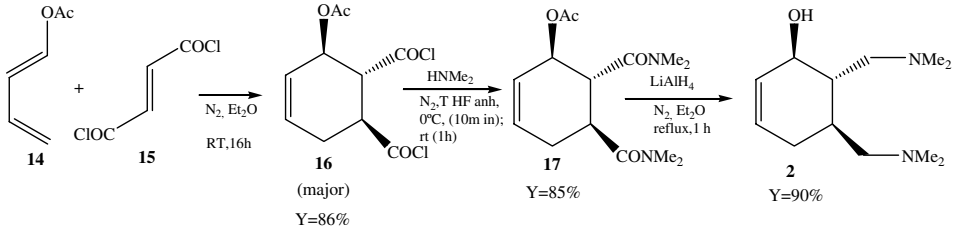
2.2. Synthesis of platinum(II) complexes

Several assays were performed, under different reaction conditions, in order to optimize the preparation of the platinum complexes from ligands **1** to **4**. Thus, when ligands **1** and **2** reacted with K_2PtCl_4 under acidic conditions, coordination to platinum took place by the double bond, and cationic complexes **5** and **6** were, respectively, obtained, instead of the usual seven-membered ring chelates, which would result from the coordination of platinum atom to both nitrogen atoms of the amino groups (see Schemes 8 and 9). In contrast, when reactions were carried out under neutral conditions a mixture of polymeric products was obtained, but not the desired platinum complexes.

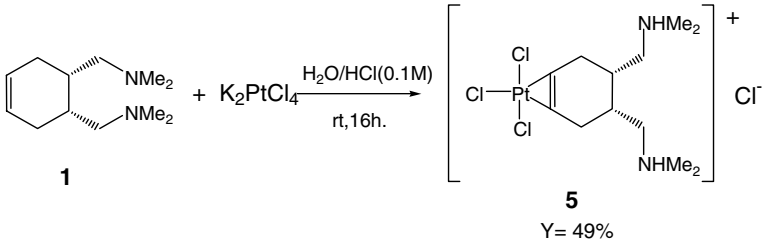
Complexes **5** and **6** were studied, in solid state, by elemental analysis, mass spectrometry and FT-IR spectroscopy, and in solution, by high field ^1H NMR spectroscopy. Moreover, the structure of complex **5**



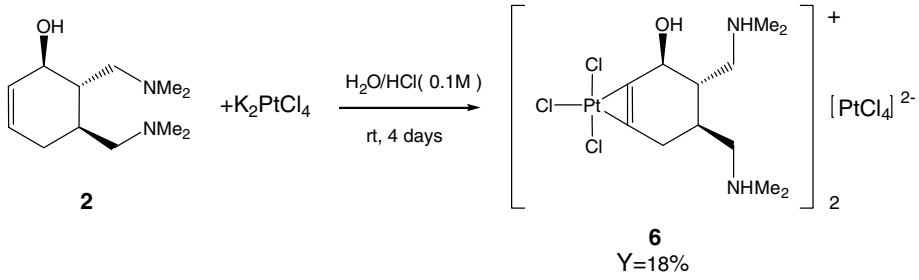
Scheme 6. Synthetic pathway of ligand **3**.



Scheme 7. Synthetic pathway of ligand **2**.



Scheme 8. Synthetic pathway of complex **5**.



2

6
Y=18%

Scheme 9. Synthetic pathway of complex **6**.

was confirmed by X-ray diffraction analysis on single crystals. A complementary conductivity study of the complex **6** was made to find out its counter-ion nature. Comparing conductivity of compound **6** (138.6 Ω^{-1} cm^2 mol^{-1}) to bibliographic data [14] it can be assumed that compound **6** is an electrolyte with an ion charge ratio 2:1 (see Table 1).

Formation of these two unusual complexes could be attributed to the acidic conditions of the reaction medium and to the steric hindrance exerted by the methyl groups of the NMe_2 subunits.

Complex **5** is been evaluated as potential cytostatic agent. It has a peculiar structure that could facilitate the formation of DNA adducts, which is the main target of our platinum compounds. This is thought on the basis that carbon–platinum bond has an enhanced *trans* effect and, on the other hand, because this compound has three labile ligands, and consequently three possible sites to coordinate to DNA.

In order to force the coordination of platinum atom to the amino groups, the aromatic ligand **3** was prepared and reacted with platinum reagents under different conditions, but in any case coordination to platinum atom took place, only the corresponding salt **7** was isolated (Scheme 10). This new product was characterized by ^1H NMR, FT-IR, MS and elemental analysis and its structure was confirmed by X-ray diffraction analysis on single crystals.

Table 1
Conductivity of compound **6**, using DMF as a solvent; $\Lambda_M = k/c$

Concentration, c (M)	Conductivity, k (μS cm^{-1})	Λ_M (Ω^{-1} cm^2 mol^{-1})
1.053×10^{-3}	145.9	138.6

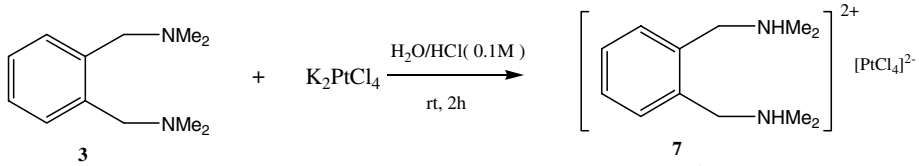
2.3. Structure determination of compounds 5 and 7 by X-ray crystallography

2.3.1. Compound 5

Details about structure determination are given in Section 3. Crystallographic data and selected bond distances and angles are quoted in Tables 2 and 3. In Fig. 3, an ORTEP view of the X-ray crystal structure of **5** is shown. This molecular representation shows a cationic complex with chloride as a counter-ion. Platinum(II) atom has a square planar coordination geometry. The CH=CH group, and consequently the ligand, is located perpendicular to the plane containing platinum and chlorine atoms. Angles of the CH=CH moiety indicate that the double bond geometry is not exactly coplanar. Moreover, C3′–C4′ length is 1.39 Å, higher than the length expected for a non-coordinated olefin. These two experimental facts are consistent with a back-donation effect. Finally, ammonium groups are located separately to minimize both, the charge repulsion between the N^+ centres and the steric repulsion between methyl groups.

2.3.2. Compound 7

Details about structure determination are given in Section 3 and also in the supplementary material. Crystallographic data and selected bond distances and angles are quoted in Tables 2 and 4. In Fig. 4 an ORTEP view of the X-ray crystal structure of **7** is shown. In this compound ammonium groups are also located separately, far away from each other respect to the planar benzene ring in order to minimize both, charge repulsion between the positively charged nitrogen atoms and the steric repulsion between methyl groups.



3

7
Y=76%

Scheme 10. Synthetic pathway of complex **7**.

Table 2
Crystal data for compounds **5** and **7**

Complex	**5**	**7**
Molecular formula	$C_{12}H_{24}Cl_4N_2Pt$	$C_{12}H_{22}Cl_4N_2Pt$
Molecular weight (g/mol)	533.22	531.21
T (K)	293(2)	293(2)
λ(Mo Kα) (Å)	0.71069	0.71069
Crystallographic system	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	$P\bar{1}$
a (Å)	10.8650(10)	7.372(9)
b (Å)	12.1680(10)	10.261(5)
c (Å)	13.2060(10)	12.3310(10)
α (°)	90	68.5210(10)
β (°)	90	86.8400(10)
γ (°)	90	82.8590(10)
V (Å^3)	1745.9(3)	861.2(11)
Z	4	2
D_{calc} (Mg m^{-3})	2.029	2.048
μ(mm^{-1})	8.638	8.756
F(000)	1024	508
Θ Range (°)	2.51–31.60	2.23–31.71
h, k, l Ranges	$0 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 16$, $0 \leqslant l \leqslant 19$	$-9 \leqslant h \leqslant 9$, $-13 \leqslant k \leqslant 14$, $0 \leqslant l \leqslant 18$
Number of registered reflections	11 617	6209
Number of independent reflections	2587	3949
R_{int} on F	0.0490	0.0258
Method of refinement	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Number of data	2587	3949
Number of parameters	173	188
Goodness-of-fit on F^2	1.089	1.059
R final [$I > 2\sigma I$]	$R_1 = 0.0377$, $wR_2 = 0.0889$	$R_1 = 0.0404$, $wR_2 = 0.1016$
R index (all data)	$R_1 = 0.0464$, $wR_2 = 0.1008$	$R_1 = 0.0404$, $wR_2 = 0.1016$
Largest difference peak and hole (e Å^{-3})	0.847 and −0.877	0.797 and−0.551

3. Experimental

3.1. Materials and methods

All reactants were purchased from commercial suppliers and used without further purification. Reactions that required an inert atmosphere were conducted under dry nitrogen and the glassware was oven dried (120 °C). THF, Et_2O and benzene were distilled from sodium/benzofenone prior to use. Elemental analyses (C, H, N, S) were carried out on a Carlo Erba EA1108. Infrared spectra were recorded on a FT-IR NICOLET 510 spectrometer in a 4000–400 cm^{-1} range. ^{1}H NMR spectra were obtained on a Varian Gemini-200, Varian Unity-300 plus or Varian VXR-500, using $CDCl_3$ or DMSO-d_6 as solvents and chemical shifts are given in ppm relative to tetramethylesilane (TMS). ^{13}C NMR and DEPT experiments were recorded at 50 MHz or 75 MHz and were referenced to the 77.0 ppm resonance of chloroform. Mass spectra were run on a Fisons VG Quattro triple quadrupole analyser in the 1800–200 m/z range, using MeCN–H_2O as solvent under electrospray (ESP-MS), or FAB(+) mode on a Hewlett–Packard 5890 mass spectrometer using a chemical ionisation technique (conditions are specified for each case). Melting points were measured on a Galenkamp and on a Stuart Scientific SMP3 apparatuses. Conductivity was measured on a CRISON Micro CM 2200 equipment.

3.2. Synthesis of cis-cyclohex-4-ene-1,2-dicarboxylic acid (*10*)

3,3,6,6-Tetrahydrophthalic anhydride (**9**) (1.178 g, 7.09 mmol) was dissolved in acetic acid (2 mL) and water (10 mL). Then, 0.25mL of hydrochloric acid was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness and pure dicarboxylic acid **10** was obtained in quantitative yield (1.198 g). mp = 169–170 °C. Anal. Found: C, 56.51; H, 6.01. Calc. for $C_8H_{10}O_4$: C, 56.47; H, 5.92%. IR (cm^{-1}): 3300–2300 (COO–H), 1680 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.36–2.69 (4H, m, H3, H6), 3.10 (2H, dd, $J_1 = 5.1$ Hz, $J_2 = 5.1$ Hz, H1, H2), 5.69 (2H, s, H4, H5); ^{13}C NMR (50 MHz, CD_3OD, δ in ppm): 23.2 (C3, C6), 36.8 (C1, C2), 122.3 (C4, C5), 173.3 (C1′, C1″); MS (70 eV, DIP–CI–NH_3, m/z, %): 205 (10) $[M + N_2H_7]^+$, 188 (100) $[M + NH_4]^+$, 171 (3) $[M + H]^+$.

3.3. Synthesis of cis-N,N,N′,N′-tetramethyl-4-cyclohexene-1,2-dicarboxamide (*11*)

To a suspension of **10** (300 mg, 1.765 mmol) in anhydrous benzene (2 mL) hexamethylphosphorous triamide (0.32 mL, 1.765 mmol) was added and the reaction mixture was maintained under reflux for 30 min. The resulting cloudy solution was allowed to cool to room temperature and a saturated aqueous solution of $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous layer was extracted with methylene chloride (4 × 2 mL). The organic phases were combined together, dried over anhydrous $MgSO_4$ and concentrated to dryness, affording a colourless oil that rapidly solidified to form a white solid. The solid was washed with hexane and purified by crystallization from ether at −78 °C (Yield: 391 mg, 88%). mp = 65–70 °C. Anal. Found: C, 64.31; H, 8.95; N, 12.45. Calc. for $C_{12}H_{20}N_4O_2$: C, 64.26; H, 8.99; N, 12.49%. IR (cm^{-1}): 1645 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.03–2.12 (2H, m, H3, H6), 2.31–2.47 (2H, m, H3, H6), 2.73 (3H, s, H1‴ or H1^{iv} or H1^{v} or H1^{vi}), 2.75 (3H, s, H1‴ or H1^{iv} or H1^{v} or H1^{vi}), 2.85 (3H, s, H1‴ or H1^{iv} or H1^{v} or H1^{vi}), 2.87 (3H, s, H1‴ or H1^{iv} or H1^{v} or H1^{vi}), 2.85–2.92 (2H, m, H1, H2), 5.52–5.55 (2H, m, H4, H5); ^{13}C

Table 3
Selected bond lengths (Å) and angles (°) for compound **5**

Bond lengths (Å)		Bond angles (°)	
Pt–C(4′)	2.167(10)	C(4′)–Pt–C(3′)	37.3(3)
Pt–C(3′)	2.180(10)	C(4′)–Pt–Cl(3)	93.4(3)
Pt–Cl(3)	2.298(3)	C(3′)–Pt–Cl(3)	98.5(3)
Pt–Cl(2)	2.304(3)	C(4′)–Pt–Cl(2)	89.2(3)
Pt–Cl(4)	2.316(3)	C(3′)–Pt–Cl(2)	85.4(3)
N(1)–C(1‴)	1.484(13)	Cl(3)–Pt–Cl(2)	176.10(12)
N(1)–C(1^{iv})	1.49(2)	C(4′)–Pt–Cl(4)	163.5(3)
N(1)–C(1)	1.494(13)	C(3′)–Pt–Cl(4)	158.4(2)
N(2)–C(1^{v})	1.476(13)	Cl(3)–Pt–Cl(4)	87.94(13)
N(1)–C(1^{vi})	1.48(2)	Cl(2)–Pt–Cl(4)	88.74(12)
N(1)–C(1″)	1.494(13)	C(4′)–C(3′)–Pt	70.8(6)
C(3′)–C(4′)	1.390(13)	C(2′)–C(3′)–Pt	120.0(7)
C(3′)–C(2′)	1.513(13)	C(3′)–C(4′)–Pt	71.9(6)
C(4′)–C(5′)	1.528(13)	C(5′)–C(4′)–Pt	120.9(8)
C(5′)–C(6′)	1.545(12)	C(1‴)–N(1)–C(1^{iv})	110.2(9)
C(1′)–C(6′)	1.519(13)	C(1‴)–N(1)–C(1)	115.8(8)
C(6′)–C(1″)	1.531(14)	C(1)–N(1)–C(1^{iv})	111.1(8)
C(1′)–C(1)	1.55(2)	C(1‴) N(1)–H(N1)	106.4(5)
C(1′)–C(2′)	1.552(12)	C(1^{iv})–N(1)–H(N1)	106.4(6)
		C(1)–N(1) H (N1)	106.4(5)
		C(1^{v})–N(2)–C(1^{vi})	112.3(9)
		C(1^{v})–N(2)–C(1″)	109.3(9)
		C(1^{vi})–N(2)–C(1″)	112.3(8)
		C(4′)–C(3′)–C(2′)	121.4(8)
		C(4′)–C(5′)–C(6′)	113.8(8)
		C(1′)–C(6′)–C(1‴)	112.1(8)
		C(3′)–C(4′)–C(5′)	121.5(8)
		C(1)–C(1′)-C-(2′)	111.9(8)
		C(1″)–C(6′)–C(5′)	112.1(7)
		C(6′)–C(1′)–C(1)	112.8(7)
		C(6′)–C(1′)–C(2′)	106.4(8)
		C(1)–C(1′)–C(2′)	111.9(8)
		C(3′)–C(2′)–C(1′)	109.5(7)
		N(2)–C(1″)–C(6′)	112.8(9)
		N(1)–C(1)–C(1′)	113.5(7)

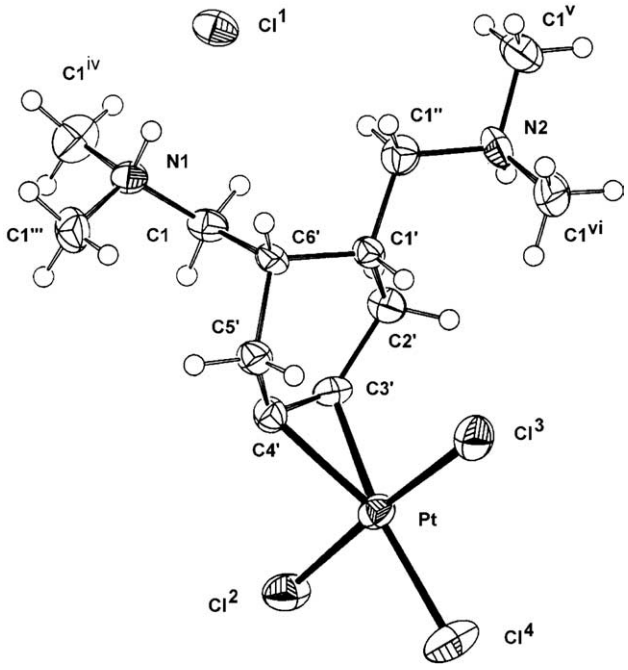


Fig. 3. ORTEP view of molecule **5**.

Table 4
Selected bond lengths and angles for compound **7**

Bond lengths (Å)		Bond angles (°)	
Pt–Cl3	2.2935(13)	Cl3–Pt–Cl4	179.20(4)
Pt–Cl4	2.2962(14)	Cl3–Pt–Cl2	89.17(6)
Pt–Cl2	2.3032(15)	Cl4–Pt–Cl2	90.15(6)
Pt–Cl1	2.3139(15)	Cl3–Pt–Cl1	90.30(6)
N1–C1‴	1.473(7)	Cl4–Pt–Cl1	90.39(6)
N1–C1	1.490(6)	Cl2–Pt–Cl1	179.11(4)
N1–C1^{iv}	1.517(8)	C1‴–N1–C1	110.5(5)
N2–C1^{vi}	1.484(7)	C1‴–N1–C^{iv}	110.5(5)
N2–C1^{v}	1.493(7)	C1–N1–C1‴	111.0(4)
N2–C1″	1.530(7)	C1^{vi}–N2–C1^{v}	112.3(5)
C1–C1′	1.478(6)	C1^{vi}–N2–C1″	109.8(5)
C1′–C6′	1.385(7)	C1^{v}–N2–C1″	112.3(5)
C1′–C2′	1.434(6)	C6′–C1′–C2′	116.9(4)
C6′–C5′	1.371(8)	C6′–C1′–C1	119.5(4)
C5′–C4′	1.395(8)	C2′–C1′–C1	123.5(4)
C4′–C3′	1.320(8)	C5′–C6′–C1′	122.7(5)
C3′–C2′	1.409(6)	C1′–C1–N1	112.5(4)
C2′–C1″	1.493(6)	C6′–C5′–C4′	119.6(5)
		C4′–C5′–C6′	119.8(5)
		C4′–C3′–C2′	122.8(5)
		C3′–C2′–C1′	118.3(4)
		C3′–C2′–C1″	117.8(4)
		C1′–C2′–C1″	123.9(4)
		C2′–C1″–N2	112.5(4)

NMR (50 MHz, CD_3 OD, δ in ppm): 26.5 (C3, C6), 35.5 (C1^{iv}, C1^{vi}), 36.0 (C1, C2), 37.4 (C1‴, C1^{v}), 124.9 (C4, C5), 174.0 (C1′, C1″); MS (70 eV, DIP–CI–NH_3, *m/z*, %) 225 (100) $[M + H]^+$, 180 (12) $[M - NMe_2]^+$, 171 (3) $[M + H]^+$.

*3.4. Synthesis of cis-N,N,N′,N′-tetramethyl-4-cyclohexene-1,2-bis (dimethylamine) (**1**)*

To a suspension of lithium aluminium hydride (70 mg, 1.837 mmol) in anhydrous ether (2 mL) a solution of diamide **11** (246 mg, 1.531 mmol) in dry tetrahydrofuran (1 mL) was added. The mixture was refluxed for 1 h and then it was quenched by a cautious successive addition of water (0.12 mL), 15% NaOH aqueous solution (0.12 mL) and water again (0.38 mL). A fine white solid precipitated, which was filtered off, washed with ether and discarded. The liquid filtrate was concentrated to dryness, obtaining a colourless oil (Yield: 300 mg, 82%). Anal. Found: C, 73.28; H, 12.36; N, 14.20. Calc. for $C_{12}H_{24}N_2$: C, 73.14; H, 12.32; N, 14.27%. IR (cm^{-1}): 3020, 2970, 2940, 2900, 2860, 2820, 2770, 1650, 1095; ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.20 (12H, s, H1‴, H1^{iv}, H1^{v}, H1^{vi}), 1.87–2.30 (10H, m, H1′, H2′, H5′, H6′, H1, H1″), 5.64 (2H, s, H3′, H4′); ^{13}C NMR (50 MHz, CD_3OD, δ in ppm): 28.3

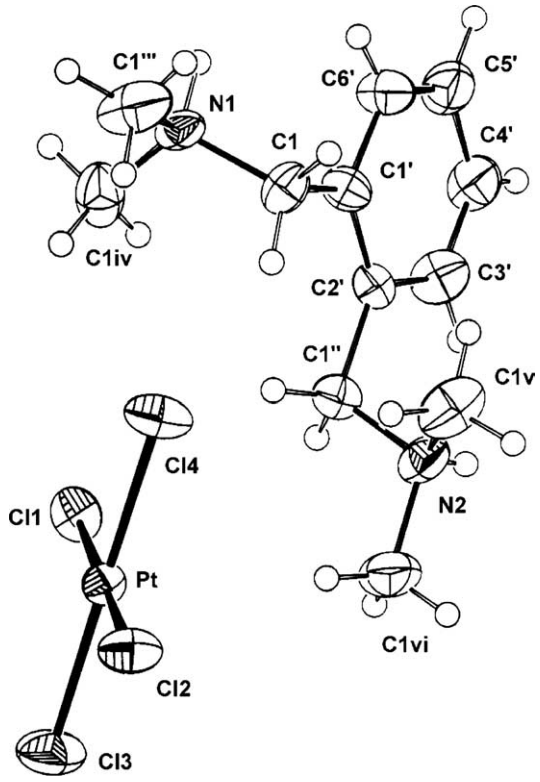


Fig. 4. ORTEP view of molecule **7**.

(C2′, C5′), 33.0 (C1′, C6′), 46.0 (C1‴ $C1^{iv}$, $C1^{v}$, $C1^{vi}$), 60.6 (C1, C1″), 125.9 (C3′, C4′); MS (70 eV, DIP–CI–NH_3, *m*/*z*, %): 214 (3) $[M + NH_4]^+$, 197 (33) $[M + H]^+$, 184 (100) $[M - Me]^+$.

3.5. Synthesis of N,N,N′,N′-tetramethyl-phthalamide (*13*)

To a suspension of phthalic acid **12** (1 g, 6.02 mmol) in anhydrous benzene (10 mL) hexamethylphosphorous triamide (1.1 mL, 6.02 mmol) was added and the mixture kept under reflux for 30 min. The resulting cloudy solution was allowed to cool to room temperature and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The layers were separated and the aqueous phase was extracted with methylene chloride (4 × 5 mL). The organic solutions were combined together, dried over anhydrous $MgSO_4$ and concentrated to dryness, obtaining a white solid (Yield: 1.32 g, 100%). mp = 117–119 °C. Anal. Found: C, 65.48; H, 7.29; N, 12.78. Calc. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72%. IR (cm^{-1}): 3019, 2932, 2782, 1631 (C=O, st), 1591, 1437, 1395, 1265, 1211, 1057. ^1H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.93 (6H, s, $H1^{iv}$, $H1^{v}$), 3.07 (6H, s, H1‴, $H1^{vi}$), 7.28–7.34 (2H, m, H4, H5), 7.38–7.43 (2H, m, H3, H6). ^{13}C NMR (50 MHz, CD_3 OD, δ in ppm): 34.9 (C1‴, $C1^{iv}$, $C1^{v}$, $C1^{vi}$), 126.4 (C3, C6), 128.7 (C4, C5), 135.0 (C1, C2), 170.2 (C1′, C1″). MS (70 eV, DIP–CI–NH_3, *m*/*z*,%): 176 (3) [M − 3Me], 222 (11) $[M + 2H^+]$, 235 (100), 238 (23) $[M + NH_4^+]$.

3.6. Synthesis of N,N-dimethyl-1-[2-(N,N-dimethyl-amino-methyl)-phenyl]-methylamine (*3*)

To a suspension of lithium aluminium hydride (457 mg, 12.03 mmol) in anhydrous ether (10 mL) a solution of diamide **13** (1323 mg, 6.01 mmol) in dry tetrahydrofuran (10 mL) was added. The mixture was refluxed for 1 h and then it was quenched by successive addition of water (0.9 mL), 15% (w/w) aqueous NaOH solution (0.9 mL) and water (2.7 mL). A white precipitate was formed, which was filtered off, washed with ether and discarded. The filtrate was concentrated to dryness resulting a colourless oil (Yield: 900 mg, 78%). Anal. Found: C, 75.01; H, 10.39; N, 14.53. Calc. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57%. IR (cm^{-1}): 3066, 3023, 2973, 2942, 2855, 2815, 2765, 1653, 1458, 1366, 1308, 1022; ^1H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.23 (12H, s, H1‴, $H1^{iv}$, $H1^{v}$, $H1^{vi}$), 3.51 (4H, s, H1, H1″), 7.19–7.34 (4H, m, H3′, H4′, H5′, H6′); ^{13}C NMR (50 MHz, CD_3OD, δ in ppm): 45.6 (C1″, $C1^{iv}$, $C1^{v}$, $C1^{vi}$), 61.2 (C1, C1″), 126.7 (C4′, C5′), 130.1 (C3′, C6′), 137.9 (C1′, C2′); MS (70 eV, DIP–CI–NH_3, *m*/*z*, %): 162 (5) [M − 2Me], 193 (100) $[M + H^+]$, 194 (14) $[M + 2H^+]$.

3.7. Synthesis of (1R*,5S*,6R*)-5,6-bis-(chlorocarbonyl)-cyclohex-2-en-1-yl acetate (*16*) [15]

A solution of 1-acetoxy-1,3-butadiene **14** (0.77 mL, 6.54 mmol) in anhydrous ether (2 mL) was added to a solution of fumaryl chloride **15** (0.71 mL, 6.54 mmol) in anhydrous ether (2 mL). Both solutions were previously cooled at 0 °C before mixing. After 1 h the reaction mixture was allowed to reach room temperature and it was maintained under these conditions for 16 h. The mixture was concentrated to dryness obtaining a yelow oil (Yield: 1.49 g, 86%). Anal. Found: C, 45.37; H, 3.93. Calc. for $C_{10}H_{10}Cl_2O_4$: C, 45.31; H, 3.80; Cl, 26.75%. IR (cm^{-1}): 3030, 2938, 2870, 1788 (C=O, st), 1748 (C=O, st), 1435, 1373, 1227, 1088, 1022, 854; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 2.01 (3H, s, H2), 2.22–2.28 (1H, m, H4′a), 2.79–2.84 (1H, m, H4′b), 3.46 (1H, dd, $J_1 = 4.0$ Hz, $J_2 = 11.5$ Hz, H6′), 3.52 (1H, ddd, $J_1 = 5.5$ Hz, $J_2 = J_3 = 11.5$ Hz, H5′), 5.75–5.77 (1H, m, H1′), 6.02–6.01 (2H, m, H2′, H3′); ^{13}C NMR (75 MHz, CD_3OD, δ in ppm): 20.5 (C2), 28.1 (C4′), 48.7 (C5′), 56.9 (C6′), 65.1 (C1′), 123.4 (C3′), 129.7 (C2′), 169.7 (C1), 172.2 (C1″ or C1‴), 174.9 (C1″ or C1‴); MS (70 eV, DIP–CI–NH_3, *m*/*z*,%): 300 (3) $[M + N_2H_7^+]$, 283 (12) $[M + NH_4^+]$, 282 (100) $[M - Cl + OH + N_2H_7^+]$.

3.8. Synthesis of (1R*,5S*,6R*)-5,6-bis(N,N′-dimethyl-carbamoyl)cyclohex-2-en-1-yl acetate (*17*) [16]

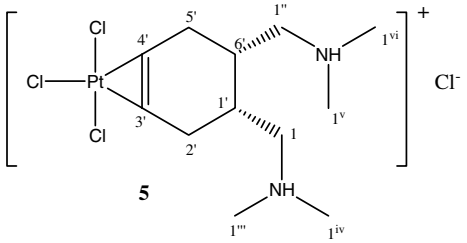
A solution of compound **16** (4.72 g, 17.80 mmol) in anhydrous THF (6 mL) was prepared and cooled to 0

°C. To this solution dimethylamine (53 mL, 106 mmol) 2 M in anhydrous THF was added at once and the mixture was allowed to reach room temperature and it was maintained under these conditions for 1 h. The mixture was concentrated to dryness resulting a brown oil, which was purified by flash column chromatography, using SiO_2 as stationary phase and ethyl acetate/methanol mixtures of increasing polarity as mobile phases. The desired product was eluted with ethyl acetate/MeOH 80:20, affording 4.27 g of a yellow oil (85% yield). Anal. Found: C, 59.60; H, 7.89; N, 9.99. Calc. for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92%. IR (cm^{-1}): 3030, 2910, 1725 (C=O, st), 1635 (C=O, st), 1485, 1390, 1220, 1125, 1005; ^1H NMR (200 MHz, $CDCl_3$, δ in ppm): 2.01 (3H, s, H2), 2.42–2.07 (2H, m, H4′), 2.83 (3H, s, $H1^{iv}$), 2.94 (3H, s, $H1^{vi}$), 3.14 (3H, s, $H1^{v}$), 3.20 (3H, s, $H1^{vii}$), 3.36–3.54 (2H, m, H5′, H6′), 5.64–5.69 (1H, m, H1′), 5.72–5.82 (1H, m, H2′ or H3′), 6.01–6.09 (1H, m, H2′ or H3′); ^{13}C NMR (50 MHz, CD_3OD, δ in ppm): 21.0 (C2), 28.3 (C4′), 34.1 (C5′), 35.6 ($C1^{iv}$, $C1^{v}$), 37.0 ($C1^{vi}$), 37.4 ($C1^{vii}$), 43.8 (C6′), 63.8 (C1′), 123.5 (C2′ or C3′), 131.5 (C2′ or C3′), 170.2 (C1), 170.3 (C1″), 175.0 (C1‴); MS (70 eV, DIP–CI–NH_3, m/z,%): 300 (13) $[M + NH_4^+]$, 283 (100) $[M + H^+]$, 223 (10) [M − AcO].

3.9. Synthesis of (1R*,5S*,6S*)-5,6-bis[(N,N-dimethylamino)methyl]cyclohex-2-en-1-ol (2)

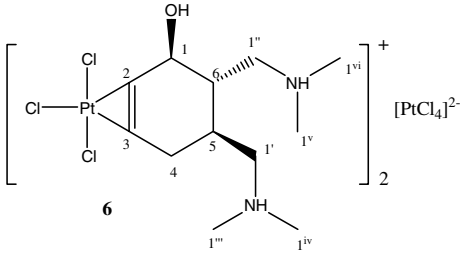
A solution of diamide **17** (56 mg, 0.20 mmol) in dry tetrahydrofuran (2 mL) was added to a suspension of lithium aluminium hydride (13 mg, 0.36 mmol) in anhydrous ether (1 mL). The mixture was refluxed for 1 h and then it was quenched by cautious successive addition of water (0.025 mL), 15% NaOH aqueous solution (0.025 mL) and water again (0.08 mL). A fine white precipitate formed which was filtered off, washed with ether and discarded. The filtrate was concentrated to dryness resulting in a yellow oil (Yield: 38.2 mg, 90%). Anal. Found: C, 67.86; H, 11.40; N, 13.22. Calc. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19% IR (cm^{-1}): 3224 (O–H, st), 3025, 2944, 2847, 2819, 2768, 1651, 1485, 1460, 1263, 1150, 1067, 1041; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.70–1.78 (2H, m, H5, H6), 1.93–1.99 (1H, m, H4a), 2.02–2.06 (1H, m, H4b), 2.16 (6H, s, H1‴, $H1^{iv}$), 2.17–2.22 (3H, m, H1′, H1a″), 2.24 (6H, s, $H1^{v}$, $H1^{vi}$), 2.81 (1H, dd, $J_1 = J_2 = 12.5$ Hz, H1b″), 4.23 (1H, s, H1), 5.46–5.70 (2H, m, H2, H3); ^{13}C NMR (50 MHz, CD_3 OD, δ in ppm): 25.5 (C4), 33.5 (C5), 34.6 (C6), 45.5 (C1‴), 45.6 ($C1^{iv}$), 45.7 ($C1^{v}$), 45.8 ($C1^{vi}$), 61.4 (C1″), 63.1 (C1′), 66.7 (C1), 124.5 (C3), 130.33 (C2); MS (70 eV, DIP–CI–NH_3, m/z, %): 168 (1) $[M - NMe_2]$, 212 (1) [M], 214 (100) $[M + 2H^+]$.

3.10. Synthesis of cis-trichloro-η^2-{N,N-dimethyl-1-[6-(N,N-dimethylammonium-methyl)-ciclohex-3-ene-1-yl]-methyl-ammonium} platinum(II) chloride (5)



A solution of the ligand **1** (98.0 mg, 0.5 mmol) in water (7 mL) and hydrochloric acid 1 M (2 mL) were added to a solution of K_2 [$PtCl_4$] (207.5 mg, 0.5 mmol) in water (10 mL). The mixture was stirred at room temperature for two days. A yellow crystalline solid formed and it was filtered out, washed with cold distilled water and dried under vacuum. Slow evaporation of water from the mother liquor produced additional yellow crystals, which were filtered out (Overall yield 131 mg, 49%). mp = 228–230 °C. Anal. Found: C, 27.29; H, 5.44; N 5.22. Calc. for $C_{12}H_{26}Cl_4N_2$ Pt: C, 26.93; H, 4.90; N, 5.23%. IR (cm^{-1}): 3442, 3021, 2969, 2734, 2641, 2589, 2518, 2483, 1624, 1483, 1420. ^1H NMR (500 MHz, [D_6] DMSO, δ in ppm): 1.94 (2H, dd, $J_1 = 16.1$ Hz, $J_2 = 6.0$ Hz, H2b′, H5′a), 2.19 (2H, dd, $J_1 = 16.5$ Hz, $J_2 = 4.0$ Hz, H2a′, H5′a), 2.98 (2H, s; H1′, H2′), 2.77 (12H, s, H1‴, $H1^{iv}$, $H1^{v}$, $H1^{vi}$), 2.89–2.92 (2H, m, H1a, H1a″), 3.17–3.19 (2H, m, H1b, H1b″), 5.65 (2H, s, H3′, H4′), 10.15 (2H, s, NH). FAB-MS [FAB(+), NBA, CH_3–CN as solvent, m/z]: 429 (35), 460 (28), 488 (10), 514 (12), 577 (100).

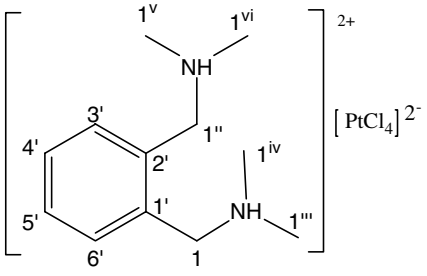
3.11. Synthesis of {(1S*,5S*,6S*)-trichloro-η^2[-5,6-bis(N,N-dimethylammonium-methyl)-cyclohex-2-en-1-ol]platinum (II)} tetrachloroplatinate(II) (6)



A solution of the ligand **2** (106 mg, 0.5 mmol) in water (10 mL) and hydrochloric acid 1 M (2 mL) were added to a solution of K_2[$PtCl_4$] (207 mg, 0.5 mmol) in water (10 mL). The solution was stirred at room temperature for four days. The orange solid formed was

filtered out, washed with cold distilled water and dried under vacuum (Yield: 60 mg, 18%). mp = 210–212 °C (decomp.). Anal. Found: C, 20.74; H, 3.93; N, 3.96. Calc. for $C_{24}H_{52}Cl_{10}N_4O_2Pt_3$: C 21.06%, H 3.83; N 4.09%. IR (cm^{-1}): 3451, 3035, 2980, 2749, 1643, 1501, 1470, 1395, 1007, 947. ^1H NMR (300 MHz, [D_6] DMSO, δ in ppm): 1.96–2.01 (2H, m, H_4), 2.15 (1H, s, H6), 2.26–2.31 (1H, m, H5), 2.81 (12H, s, H1‴, $H1^{iv}$, $H1^{v}$, $H1^{vi}$), 3.06–3.07 (4H, m, H1′, H1″), 3.98 (1H, s, H1), 5.47 (1H, s, OH), 5.70 (2H, s, H2, H3), 9.49 (1H, s, NH), 9.72 (1H, s, NH). FAB-MS [FAB(+), NBA, *m*/*z*]: 346 (70); 385 (30), 423 (58) [M − Cl-4Me], 443 (52), 460 (100), 479 (20) [M − Cl], 482 (25), 499 (28), 538 (30), 554 [M − Cl+NBA], 575 (90), 593 (20) [M − 2Cl + NBA]. Conductivity measurements: Λ_M = 138.6 Ω^{-1} cm^2 mol^{-1} for a concentration 10^{-3} M in DMF.

3.12. Synthesis of {N,N-dimethyl-1-[(2-(N,N-dimethyl-ammonium-methyl)-1-phenyl-]-methylammonium} tetrachloroplatinate(II) (7)



7

A solution of the ligand **3** (96.0 mg, 0.5 mmol) in water (5 mL) and hydrochloric acid 1 M (2 mL) was added to a solution of $K_2[PtCl_4]$ (207 mg, 0.5 mmol) in water (7 mL). The reaction mixture was stirred at room temperature for 2 h. The orange solid formed was filtered off, washed with cold distilled water and dried under vacuum. Slow concentration of the filtrate produced additional crystals, which were filtered off, affording an overall yield of 201 mg, 76%. mp = 224–226 °C (decomp.). Anal. Found: C, 27.34; H, 4.28; N, 5.16. Calc. for $C_{12}H_{22}Cl_4N_2Pt$: C, 27.12; H, 4.14; N, 5.27%. IR (cm^{-1}): 3451, 3035, 2980, 2749, 1643, 1501, 1470, 1395, 1007, 947. ^1H NMR (300 MHz, [D_6] DMSO, δ in ppm): 2.76 (12H, d, $J = 3.2$ Hz, H1‴, $H1^{iv}$, $H1^{v}$, $H1^{vi}$), 4.53 (4H, d, $J = 3.8$ Hz, H1, H1″), 7.57 (2H, dd, $J_1 = 3.8$ Hz, $J_2 = 2.2$ Hz, H3′, H6′), 7.74 (2H, $J_1 = 3.7$ Hz, $J_2 = 2.3$ Hz, H4′, H5′), 10.44 (2H, s, NH). FAB-MS [FAB(+), NBA, *m*/*z*]: 360 (22), 385 (20), 423 (30), 460 (18), 470 (20), 555 (22), 593 (100).

3.13. X-ray diffraction analysis

Suitable crystals ($0.1 \times 0.1 \times 0.2$ mm) from compounds **5** and **7** were selected and mounted on a MAR345 apparatus with image plate detector. Unit-cell parameters were determined from automatic centring of reflections and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. Lorentz-polarization and absorption corrections were made.

The structure was solved by direct methods and refined by full-matrix least-squares method using SHELXS-97 computer program [17], on the basis of the non-equivalent reflections by symmetry (very negative intensities were not assumed). The function minimized was: $\sum w[(F_o)^2 - (F_c)^2]^2$, where $w = [\sigma^2(I) + (0.0745P)^2 + 0.4463P)^{-1}]$, and $P = [(F_o)^2 + 2(F_c)^2]/3$; f, f' and f'' were taken from the International Tables of X-ray Crystallography [18]. All the H atoms were computed and refined, using a riding model, with isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom which are linked. The final R (on F) factors and goodness of fit are shown in Table 2. Number of refined parameters was 127. Maximum shift/esd = 0.00. Mean shift/esd = 0.00. Refinement of F^2 was done against all reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt), etc., and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on all data will be even larger. All esds (except the esd in the dihedral angle between two least square planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving least square planes.

Hydrogen coordinates as well as anisotropic thermal parameters are included as supplementary material. Detailed information about the crystal structure determination of compounds **5** and **7** is given as supporting information which has been deposited with the Cambridge Crystallographic Data Centre.

4. Supplementary materials

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 268228 and 268229 for

compounds **5** and **7**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ UK [fax (int code): +44 1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk].

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