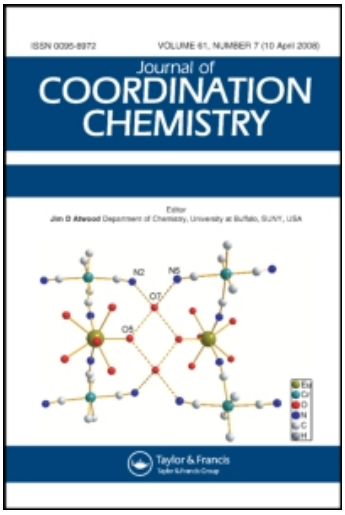

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Synthesis and Characterization of a Series of Water Soluble Amidomalonato-(lR,2R-Cyclohexanediamine)Platinum(II) Complexes

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SYNTHESIS AND CHARACTERIZATION OF A SERIES OF WATER SOLUBLE AMIDOMALONATO-(1*R*,2*R*-CYCLOHEXANEDIAMINE)PLATINUM(II) COMPLEXES

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A new series of water soluble platinum(II) complexes of the type [Pt(DACH)[R-CH(COO)$_2$]], wherein DACH represents 1*R*,2*R*-cyclohexanediamine and R represents formamido, acetamido, (penta-*O*-acetylgluconyl)amino, and gluconylamino have been synthesized. The modes of binding of amidodicarboxylic acid derivatives in these complexes have been determined by various spectroscopic techniques: ^{1}H, ^{13}C, and ^{195}PtNMR; 2D-COSY{^{1}H–^{1}H} and 2D-HETCOSY{^{1}H–^{13}C} NMR, MS(FAB), IR and conductivity measurements.

Keywords: Platinum(II) complexes, diamine, bioactivity, NMR, IR

INTRODUCTION

Cis-dichlorodiammineplatinum(II) (*cis*-DDP) is one of the most widely used anticancer drugs, either alone or in combination with chemotherapy.[1–3] However, its clinical applications are compromised by its dose limiting nephrotoxicty, nausea and vomiting, ototoxicity, neurotoxicity, and myelotoxicity.[4,5]

Investigators have attempted to develop new platinum complexes with a broader spectrum of antitumor activity, improved therapeutic indices, lower toxic side effects, and in particular, higher water solubility than *cis*-DDP. Numerous new platinum derivatives of the form *cis*-PtA_2X_2, wherein A_2 represents two monodentate or one bidentate amine ligand and X_2 represents two monodentate or one bidentate anionic ligand, have been synthesized and evaluated in preclinical animal studies.[6–9] Although most of the second generation platinum complexes are less nephrotoxic than the parent cisplatin, myelosuppression remains an important dose-limiting toxicity.

In an effort to reduce both nephrotoxicity and myelotoxicity, we have synthesized a new series of platinum(II) complexes of the general formula I.

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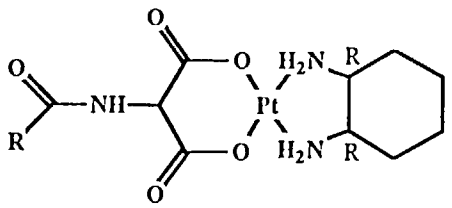


(I)

1)*R,R*-FMP	R = H
2)*R,R*-AMP	R = CH_3
3)*R,R*-AG-AMP	R = $H(CHOAc)_5$
4)*R,R*-G-AMP	R = $H(CHOH)_5$

Structure I contains 1*R*,2*R*-cyclohexanediamine (*R,R*-DACH) as its non-leaving group. In preclinical systems, DACH-platinum complexes have received special attention because of their lack of cross-resistance with *cis*-DDP and lower nephrotoxicity.[10] The anionic leaving group in structure I is a substituted malonic acid. Dicarboxylic acid ligand leaving groups that can form a five or six member ring chelation to platinum are the most chemically stable platinum complexes.[11] We report here the synthesis and characterization of four such complexes, *cis*-(acetamidomalonato-*O,O'*)(1*R*,2*R*-cyclohexanediamine-*N,N'*)platinum(II) (*R,R*-AMP, **1**), *cis*-(formamidomalonato-*O,O'*)(1*R*,2*R*-cyclohexanediamine-*N,N'*)platinum(II) (*R,R*-FMP, **2**), *cis*-[(penta-*O*-acetylgluconyl)aminomalonato-*O,O'*)](1*R*,2*R*-cyclohexanediamine-*N,N'*)platinum(II), (*R,R*-AG-AMP, **3**), and *cis*-(gluconylaminomalonato-*O,O'*)(1*R*,2*R*-cyclohexanediamine-*N,N'*)platinum(II), (*R,R*-G-AMP, **4**).

EXPERIMENTAL

Measurements

Melting (decomposition) points, uncorrected, were determined on a Gallenkamp MF-370 instrument. IR spectra were run as KBr pellets on a Nicolet-FT 170SX spectrometer. The 64.52 MHz ^{195}Pt, 75.46 MHz ^{13}C, and 300.13 MHz ^{1}H nmr spectra were run on a Bruker AM-300 WB spectrometer using a 10 mm tunable probe (a 5 mm probe for ^{1}H, and ^{13}C). An internal lock on the deuterium solvent, D_2O, DMF-d_7, and/or DMSO-d_6 was used. Except for ^{1}H, other nuclei were proton-decoupled. The ^{195}Pt spectra were obtained operating at a spectral width of 50,000 Hz, pulse width of 4 μs, acquisition time of 0.082 ms, and 15,000 to 50,000 scans. Chemical shifts are reported in ppm units, and are relative to internal tetramethylsilane (TMS) for DMF-d_7 and DMSO-d_6, and sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (Tier salt) for D_2O, and to a separate sample of Na_2PtCl_6 (0.5 g in 3 cm^3 of D_2O) for ^{195}Pt. HPLC assays were carried out with a Waters 6000 high-pressure liquid chromatograph operating at 230 nm using a Waters Microbond pack C_{18} column (3.9 × 300 mn) and a mobile phase (isocratic elution) of 5 mM hexanesulfonic acid sodium salt at a flow rate of 1.5 cm^3/min. Molar conductivities were determined using an Amber Science model 4603 solution analyzer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Materials

K_2PtCl_4 was purchased from Strem Chemicals (Newburyport, MA); 1*R*,2*R*-cyclohexanediamine (*R*,*R*-DACH) was obtained from Alfa Chemicals (Danvers, MA) and used as received. Diethylacetamido-, diethylformamido-, and diethylaminomalonate were purchased from Aldrich (Milwaukee, WI). All solvents are reagent grade and were used without further purification.

SYNTHESES

Preparation of dicarboxylic acid ligands.

Amino-, acetamido-, and formamidomalonic acids were prepared by reacting the corresponding diethyl malonate with 0.1 M barium hydroxide in methanol at room temperature for 2 to 6 hr, and then with 1 M sulfuric acid.

Aminomalonic Acid: crystalline white solid; mp 130–131 (foaming); yield 82%; IR 3550–2357 (carboxylic OH), 1706 (carboxylic C=O), 1606 (C=O of COO^-), 1378, 1228, 1109, 900.

Acetamidomalonic Acid: crystalline white solid; mp 132–133 (dec.); yield 88%, IR 3369 (amide NH), 3500–2300 (carboxylic OH), 1735 (carboxylic C=O) 1713 (amide C=O), 1533 (amide NH overtone), 1227 (carboxylic C–O).

Formamidomalonic Acid: crystalline white solid; mp 116–118 (dec.); yield 86%; IR 3386 (amide NH), 3500–2300 (carboxylic OH), 1760 (carboxylic C=O), 1696 (amide C=O), 1527 (amide NH overtone), 1307, 1181.

(Penta-*O*-acetylgluconyl)aminopropanedioic acid was prepared by reacting a solution of 7.2 g aminomalonic acid (0.060 mol) with 8.6 g of penta-*O*-acetylgluconyl chloride (0.020 mol) in the presence of diisopropylethylamine in a mixture of water and acetonitrile. After the reaction mixture was stirred for 3 hr at room temperature, the acetonitrile was removed under reduced pressure and the water solution was made basic with a saturated solution of sodium bicarbonate. This basic solution was washed with chloroform. The aqueous layer was then made acidic using 3.0 M HCl and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure to give 8.0 g of pure (penta-*O*-acetylgluconyl)aminopropanedioic acid (79% yield). IR 3402 (amide NH), 3704–2450 (carboxylic OH), 1750 (carboxylic and acetyl C=O), 1531 (amide NH overtone), 1218 (carboxylic C–O).

Preparation of gluconylaminopropanedioic acid

To a solution of 11.5 g (0.0227 mol) of (penta-*O*-acetylgluconyl)aminopropanedioic acid in 102 cm^3 of a 1:2 water-methanol mixture were added 34 cm^3 of triethylamine. The resultant mixture was stirred under a positive nitrogen atmosphere at room temperature for 24 hr. The solvent mixture was then removed and the residue was redissolved in 20 cm^3 of water and treated with Amberlite IR-120(H^+). After removal of the resin, the solution was evaporated to dryness to give the deacetylated product as a white foam (5.6 g, 83% yield). IR 3420–3391 (alcoholic OH and amide NH), 3500–2337 (carboxylic OH), 1729 (carboxylic C=O), 1637 (amide C=O), 1531 (amide NH overtone), 1225 (carboxylic C–O).

Preparation of Complexes

General Procedure for the Synthesis of cis-*(Amidomalonato*-O,O′*) (1*R,2R*-cyclo-*

hexanediamine-N,N′*)platinum(II), complexes* **1–3**, *and* cis-*(2-gluconylamino-malonato*-O,O′*)(1*R,2R-*cyclohexanediamine*-N,N′*)platinum(II),* **4**

To a freshly prepared solution of K_2PtCl_4 was added an equimolar amount of 1*R*,2*R*-cyclohexanediamine in distilled water. The mixture was reacted at room temperature under a nitrogen atmosphere protected from light for 8 hr. The resultant yellow precipitate was then washed successively with 10% HCl, H_2O, ethanol, acetone, and ether. After drying *in vacuo* over P_2O_5 overnight, the *cis*-dichloro(1*R*,2*R*-cyclohexanediamine-*N*,*N*′)platinum(II) was stirred with an equimolar amount of silver sulfate in distilled, degassed water under a nitrogen atmosphere for 24 hr in the dark. Silver chloride precipitate was removed by filtration and the filtrate was freeze dried to give faintly yellow *cis*-sulfato-DAC-platinum(II) in 90% yield. Addition of *cis*-sulfato-DAC-platinum(II) to a stoichiometric amount of barium 2-(gluconylamino)malonate (prepared *in situ*) resulted in the immediate precipitation of $BaSO_4$. The mixture was stirred at room temperature under nitrogen for 2 hr in the dark, filtered, and the filtrate was concentrated to about 2 cm^3. Addition of acetone or ethanol to this concentrated solution resulted in the precipitation of the platinum complex. The white platinum solid (**4**) was successively washed with ethanol, acetone and ether and dried *in vacuo* over P_2O_5. Decomposition point 182°C; IR 3100–3300 (NH), 2929 and 2858 (CH, CH_2), 1672 (amide C=O), 1651 (coordinated carboxyl C=O), 1388 (C–O). ^{1}H NMR (DMF-d_7): δ 8.04(d, 1H, –C(=O)NH, J_{NH-CH} = 7.31 Hz), 6.38 (dd, 2H, NH_2), 6.15 (bs, 1H, OH), 5.76 (d, 1H, CH, J_{NH-CH} = 7.31 Hz), 5.62 (m, 2H, NH_2), 5.03 (bs, 1H, OH), 4.79 (bs, 1H, OH), 4.66 (bs, 1H, OH), 4.53 (bs, 1H, OH), 3.5–4.4 (several overlapping m, 6H, sugar), 2.63 (bs, 2H, H_1+H_2), [2.20 (ud, 2H) and 1.61 (m, 2H), (H_3+H_6)], [1.70 (ud, 2H) and 1.31 (m, 2H), (H_4+H_5)]. ^{13}C NMR (DMF-d_7): δ 172.10, 171.54, 171.18 (carboxylates and amide (C=O)), 73.61, 71.84, 71.46, 70.53 and 63.72 (sugar), 62.50 (C_2), 62.20 (C_1), 58.62 ($C_{2'}$), 31.49 (C_3+C_6), 23.95 (C_4+C_5). *Anal.*; Calc. for $C_{15}H_{27}N_3O_{10}Pt.2H_2O$: C, 28.13; H, 4.88; N, 6.56%. Found: C, 28.38; H, 5.00; N, 6.47%.

Preparation of R,R-*AMP,* **1**

R,*R*-AMP was prepared in the same manner as described above and was recrystallized from DMF- ether in 70% yield. Decomp. point 246°C; IR 3200–3240 (NH), 2931, 2853 (CH, CH_2), 1617 (amide CO), 1645 (coordinated carboxyl C=O), 1400 (C–O). ^{1}H NMR (DMSO-d_6): δ 7.65 (d, 1H, –(C=O)NH, J_{NH-CH} = 8.18 Hz), 6.03 (dd, 2H, NH_2), 5.57 (d, 1H, CH, J_{NH-CH} = 8.18 Hz), 5.38 (dist. t, 2H, NH_2), 2.08 (bs, 2H, H_1+H_2), [1.82 (bd, 2H) and 1.20 (m, 2H), (H_3+H_6)], [1.45 (bd, 2H) and 1.02 (m, 2H), (H_4+H_5)]. ^{13}C NMR(D_2O): δ 176.73 and 176.48 (amido and carboxylate (C=O)), 65.56 (C_2), 65.41 (C_1), 61.84 ($C_{2'}$), 34.57 and 34.49 (C_3+C_6), 26.66 (C_4+C_5), 24.53 (CH_3 of acetamido). *Anal.*; Calc. for $C_{11}H_{19}N_3O_5Pt$: C, 28.20; H, 4.08; N, 8.97%. Found: C, 28.26; H, 4.38; N, 9.03%.

Preparation of R,R-*FMP,* **2**

This was prepared as for **4** and recrystallized from water–ethanol in 65% yield. Decomp. point 214 °C; IR 3063–3289 (NH), 2950, 2922 (CH, CH_2), 1683, 1563 (amide C=O), 1640 (coordinated carboxyl C=O), 1387 (C–O). ^{1}H NMR (DMSO-d_6): δ 8.03 (d, 1H, –C(=O)NH, J_{NH-CH} = 8.28 Hz), 8.00 (s, 1H, HC(=O), 6.08 (dd, 2H, NH_2), 5.62 (d, 1H, CH, J_{NH-CH} = 8.28 Hz), 5.41 (dist. q, 2H, NH_2), 2.08 (bt, 2H, H_1+H_2), [1.81 (bd, 2H) and 1.23 (m, 2H), (H_3+H_6)], [1.45 (bd, 2H) and 1.00 (m, 2H), (H_4+H_5)]. ^{13}C NMR (D_2O): δ 65.31 (C_2), 65.07 (C_1), 60.46 ($C_{2'}$), 34.43 (C_3+C_6), 26.62 (C_4+C_5). *Anal.*; Calc. for $C_{10}N_{17}N_3O_5Pt$: C, 26.43; H, 3.77; N, 9.24%. Found: C, 26.21; H, 3.72; N, 9.03%.

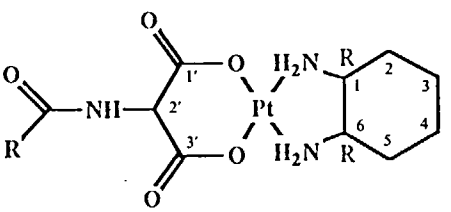
TABLE I

Selected IR bands (cm^{-1}) and molar conductances for the platinum(II) complexes

Compound	NH	Acetyl (C–O)	Amide (C=O)	Asym (C–O)	Sym (C–O)	$Ohm^{-1}/cm^{-2}/M^{-1}$
R,R-AMP, 1	3200–3240		1617	1645	1400	8
R,R-FMP, 2	3063–3289		1683	1640	1387	11
R,R-AG-AMP, 3	3213	1744	1666	1644	1375	7
R,R-G-AMP, 4	3100–3300		1672	1651	1388	8

TABLE II

^1H NMR data for the platinum(II) complexes



Compound	$C_{1,2}H$	$C_{3,6}H$	$C_{4,5}H$	NH_2	NH C_2H
Acetamidomalonic Acid					8.54(d) 4.88(d) (J_{NH-CH} = 7.95)
DAC-PtI_2[a]	2.55(bs)	2.15(bd) 1.55(m,4H)	1.15(m)	5.6(ud), 4.95(ut)	
R,R-AMP[b], 1	2.08(bs)	1.82(bd) 1.20(m)	1.45(bd) 1.02(m)	6.03(dd),5.38(bt)	7.65(d) 5.57(d) (J_{NH-CH} = 8.18)
R,R-FMP[b], 2	2.08(bt)	1.81(bd) 1.23(m)	1.45(bd) 1.00(m)	6.08(dd),5.41(dsq)	8.03(d)5.62(d) (J_{NH-CH} = 8.28)
R,R-AG-AMP[a], 3	2.45(bs)	2.09(m) 1.45(m)	1.55(bd) 1.10(bt)	6.21(dd),5.39(m)	7.41(d) 5.51(d) (J_{NH-CH} = 7.35)
R,R-G-AMP[a], 4	2.63(bs)	2.20(ud) 1.61(m)	1.70(ud) 1.31(m)	6.38(dd),5.62(m)	8.04(d) 5.76(d) (J_{NH-CH} = 7.31)

[a]DMF-d_7 (relative to TMS). [b]DMSO-d_6 (2.50); d: doublet; bd: broad doublet; t: triplet; bt: broad triplet; ud: unresolved doublet; ut: unresolved triplet; m: multiplet; dsq: distorted quartet.

Preparation of R,R-*AG-AMP*, 3:

This was prepared as described for **4** and recrystallized from methanol–ether in 55% yield. Decomp. point 189 °C; IR 3213 (NH), 2936, 2865 (CH, CH_2), 1744, 1666 (acetyl and amide C=O), 1644 (coordinated carboxyl C=O), 1375 (C–O). ^1H NMR (DMF-d_7): δ 7.41 (d, 1H, C(=O)NH, J_{NH-CH} = 7.35), 6.21 (dd, 2H, NH_2), 5.74 (t, 1H, sugar), 5.51–5.39 (mm, 4H, NH_2+CH (J_{NH-CH} = 7.35) + sugar), 5.12 (q, 1H, sugar), 4.42 (dd, 1H, sugar), 4.23 (dd, 1H, sugar), 2.45 (bs, 2H, H_1+H_2), 2.25 (s, 3H, CH_3–C(=O)), 2.09 (3xs+m, 11H, 3xCH_3–C(=O)+H_3 or H_6), [1.55 (bd, 2H) and 1.10 (bt, 2H), (H_4+H_5], 1.45 (m, 2H, H_3 or H_6). ^{13}C NMR (DMF-d_7): δ 172.11,

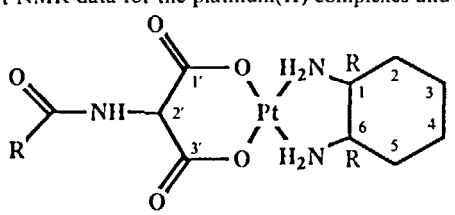
171.65, 170.89, 170.49, 170.29, 170.08, 165.68 (acetyls+amide+carboxylate C(=O)), 73.01, 70.57, and 69.76 (sugar), 63.64 (C_2), 63.13 (C_1), 61.87 (sugar), 59.57 ($C_{2'}$), 32.53 (C_3+C_6), 24.99 (C_4+C_5), 20.67, 20.58 (acetyls). *Anal.*; Calc. for: $C_{25}H_{37}N_3O_{15}Pt\cdot H_2O$: C, 36.06; H, 4.72; N, 5.05%. Found: C, 36.86; H, 4.60; N, 5.04%.

RESULTS AND DISCUSSION

In view of the difficulties in purifying platinum complexes,[12-14] the purity of each complex was determined by its elemental analysis and HPLC (>98% by HPLC). Analytical data for the platinum(II) complexes (see Experimental) are in good agreement with the chemical formulation of the proposed structure I. Molar conductivities were measured to assess the electrolytic nature of the complexes in water (Table I). The molar conductances of compounds **1–4** immediately after dissolution in distilled deionized water at room temperature are below 11 cm^2 ohm^{-1} mol^{-1}, suggesting a neutral 1:1 adduct for all of the complexes.[15]

TABLE III

^{13}C and ^{195}Pt NMR data for the platinum(II) complexes and their intermediates.



Compound	C_1	C_2	$C_{3,6}$	$C_{4,5}$	Carboxylate and Amide (C=O)	^{195}Pt
Gluconylaminomalonic acid[a]					165.90,161.15 161.01	
Gluconylaminomalonic acid[b] Barium gluconylaminomalonate[a]					173.17,168.81 175.05,174.95 174.37	
R,R-DAC-PtI_2[a]	64.52		32.40	25.21		
R,R-DAC-$PtSO_4$[a]	65.97		32.20[c]	26.56[c]		
R,R-DAC-$Pt(OH)_2$[a]	65.5[c]		35.09	26.68		
R,R-AMP,[a] **1**	65.41	65.56	34.57 34.49	26.66	176.73,176.48	−1947.36[d]
R,R-FMP,[a] **2**	65.07	65.31	34.43	26.62		−1951.31[d]
R,R-AG-AMP,[b] **3**	63.13	63.64	32.53	24.99	172.11,171,65 170.89,170.49 170.29,170.08 165.68	−1951.3[d]
R,R-G-AMP[b], 4	62.20	62.50	31.49	23.95	172.10,171.54 171.18	−1946[b]

[a]D_2O. [b]DMF-d_7. [c]two overlapping signals. [d]DMSO-d_6.

Inspection of the IR spectra of compounds **1–4** (Table I) shows strong bands around 1651 and 1375 cm^{-1} assignable to the asymmetric and symmetric carbonyl stretching of the coordinated carboxylic groups.[16] The carbonyl stretching of the

acetyl group in *R,R*-AG-AMP shows a strong absorption at 1744 cm^{-1} and the amide carbonyl stretching frequency for the complexes appears in the range 1617–1683 cm^{-1}.

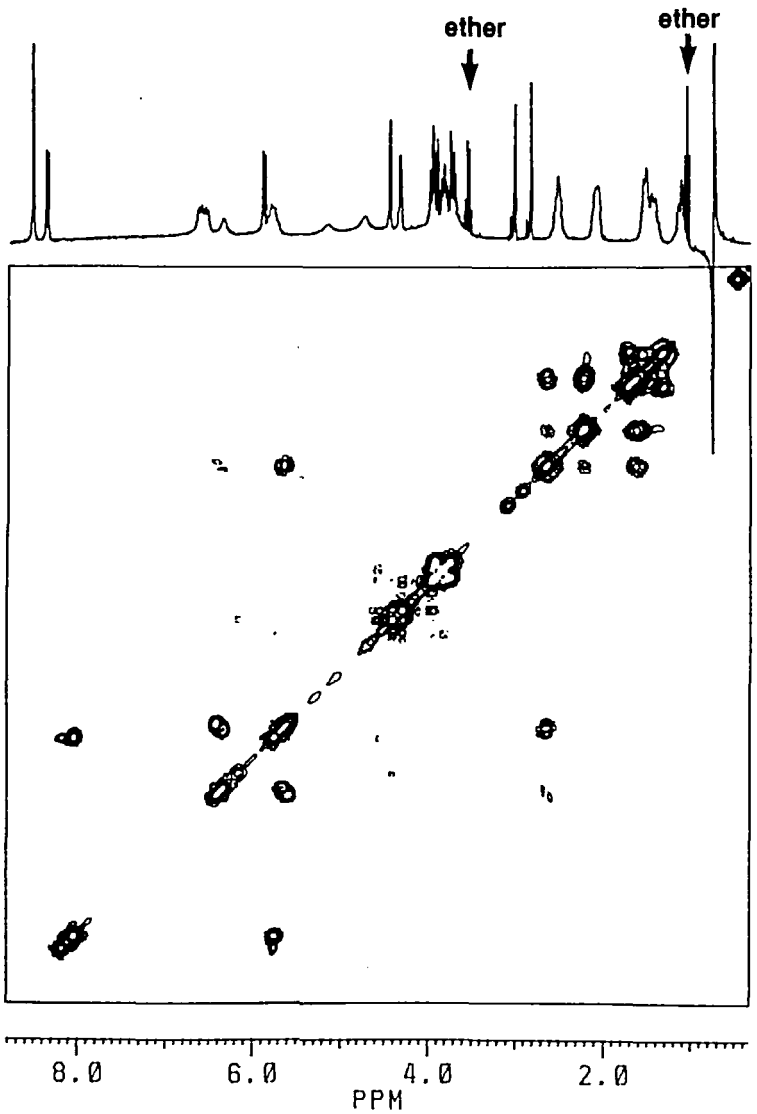


FIGURE 1 ^{1}H–^{1}H Homonuclear chemical-shift correlated (COSY) of *R,R*-G-AMP, 4.

Selected ^{1}H and ^{13}C NMR chemical shifts for each of the platinum compounds 1–4 are tabulated in Tables II and III, respectively. Complete chemical shift assignments for each complex are listed in the experimental section. 2D-COSY-{^{1}H–^{1}H}(Figure 2) and 2D-HETCOSY{^{1}H–^{13}C}(Figure 3) of *R,R*-G-AMP, as a complex representative, were carried out to facilitate the chemical shift assignments.

All of the complexes exhibit two sets of doublets around 7.65–8.04 and 5.51–5.76 ppm due to the amide-NH and the methyne proton, respectively. The methyne proton of the malonate derivatives in the platinum complexes are shifted downfield as compared to the corresponding proton in the free malonic acid derivatives. For example, the methyne proton in *R,R*-AMP appears at 5.57 ppm, while the same resonance in the free acetamidomalonic acid is observed at 4.88 ppm. This downfield chemical shift is due to the coordination of acetamidomalonic acid to platinum through its two carboxylate oxygens. The resonance peaks around 6.38–6.03 and 5.62–5.38 ppm, in the spectra of **1–4**, are exchangeable with D_2O and are assigned to the chelated amino groups. The broad singlets at 6.15, 5.03, 4.79, 4.66, and 4.53 ppm, in the spectrum of *R,R*-G-AMP, were also exchangeable with D_2O and they are assigned to the gluconyl hydroxyl groups.

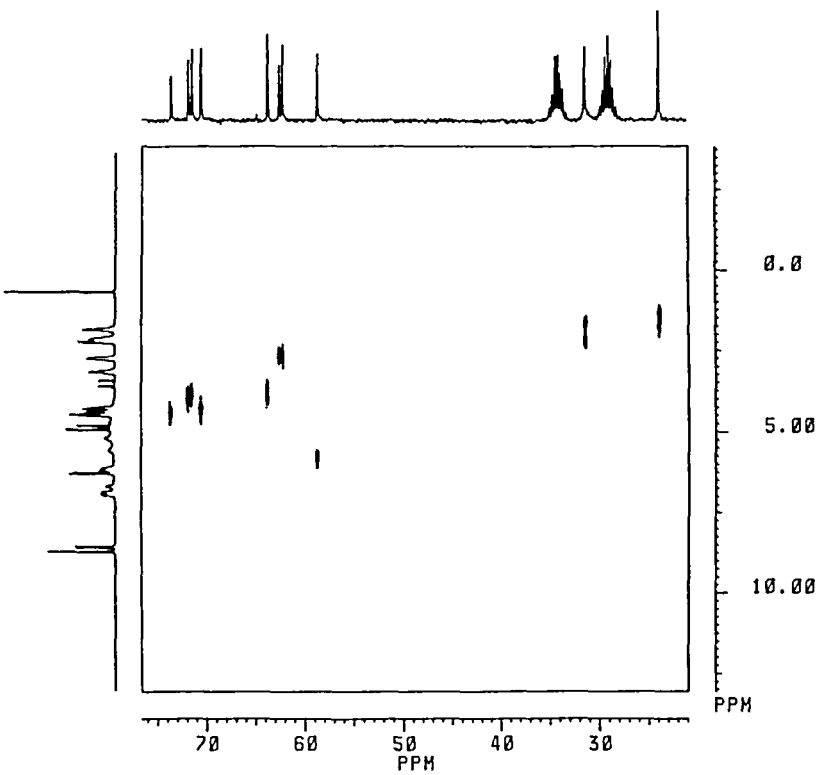


FIGURE 2 ^1H–^{13}C Heteronuclear chemical-shift correlated (HETCOSY) of *R,R*-G-AMP, 4.

^{13}C NMR of **1–4** and selected reference platinum complexes were carried out in D_2O, DMF-d_7, or DMSO-d_6 (Table III and Experimental Section). The number of carbon signals observed for each compound corresponds to that expected for a monomeric single platinum complex. The MS(FAB) spectrum of *R,R*-G-AMP shows 5 peaks at *m/z* values of 604(^{194}Pt), 605(^{195}Pt), 606(^{196}Pt), 607(^{197}Pt), and 608(^{197}Pt), a pattern expected for naturally abundant Pt isotopes, further supporting the monomeric nature of these complexes. In contrast to results reported by Gandolfi *et al.*,[17] where doubling of the number of ^{13}C signals for the cyclohexane ring

carbons of aminomalonato-DAC-platinum(II) was observed as compared to the free DACH, the ^{1}H (Table II) and ^{13}C NMR (Table III) spectra of compounds **1–4** show no evidence for the presence of more than one species.

Finally, since the chemical shifts of ^{195}Pt are very sensitive to the donor ligand,[18] ^{195}Pt NMR of structures **1–4** was carried out to elucidate the molecular environment of the platinum metal. A single broad peak was observed in the -1946 to -1951 ppm range for each of the complexes (Table III), a chemical shift region characteristic of an (*O*,*O*)-Pt system,[19] therefore ruling out chelation of the amide nitrogens to the platinum metal. Appleton *et al.*[19] reported the ^{195}Pt peak at -2026 ppm for (*N*,*O*)–Pt coordination in the reaction of *N*-acetyl glycine with diamminediaquaplatinum(II) cation, where glycine binds to the platinum metal through its amine nitrogen and carboxylate oxygen. The broadening of the ^{195}Pt signal is not surprising when one or more ^{14}N atoms are bonded to platinum. Partial decoupling of ^{195}Pt due to rapid quadruple-induced relaxation of ^{14}N broadens the platinum signals.[20] These compounds are currently undergoing preclinical evaluation as potential antitumor agents.

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