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SYNTHESIS AND PROPERTIES OF DIAMINE(ISOPROPYLIDENEMALONATO) PLATINUM(II): CRYSTAL STRUCTURE OF $O(CH_2CH_2)_2C(CH_2NH_2)_2Pt(OOC)_2C{=}C(CH_3)_2$

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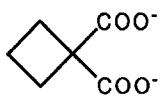
Abstract—New platinum(II) complexes of $A_2Pt(IPM)$ [A_2 = tetrahydro-4H-pyran-4,4-di(methylamine) (THPDMA), 2,2-dimethyl-1,3-propanediamine (DMPDA), *trans*-(±)-diaminocyclohexane (DACH); A = NH_3, isopropylamine (IPA), cyclopropylamine (CPA); IPM = isopropylidenemalonate] have been synthesized and characterized by means of X-ray crystallography and various spectroscopies. The crystal structure of (THPDMA)Pt(IPM)·$5H_2O$ was determined. The platinum atom adopts a typical square planar arrangement with two nitrogen atoms in the *cis* positions. The molecular structures are retained in aqueous solution at room temperature. However, the present complexes change to dimethyl sulphoxide (DMSO) adducts on standing for a long time or increasing temperature in DMSO: the monodentate amine complex produces $(A)(DMSO)Pt(OOC)_2C{=}C(CH_3)_2$, whereas the chelate amine analogue affords $A_2Pt^+(DMSO)(OOC)C(COO^-){=}C(CH_3)_2$.

Carboplatin, $(NH_3)_2Pt(O,O'\text{-CBDC})$ (CBDC = cyclobutanedicarboxylate, **I**), was formally recognized as a second generation platinum anticancer drug in 1989. Carboplatin has fewer side-effects, such as loss of high frequency hearing, and significant renal or neural toxicity, than cisplatin.[1,2] The decreased nephrotoxicity of the complex is known to be related to its greater pharmaco-kinetic stability in solution, because the nephrotoxicity of cisplatin is associated with its active hydrolysis products, which form over a period of minutes.[3] Hydrolysis of the aminoplatinum complex of this chelating dicarboxylate ligand is known to occur far more slowly than the hydrolysis of cisplatin. Accordingly, a great number of platinum(II) complexes of the CBDC ligand have been synthesized and screened as more effective anticancer agents with less nephrotoxicity.[4–7] However, no systematic research for the platinum complexes of isopropylidenemalonate, $(CH_3)_2C{=}C(COO^-)_2$ (**II**), a structural isomer of CBDC, has been carried out.



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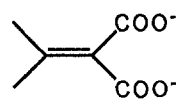

(II)

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In this report, the synthetic and structural aspects of the diamine (isopropylidenemalonato) platinum (II) complexes will be discussed along with their physicochemical properties, including their interaction with dimethyl sulphoxide.

EXPERIMENTAL

Instrumentation and materials

Elemental analysis was performed by the Advanced Analysis Center at KIST. The IR spectra in the 4000–400 cm^{-1} region were measured as KBr pellets on a MIDAC model 101025 FT-IR spectrophotometer. ^1H, ^{13}C and ^{195}Pt NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer operating at 300.00 MHz (^1H), 75.48 MHz (^{13}C) and 64.39 MHz (^{195}Pt) in pulse mode with Fourier transform. The chemical shifts were relative to $SiMe_4$ (^1H and ^{13}C) and Na_2PtCl_6 (^{195}Pt) as an internal or external standard for the indicated nuclei. The mass analysis was achieved on a Platform (Fisons Inst., Manchester, U.K.) equipped with an electro-spray source at 10 dm^3 min^{-1} using a Harvard infusion pump. For the mass analysis, appropriate amounts of samples were dissolved in a solvent mixture of MeOH–water (1 : 1, v/v) containing 1% acetic acid.

Potassium tetrachloroplatinate(II) was purchased from Kojima, and diethyl isopropylidenemalonate and all the amines were from Aldrich, except for THPDMA, which was prepared by the literature method.[8] Diethyl isopropylidenemalonate was converted to the barium salt by the literature procedure.[9] *cis*-Diamineplatinum (II) sulphates were also prepared by the literature method.[10,11]

X-ray crystallography

All the crystallographic data were obtained on an Enraf–Nonius CAD 4 automatic diffractometer with graphite-monochromated molybdenum radiation [λ ($K_{\alpha 1}$) = 0.70930 Å, λ ($K_{\alpha 2}$) = 0.71359 Å] at ambient temperature. A preliminary diffractometric investigation indicated a monoclinic system. Accurate cell dimensions were obtained from the setting angles of 25 well-centred reflections by using a least-squares procedure. During the data collection, three standard reflections monitored every hour did not reveal any systematic variation in intensity. The structure was solved by a conventional heavy atom method, followed by successive difference Fourier synthesis. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated positions and refined only for the isotropic thermal factors. All calculations were carried out on a personal computer with use of SHELXS86 or SHELXL93. Crystal parameters and procedural information corresponding to data collection and structure refinement are given in Table 1.

Preparation of $A_2Pt(IPM)$

To a suspension of 3.0 mmol of *cis*-A_2PtI_2 (A_2 = THPDMA, DMPDA, DACH; A = IPA, NH_3, CPA) in 50 cm^3 of water was added 0.94 g of silver sulphate (3.0 mmol) in 100 cm^3 of water. The reaction solution was stirred for 6 h and then the silver iodide formed was filtered off. An equimolar solution of $Ba(IPM)\cdot 2H_2O$ (0.95 g) in 50 cm^3 of water was dropped into the filtrate of A_2PtSO_4, and the reaction mixture was stirred for a further 3 h. After barium sulphate was filtered off, the filtrate was condensed to 5 cm^3, to which excess acetone was added to precipitate solid product.

(THPDMA)Pt(IPM). Yield 85%, m.p. 172°C (dec.). ^1H NMR (D_2O, ppm): 1.52 (br, 4H); 1.92 (s, 6H); 2.48(s, 4H); 3.71 (br, 4H). IR (KBr, cm^{-1}): ν_{as} (COO) 1644, 1618; ν_s (COO) 1325. MS: m/z = 482 $[M+H]^+$. Recrystallization of the pro-

Table 1. Crystal parameters and experimental details for (THPDMA)Pt(IPM)

Formula	$C_{13}H_{22}N_2O_4Pt\cdot 5H_2O$
Formula weight	571.10
Space group	$P2_1$
a (Å)	12.473(3)
b (Å)	11.423(1)
c (Å)	14.424(3)
β (°)	96.24(2)
V (Å^3)	2043.1(7)
Z	4
D_{calc}(g cm^{-3})	1.858
Crystal size (mm)	0.2 × 0.2 × 0.3
μ (mm^{-1})	6.92
Scan method	ω–2θ
Data collected	$\pm h, k, l$
Scan range	$3 < 2\theta < 50°$
No. of unique data	3409
No. of reflections used, $F > 4\sigma(F)$	3365
No. of parameters refined	443
Max. in $\Delta\rho$ (e Å^{-3})	0.93
GOF	1.079
R	0.027
R_w2[a]	0.063

[a] $R_w2 = \{\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]\}^{1/2}$.

duct in water gave crystals suitable for X-ray crystallography.

(DMPDA)Pt(IPM). Yield 87%, m.p. 164°C (dec.). Found (calc. for $C_{11}H_{20}N_2O_4Pt \cdot 2H_2O$): C, 27.7 (27.8); H, 5.4 (5.1); N, 6.0 (5.9). ^1H NMR (D_2O, ppm): 0.92 (s, 6H); 1.92 (s, 6H); 2.27 (s, 4H). IR (KBr, cm^{-1}): ν_{as} (COO) 1642, 1599; ν_s (COO) 1387. ^{195}Pt NMR (DMSO, ppm): −1928.

(DACH)Pt(IPM). Yield 82%, m.p. 182°C (dec.). Found (calc. for $C_{12}H_{20}N_2O_4Pt \cdot H_2O$): C, 31.0 (30.7); H, 4.3 (4.7); N, 5.8 (6.0). ^1H NMR (D_2O, ppm): 1.18–1.41 (m, 4H); 1.60–1.64 (m, 2H); 1.99 (s, 6H); 2.05–2.10 (m, 2H); 2.39–2.42 (m, 2H). IR (KBr, cm^{-1}): ν_{as} (COO) 1640, 1611; ν_s (COO) 1346. MS: $m/z = 452$ $[M+H]^+$.

$(IPA)_2Pt(IPM)$. Yield 75%, m.p. 119°C (dec.). Found (calc. for $C_{12}H_{24}N_2O_4Pt \cdot H_2O$): C, 30.1 (30.4); H, 5.3 (5.5); N, 5.9 (5.9). ^1H NMR (D_2O, ppm): 1.32 (d, 12H); 1.98 (s, 6H); 2.95 (m, 2H). IR (KBr, cm^{-1}): ν_{as} (COO) 1644, 1588; ν_s (COO) 1368. ^{195}Pt NMR (DMSO, ppm): −1815. MS: $m/z = 456$ $[M+H]^+$.

$(NH_3)_2Pt(IPM)$. Yield 89%, m.p. 165°C (dec.). Found (calc. for $C_6H_{12}N_2O_4Pt$): C, 19.2 (19.4); H, 3.2 (3.3); N, 7.3 (7.6). ^1H NMR (D_2O, ppm): 1.95(s, 6H). IR (KBr, cm^{-1}): ν_{as} (COO) 1638; ν_s (COO) 1348. MS: $m/z = 372$ $[M+H]^+$.

$(CPA)_2Pt(IPM)$. Yield 72%, m. p. 126°C (dec.). Found (calc. for $C_{12}H_{20}N_2O_4Pt \cdot H_2O$): C, 30.9 (30.7); H, 4.1 (4.7); N, 5.6 (6.0). ^1H NMR (D_2O, ppm): 0.53–0.70 (m, 8H); 1.90 (s, 6H); 2.25 (m, 2H). IR (KBr, cm^{-1}): ν_{as} (COO) 1640, 1601; ν_s (COO) 1368.

RESULTS AND DISCUSSION

Synthesis

The reaction of diamineplatinum(II) sulphate with barium isopropylidenemalonate in water afforded the title complexes according to the general method shown in eqs (1) and (2). All these platinum complexes were established by chemical analyses and spectroscopic data along with the X-ray crystal structure for the THPDMA complex.

$$A_2PtI_2 + Ag_2SO_4 \xrightarrow[R.T.]{H_2O} A_2PtSO_4 + 2AgI \quad (1)$$

$$A_2PtSO_4 + Ba(IPM) \xrightarrow[R.T.]{H_2O} A_2Pt(IPM) + BaSO_4 \quad (2)$$

A_2 = THPDMA, DMPDA, DACH;

A = IPA, NH_3, CPA

All the present complexes were obtained as white or light yellow crystalline solids which are fairly air-stable up to 119–182°C. They are moderately soluble in water and stable in solution at room temperature.

Crystal structure

There are two independent complex molecules in the asymmetric region of the monoclinic unit cell and the features of the two molecules are identical within error limits. The molecular structure and labelling scheme for (THPDMA)Pt(IPM) is shown in Fig. 1. Bond distances and bond angles are listed in Table 2. The local geometry around the platinum atom is approximately square planar: Pt—N(1), Pt—N(2), Pt—O(1) and Pt—O(2) distances are 1.999(9), 2.007(8), 2.024(7) and 2.041(7) Å, respectively, and bond angles N(2)—Pt—N(1), N(1)—Pt—O(2), N(2)—Pt—O(1) and O(2)—Pt—O(1) are 94.9(4), 176.2(4), 177.3(4) and 92.4(3)°, respectively. Both THPDMA and IPM ligands are coordinated to the platinum atom in a bidentate fashion

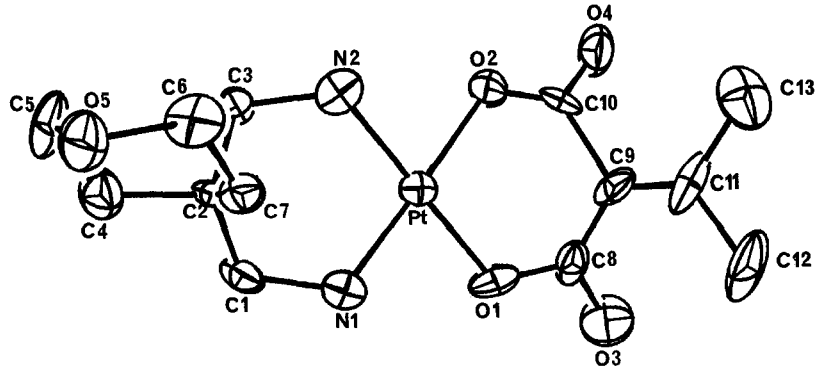

Fig. 1. ORTEP drawing of (THPDMA)Pt(IPM) along with the atomic labelling scheme. Molecule 2, hydrogen atoms and solvated molecules are omitted for clarity.

Table 2. Selected bond distances (Å) and bond angles (°) for (THPDMA)Pt(IPM)

Pt(1)—O(1)	2.024(7)	Pt(1)—O(2)	2.041(7)
Pt(1)—N(1)	1.999(9)	Pt(1)—N(2)	2.007(8)
O(1)—C(8)	1.30(2)	O(2)—C(10)	1.27(1)
O(3)—C(8)	1.20(1)	O(4)—C(10)	1.22(1)
N(1)—C(1)	1.47(2)	N(2)—C(3)	1.49(1)
C(1)—C(2)	1.54(1)	C(2)—C(3)	1.55(1)
C(2)—C(4)	1.52(2)	C(2)—C(7)	1.52(2)
C(4)—C(5)	1.50(2)	C(5)—O(5)	1.46(2)
O(5)—C(6)	1.42(2)	C(6)—C(7)	1.52(1)
C(8)—C(9)	1.50(2)	C(9)—C(10)	1.51(2)
C(9)—C(11)	1.36(2)	C(11)—C(12)	1.47(2)
C(11)—C(13)	1.48(2)	Pt(2)—O(21)	2.003(7)
Pt(2)—O(22)	2.010(8)	Pt(2)—N(21)	2.039(8)
Pt(2)—N(22)	2.038(9)	O(21)—C(30)	1.30(1)
O(22)—C(28)	1.25(2)	O(23)—C(28)	1.24(1)
O(24)—C(30)	1.22(1)	N(21)—C(21)	1.49(1)
N(22)—C(23)	1.47(2)	C(21)—C(22)	1.53(2)
C(22)—C(23)	1.53(2)	C(22)—C(24)	1.56(1)
C(22)—C(27)	1.55(2)	C(24)—C(25)	1.51(2)
C(25)—O(25)	1.42(1)	O(25)—C(26)	1.43(2)
C(26)—C(27)	1.53(2)	C(28)—C(29)	1.50(2)
C(29)—C(30)	1.51(2)	C(29)—C(31)	1.35(2)
C(31)—C(32)	1.47(2)	C(31)—C(33)	1.50(2)

O(2)—Pt(1)—O(1)	92.4(3)	O(3)—C(8)—O(1)	120.3(11)
O(4)—C(10)—O(2)	120.5(10)	N(1)—Pt(1)—O(1)	86.8(4)
N(1)—Pt(1)—O(2)	176.2(4)	N(2)—Pt(1)—O(1)	177.3(4)
N(2)—Pt(1)—O(2)	85.8(3)	N(2)—Pt(1)—N(1)	94.9(4)
C(1)—N(1)—Pt(1)	120.4(7)	C(2)—C(1)—N(1)	114.8(9)
C(2)—C(3)—N(2)	113.6(8)	C(3)—N(2)—Pt(1)	120.1(6)
C(3)—C(2)—C(1)	110.7(9)	C(4)—C(2)—C(1)	107.6(9)
C(4)—C(2)—C(3)	108.0(9)	C(5)—C(4)—C(2)	114.9(10)
O(5)—C(5)—C(4)	110.6(9)	C(6)—O(5)—C(5)	109.6(9)
C(6)—C(7)—C(2)	113.5(9)	C(7)—C(2)—C(1)	109.8(9)
C(7)—C(2)—C(3)	112.4(8)	C(7)—C(2)—C(4)	108.2(9)
C(7)—C(6)—O(5)	110.4(9)	C(8)—O(1)—Pt(1)	123.5(7)
C(9)—C(8)—O(1)	117.9(10)	C(9)—C(8)—O(3)	121.7(12)
C(9)—C(10)—O(2)	118.2(9)	C(9)—C(10)—O(4)	121.3(10)
C(10)—O(2)—Pt(1)	123.7(6)	C(10)—C(9)—C(8)	117.1(9)
C(11)—C(9)—C(8)	120.8(10)	C(11)—C(9)—C(10)	122.0(10)
C(12)—C(11)—C(9)	124.1(13)	C(13)—C(11)—C(9)	121.9(12)
C(13)—C(11)—C(12)	113.8(13)	O(22)—Pt(2)—O(21)	92.4(3)
O(23)—C(28)—O(22)	124.2(11)	O(24)—C(30)—O(21)	118.9(10)
N(21)—Pt(2)—O(21)	84.8(3)	N(21)—Pt(2)—O(22)	176.3(4)
N(22)—Pt(2)—O(21)	177.1(4)	N(22)—Pt(2)—O(22)	87.5(4)
N(22)—Pt(2)—N(21)	95.2(4)	C(21)—N(21)—Pt(2)	118.3(6)
C(22)—C(21)—N(21)	115.3(9)	C(22)—C(23)—N(22)	114.4(9)
C(23)—N(22)—Pt(2)	118.9(8)	C(23)—C(22)—C(21)	110.9(9)
C(24)—C(22)—C(21)	112.2(8)	C(24)—C(22)—C(23)	110.7(9)
C(25)—C(24)—C(22)	111.4(9)	O(25)—C(25)—C(24)	113.0(8)
C(26)—O(25)—C(25)	112.3(8)	C(26)—C(27)—C(22)	114.1(9)
C(27)—C(22)—C(21)	106.7(9)	C(27)—C(22)—C(23)	107.1(9)
C(27)—C(22)—C(24)	109.0(8)	C(27)—C(26)—O(25)	110.2(10)
C(28)—O(22)—Pt(2)	121.8(7)	C(29)—C(28)—O(22)	119.7(9)
C(29)—C(28)—O(23)	116.1(12)	C(29)—C(30)—O(21)	118.0(9)
C(29)—C(30)—O(24)	123.1(10)	C(30)—O(21)—Pt(2)	122.1(6)
C(30)—C(29)—C(28)	116.0(9)	C(31)—C(29)—C(28)	124.1(10)
C(31)—C(29)—C(30)	119.9(10)	C(32)—C(31)—C(29)	124.2(10)
C(33)—C(31)—C(29)	121.5(11)	C(33)—C(31)—C(32)	114.3(11)

in the *cis* position to provide a suitable bite angle. The bite angles N(2)—Pt—N(1) [94.9(4)°] and O(2)—Pt—O(1) [92.4(3)°] are slightly splayed out, with the concomitant closing of N(1)—Pt—O(1) [86.8(4)°] and N(2)—Pt—O(2) [85.8(3)°]. The bite angles of THPDMA and IPM are partly responsible for the slight distortion from a square plane. The bond lengths of C(8)—O(3) [1.20(1) Å] and C(10)—O(4) [1.22(1) Å] are shorter than C(8)—O(1) [1.30(2) Å] and C(10)—O(2) [1.27(1) Å], consistent with typical monodentate carboxylates in other platinum(II) complexes.[12] The conformations of three six-membered rings are typical boat forms. Interestingly, the tetrahydropyran ring of the THPDMA ligand roughly parallels the isopropylidene group of IPM. Even though the IPM ligand is an α, β-unsaturated system, its π electrons are less delocalized, presumably owing to bending between the plane O(1), O(2), C(8), C(10) and the plane C(11), C(9), C(12), C(13). The bond length [1.36(2) Å] of the double bond C(9)=C(11) corresponds to that [1.34 Å] of a general ethylene group.[13] Also, the bond lengths C(8)—C(9) [1.50(2) Å] and C(9)—C(10) [1.51(2) Å] approach a typical single bond.[14]

NMR studies in DMSO solution

For the present complexes, the resonance of the methyl protons of the IPM ligand appears in the range of 1.90–1.99 ppm as a singlet in D_2O, which is shifted downfield by 0.11—0.20 ppm relative to that (1.79 ppm) of Ba(IPM). Such a result indicates that both carboxylate groups are symmetrically coordinated to the platinum atom in aqueous solution. All the complexes are stable for more than 30 days in aqueous solution. However, the complexes in DMSO solution change to DMSO adducts on standing for a long time or heating. In order to investigate the transformation properties of the complexes in DMSO, each NMR spectrum of $(IPA)_2Pt(IPM)$ and (DMPDA)Pt(IPM) was compared with that of the same compound heated up to 90°C. When a solution of $(IPA)_2Pt(IPM)$ [δ (^{195}Pt) = −1815 ppm] was heated to 90°C in DMSO, an additional ^{195}Pt resonance was observed at −2707 ppm, indicating formation of a DMSO adduct. In the case of (DMPDA)Pt(IPM) [δ (^{195}Pt) = −1928 ppm], a new peak was also observed at −2871 ppm in the spectrum of the heated sample. Also, in the ^1H NMR spectra of each heated sample (Fig. 2) additional peaks appear assignable to the protons of each DMSO adduct. For a fresh DMSO solution of $(IPA)_2Pt(IPM)$ (Fig. 2a), the chemical shift of the methyl protons of the IPM ligand appears at 1.75 ppm and the coordinated isopropylamine exhibits resonances at 1.19 ($-CH_3$), 2.80 (=CH—) and 4.96 ppm ($-NH_2$). When this solution was heated, its NMR spectrum (Fig. 2b) shows that the isopropylamine ligand was partially dissociated and a DMSO adduct was formed. A DMSO molecule seems to replace one of the two isopropylamine ligands of the complex. The chemical shifts at 0.95 ($-CH_3$), 2.97 (=CH—) and 5.13 ppm ($-NH_2$) were confirmed to be ascribed to the dissociated free IPA.

In the (DMPDA)Pt(IPM) system, the proton resonances of the chelating amine ligand appear at 0.76 ($-CH_3$), 2.01 ($-CH_2-$) and 5.27 ppm ($-NH_2$) before heating (Fig. 2c), but after heating (Fig. 2d), new resonances were also observed, which may be attributed to an unsymmetrical DMSO adduct partially decarboxylated by heating.

The ^{13}C NMR spectra of the carboxylate group of the heated samples also exhibit an important feature of the structure of the DMSO adducts (Fig. 3). The spectrum of heated $(IPA)_2Pt(IPM)$ shows two ^{13}C resonances at 174.89 and 174.74 ppm for the carboxylate group, which indicates that both carboxylates are unsymmetrically coordinated to the platinum atom. In contrast, the chemical shifts at 182.90 and 176.54 ppm for heated (DMPDA)Pt (IPM) suggest that uncoordinated (182.90 ppm) and coordinated (186.54 ppm) carboxylate groups co-exist.[12] Thus, the DMSO solution of $(IPA)_2Pt$ (IPM) produces free IPA and (IPA)(DMSO)Pt (IPM), whereas that of (DMPDA)Pt (IPM) affords $(DMPDA)Pt^+(DMSO)(OOC)C(COO^-)=C(CH_3)_2$ on standing for a long time or increasing temperature, according to scheme I.

In conclusion, the molecular structures of diamine (isopropylidenemalonato)platinum(II) complexes are maintained in aqueous solution at room temperature. However, these complexes change to DMSO adducts on standing for a long time or increasing the temperature in DMSO solution: the monodentate amine complex produces partially deaminated $(A)(DMSO)Pt(OOC)_2C=C(CH_3)_2$, whereas the chelate amine analogue affords partially decarboxylated $A_2Pt^+(DMSO)(OOC)C(COO^-)=C(CH_3)_2$. Such results indicate that caution should be taken when preparing sample solutions of platinum complexes for efficacy testing if DMSO is used in combination with water as a solubilizing agent.

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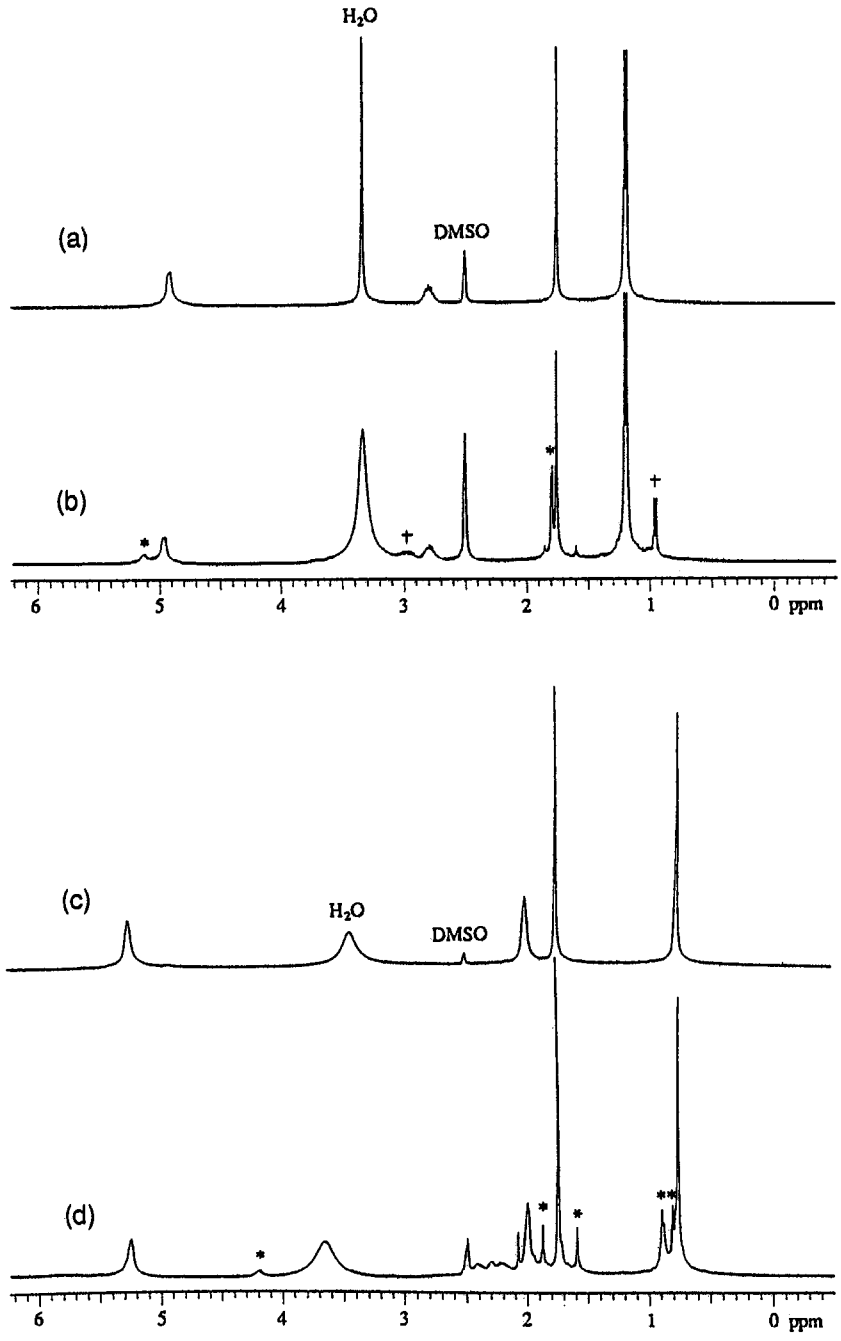


Fig. 2. ^{1}H NMR spectra of $(IPA)_2Pt(IPM)$ in DMSO before (a) and after heating (b) [asterisk represents the spectrum of (IPA)(DMSO)Pt(IPM); dagger represents dissociated free IPA], and of (DMPDA)Pt(IPM) in DMSO before (c) and after heating (d) [asterisk represents the spectrum of $(DMPDA)Pt^+(DMSO)(OOC)C(COO^-)=C(CH_3)_2$].

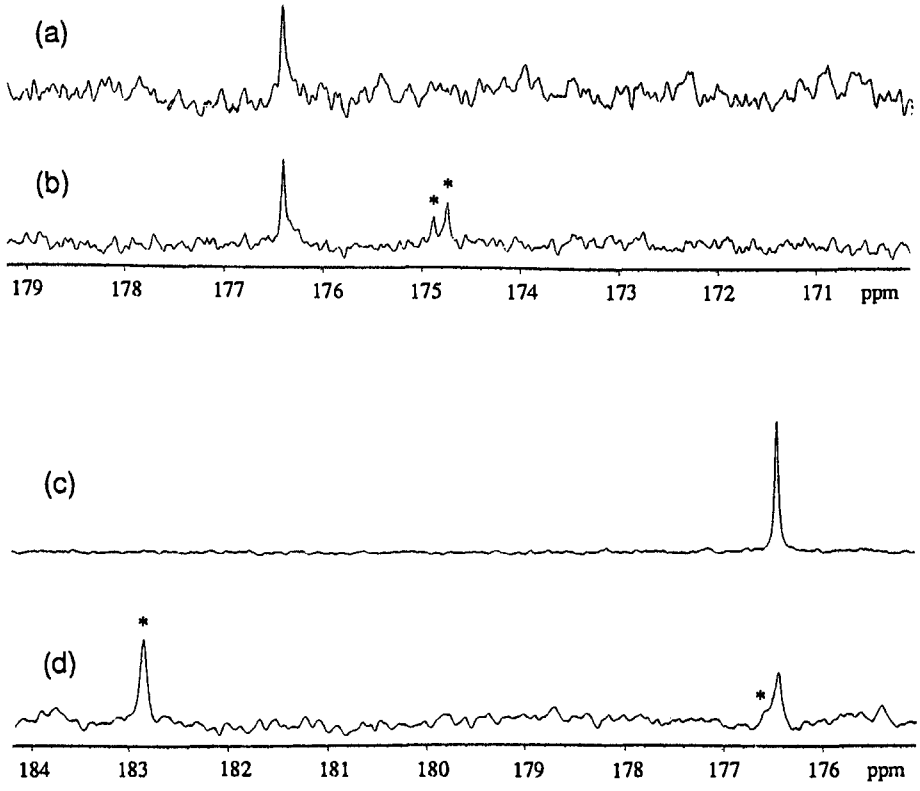
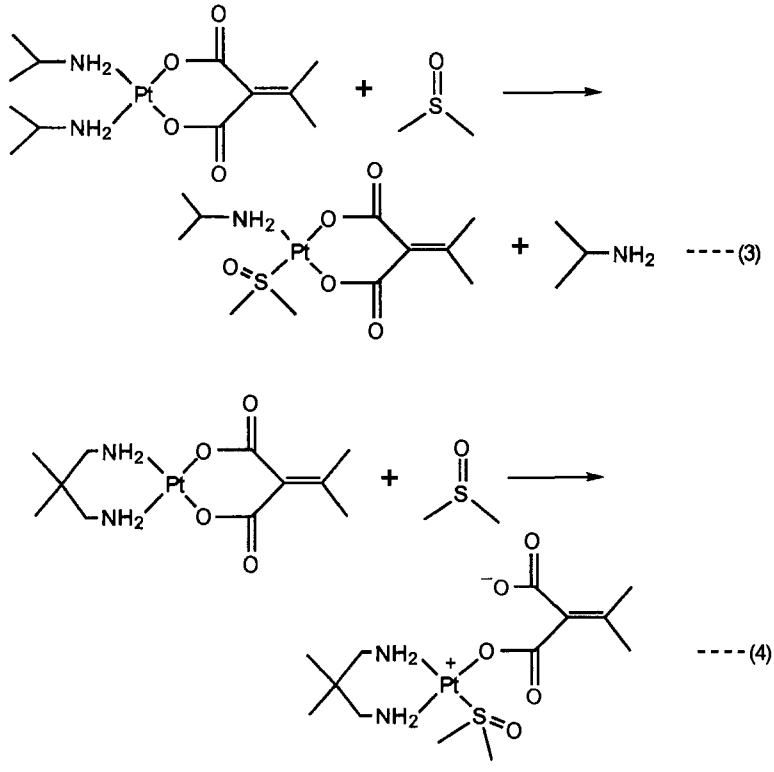


Fig. 3. ^{13}C NMR spectra of carboxylate group of $(IPA)_2Pt(IPM)$ in DMSO before (a) and after heating (b) [asterisk represents the spectrum of (IPA)(DMSO)Pt(IPM)], and of (DMPDA)Pt(IPM) in DMSO before (c) and after heating (d) [asterisk represents the spectrum of $(DMPDA)Pt^+(DMSO)(OOC)C(COO^-)=C(CH_3)_2$].



Scheme I.

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