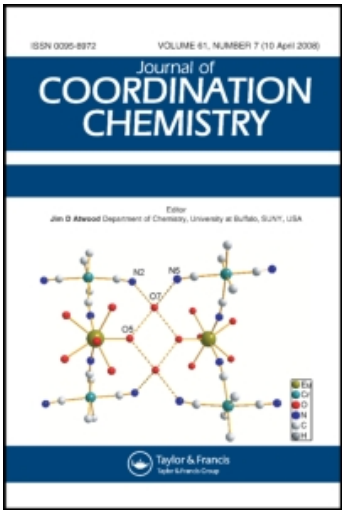


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

SYNTHESIS, CHARACTERIZATION, AND REPRESENTATIVE CRYSTAL STRUCTURE OF LIPOPHILIC PLATINUM^{II} (HOMOPIPERAZINE)CARBOXYLATE COMPLEXES

Mohammad S. Ali[a]; Christopher A. Powers[b]; Kenton H. Whitmire[b]; Ilse Guzman-Jimenez[b]; Abdul R. Khokhar[a]
[a] Department of Clinical Investigation, Box 52, The University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA [b] Department of Chemistry, MS 60, Rice University, Houston, TX, USA

To cite this Article Ali, Mohammad S. , Powers, Christopher A. , Whitmire, Kenton H. , Guzman-Jimenez, Ilse and Khokhar, Abdul R.(2001) 'SYNTHESIS, CHARACTERIZATION, AND REPRESENTATIVE CRYSTAL STRUCTURE OF LIPOPHILIC PLATINUM^{II} (HOMOPIPERAZINE)CARBOXYLATE COMPLEXES', Journal of Coordination Chemistry, 52: 3, 273 — 287
To link to this Article: DOI: 10.1080/00958970108022593
URL: http://dx.doi.org/10.1080/00958970108022593

J. Coord. Chem., 2001, Vol. 52, pp. 273–287
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS, CHARACTERIZATION, AND REPRESENTATIVE CRYSTAL STRUCTURE OF LIPOPHILIC PLATINUM^{II} (HOMOPIPERAZINE)CARBOXYLATE COMPLEXES

MOHAMMAD S. ALI[a], CHRISTOPHER A. POWERS[b], KENTON H. WHITMIRE[b], ILSE GUZMAN-JIMENEZ[b] and ABDUL R. KHOKHAR[a,*]

[a]*Department of Clinical Investigation, Box 52, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston TX 77030, USA;* [b]*Department of Chemistry, MS 60, Rice University, 6100 Main Street, Houston, TX 77005, USA*

(Received 2 January 2000; In final form 3 May 2000)

A series of new lipophilic platinum(II) complexes of the type [Pt(HPIP)L_2] and [Pt(HPIP)L] (where HPIP = homopiperazine; L = acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, nonanoate, decanoate, undecanoate, laureate, tridecanoate, myristate, pentadecanoate, palmitate, or heptadecanoate; and LL = oxalate, or tartronate) were synthesized and characterized by elemental analysis, IR, ^{13}C NMR, and ^{195}Pt NMR. In addition, the crystal structure of a representative complex [Pt^{II}(HPIP)(pentadecanoate)$_2$], was determined by X-ray diffraction. The crystals were monoclinic, space group $P2_1/c$, with $a = 28.212(6)$ Å, $b = 3.661(3)$ Å, $c = 10.218(2)$ Å, and $Z = 4$. A total of 3940 reflections were collected, and the structure refined to $R1 = 0.0522$ and $wR2 = 0.1333$. The slightly distorted square plane of the platinum included the amino groups of the HPIP molecule in *cis* positions and oxygens from two monodentate pentadecanoates. The HPIP molecule was in a boat conformation and formed five- and six-member chelating rings with platinum. Together, these molecules formed an intricate network of intermolecular hydrogen bonds that held the crystal lattices together.

Keywords: Platinum(II); Homopiperazine; Carboxylate; Synthesis; Crystal structure

*Corresponding author. Tel.: 713-792-2837, Fax: 713-792-6759, e-mail: akhokhar@mdanderson.org

INTRODUCTION

Cisplatin [1] is one of the most effective platinum(II) oncolytic agents against cancers of the testes, ovaries, bladder, head and neck [2–4]. It is also an important adjunct in treating cancers of the cervix, lung, and breast. However, its drawbacks include nephrotoxicity, nausea, vomiting, myelosuppression, ototoxicity, neurological complications, and the development of resistance by tumor cells [5–7].

To rationalize the activities of cisplatin and its analogs and to design newer, more active molecules, researchers have tried altering both the leaving groups and the non-leaving amine ligands. The resulting alteration of pharmacodynamics has resulted in good *in vitro* activity [8] and *in vivo* efficacy [9] against cisplatin-resistant tumors. For instance, displacing the labile chlorides with CBDCA as a leaving group and NH_3 with a non-leaving amine ligand resulted in carboplatin [10], a second-generation platinum(II) complex for clinical use. Yet, although it is relatively less toxic than cisplatin, carboplatin still has drawbacks of limited clinical effectiveness and intrinsic acquired drug resistance. Consequently several other analogs containing different isomers of 1,2-DACH such as oxaliplatin (*trans-l*-1,2-DACH-oxalatoplatinum(II)) have been formulated and entered in clinical trials [11]. Unfortunately, 1,2-DACH containing platinum complexes have been plagued by low solubility, poor stability and difficult formulation, which in turn has restricted the development of some promising analogues [9a]. Hence a new approach to modifying the therapeutic index has been introduced: the use of liposomes as drug delivery system [12]. Liposomes have gained considerable attention as drug carriers because they are easy to prepare, are biodegradable [13, 14] and by their nature, are able to entrap drugs, thus providing a way to prevent toxicity and preserve antitumor activity [15]. Because cisplatin has low lipophilicity a low entrapment efficiency, and a high rate of drug leakage [16] our objective over the last few years has been to synthesize a series of highly lipid-soluble platinum(II) complexes designed for liposome entrapment [17]. Such complexes have shown high entrapment efficiency and good antitumor activity [18]. One of these complexes, LNDDP (liposome-entrapped *cis*-bis(neodecanoato)(*trans*- 1(*R*), 2(*R*)-diaminocyclohexane)platinum(II), was developed in our laboratory, and is currently in clinical trials [19], at MD. Anderson Cancer Center.

More recently we demonstrated good *in vitro* activity of homopiperazine-Pt(II) and -Pt(IV) complexes with different equatorial and axial ligands as leaving groups [17f]. Since then, we have continued to develop newer, more

effective lipid-soluble platinum(II) complexes that are also capable of high antitumor activity. We report here the synthesis and characterization of large (five- and six-member) ring chelate complexes of the types $[Pt^{II}(HPIP)L_2]$ and $[Pt^{II}(HPIP)L]$, along with the crystal structure of a representative complex $[Pt^{II}(HPIP)(pentadecanoate)_2]$.

EXPERIMENTAL

Chemicals

K_2PtCl_4 was purchased from Johnson Mathey (Seabrook, NH). HPIP, acetic acid, propionic acid, butyric acid, valeric acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, heptadecanoic acid, oxalic acid, and tartronic acid were purchased from Aldrich Chemical Co. (Milwaukee, WI). Silver nitrate, silver sulfate, sodium hydroxide, HCl, H_2O_2, and KI were purchased from Fisher Scientific Co. (Houston, TX).

Physical Measurement

Elemental analyses of the complexes were performed by Robertson Laboratories, Inc. (Madison, NJ). The infrared (IR) spectra of the complexes in the ranges of $600-4000\,cm^{-1}$ and $100-600\,cm^{-1}$ were recorded by us, in KBr and polyethylene pellets, respectively, using a Perkin Elmer 2000 spectrophotometer. ^{195}Pt nuclear magnetic resonance (NMR) spectra were recorded in a solution of methanol, DMF or acetone using an IBM NR200/AP spectrometer. Na_2PtCl_6 (0.2 M) in D_2O at 0.00 ppm was used as an external reference for ^{195}Pt shifts.

Preparation of Sodium Salts

Sodium Acetate NaOH (4.39 mL 83.33 mmol) in 20 mL of water was added drop wise to acetic acid (5.0 g, 83.33 mmol) in 250 mL of ethanol. The reaction mixture was stirred for 30 min and evaporated to dryness under reduced pressure at room temperature. A colorless sticky material formed. This was dissolved in 200 mL of acetone and evaporated to dryness. To the evaporated material was added 10 mL of ether. This was evaporated to dryness, collected, and dried in vacuum (yield, 95%).

Sodium Salts The sodium salts of acetic, propionic, butyric, velaric, hexanoic, heptanoic, octanoic, nonanoic, decanoic, undecanoic, lauric, tridecanoic, myristic, pentadecanoic, palmitic, and heptadecanoic acids were prepared in a manner similar to that described above.

Synthesis of Platinum Complexes

[Pt^{II}(*HPIP*)(*acetate*)$_2$] (*Complex* 1) K_2PtCl_4 (10.00 g, 24.09 mmol) was dissolved in 300 mL of deionized water and filtered. KI (31.99 g, 192.72 mmol) was added to this solution and the reaction mixture was stirred for 30 min. Then, HPIP (2.41 g, 24.09 mmol) dissolved in 200 mL of water was added drop wise to the reaction mixture while stirring. A dark brown solid separated. The stirring was continued for 2 h and the solid was filtered, dissolved in 100 mL DMF and filtered. The filtrate was concentrated to 10 mL under reduced pressure and precipitated with excess water to get yellow [Pt(HPIP)I_2], which was filtered and dried in vacuum. Silver nitrate (3.71 g, 21.85 mmol) was dissolved in 300 mL of water, and [Pt^{II}(HPIP)I_2] (6.00 g, 10.92 mmol) was added as a solid. The reaction mixture was stirred for 24 h in the dark. The AgI precipitate was filtered off, and the filtrate was concentrated to 20 mL under reduced pressure. To this solution, 50 mL of 1:1 HCl : H_2O was added with constant stirring giving a yellow precipitate of [Pt(HPIP)Cl_2]. This was filtered, washed with water, acetone, and dried under vacuum (yield, 82.5%). To a suspension of [Pt^{II}(HPIP)Cl_2] (0.50 g, 1.36 mmol) in 250 mL of water was added an aqueous solution of Ag_2SO_4 (0.42 g, 1.36 mmol). The reaction mixture was then continuously stirred in the dark for 24 h at room temperature. AgCl precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. A pale yellow solid of [Pt^{II}(HPIP)(OSO_3)H_2O] was obtained and dried *in vacuo* (yield, 82.0%). [Pt(HPIP)(SO_4)(H_2O)] (1.69 g, 4.00 mmol) was reacted with sodium acetate (1.73 g, 8.00 mmol) dissolved in 200 mL of methanol. The reaction mixture was stirred at room temperature for four days. A very fine precipitate of Na_2SO_4 formed, which was filtered off. The filtrate was evaporated to dryness, redissolved in methanol, filtered through a Millipore GV fine filter paper (pore size 0.22 μM), and evaporated to dryness. Finally, the solid obtained was recrystallized from acetone giving white crystalline compound [$Pt^{(II)}$(HPIP)(acetate)$_2$] (yield, 80%).

Complexes 1 – 16 were prepared in a similar manner.

[Pt^{II}(*HPIP*) (*heptadecanoate*)$_2$] (*Complex* 14) (100 mg) was dissolved in 100 mL, of methanol, after which the volume of the solution was reduced to 50 mL, and filtered. The filtrate was allowed to slow evaporation at room

temperature. Within two weeks colorless needle-like crystals were separated from the solution. The crystals were used for X-ray crystallography.

[*Pt*(II)(*HPIP*)(*oxalate*)] (*Complex* 17) [Pt^{II}(HPIP)(OSO_3)H_2O] (1.25 g, 3.05 mmol) was dissolved in 50 mL of water and then added to an aqueous solution of sodium oxalate (0.44 g, 3.05 mmol) prepared *in situ*. The reaction mixture was stirred for 24 h, filtered, concentrated to 10 mL under reduced pressure, and finally cooled at 6°C for 24 h to obtain a white product. This was filtered, washed with cold water, and dried in vacuum (yield, 62.5%).

[$Pt^{(II)}$(HPIP)(tartronate)] (complex 18) was prepared in the same way.

Crystallographic Measurements

Crystals were encapsulated in a thin shell of epoxy cement and mounted on the tip of a glass fiber. Data were collected with a Rigaku AFC5S automated four-cycle diffractometer using the EXAN 5.0 software package [20] and were corrected for Lorentz/polarization effects and absorption (ψ-scan). Data collection and refinement parameters are summarized in Table I Scattering patterns were taken from the literature [21]. The structure was solved using a personal computer loaded with the SHELXTL-PLUS software package [22]. Refinement of F^2 for all reflections, except those with very negative F^2 values, was performed with a personal computer loaded with SHELXL-93 software [23]. Weighted R factor (R_w) and goodness-of-fit (S) values were based on F^2, while conventional R factor (R) values were based on F with F set to 0 for negative F^2. The observed criterion of F^2 was used only for calculating observed R factors and was not relevant to the choice of refinement. R factors based on F^2 were statistically about twice as large as those based on F, and R factors based on all of the data were even larger. The weighting factor $w=[\sigma^2(Fo^2)+(xP)^2+Yp]^{-1}$, where $P=(Fo^2+2Fc^2)/3$, was refined for x and y.

RESULTS AND DISCUSSION

Synthesis of Platinum Complexes

The steps involved in the preparation of platinum(II) complexes of the type [Pt(HPIP)(L_2)], and [Pt(HPIP)(L)] are shown in Scheme 1. [Pt^{II}(HPIP)Cl_2] was prepared according to Dhara's method [24]. This method was adopted because it is rapid, easy and gives much higher yield rather when K_2PtCl_4 is treated directly with homopiperazine. Reaction of K_2PtCl_4 mixed with an

TABLE I Crystal and structure refinement data for [Pt^{II}(HPIP)(pentadecanoate)$_2$]

Empirical formula	$C_{35}H_{70}N_2O_4Pt$
Formula weight	777.02
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
	a, Å = 28.212(6)
	b, Å = 3.661(3)
	c, Å = 10.218(2)
Volume	3920.3(13) Å^3
Z	4
Density (calculated)	1.318 Mg/m^3
Absorption coefficient	3.614 mm^{-1}
F(000)	1616
Crystal size	0.56 × 0.47 × 0.075 mm
θ range for data collection	2.08 to 22.31°
Limiting indices	$-30 < h < 27$, $-13 < k < 0$, $0 < l < 9$
Reflections collected	3940
Independent reflections	3656 (R(int) = 0.0383)
Absorption correction	Psi-scans
Max. transmission	1.0000
Min. transmission	0.5697
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3656/0/379
Goodness-of-fit on F^2	1.003
Final R indices [$I > 2\sigma(I)$][a]	$R1 = 0.0522$, $wR2 = 0.1333$
R indices (all data)	$R1 = 0.0943$, $wR2 = 0.1507$
Largest diff. peak and hole	1.346 and −1.398 e A^{-3}

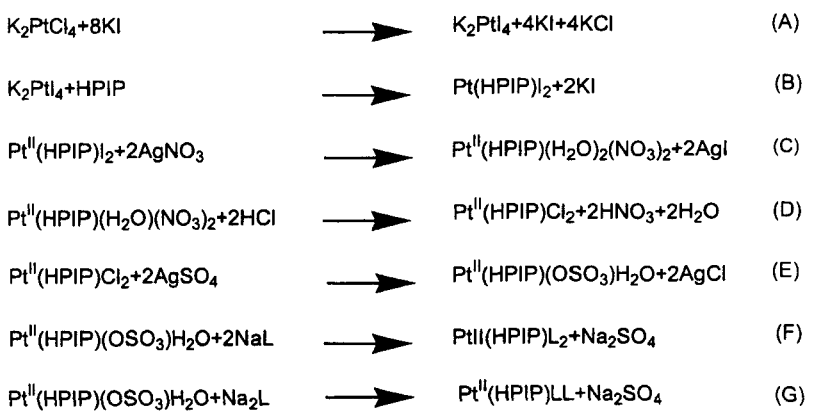
[a] $R_1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$. $Rw = [\Sigma w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]^{1/2}$. $w = [\sigma^2(Fo^2) + (aP)^2 + bP]^{-1}$. $P = (Fo^2 + 2Fc^2)/3$. The large residual peak was located close to the platinum atom.

excess of KI produced K_2PtI_4 in solution (reaction A). K_2PtI_4 was then reacted with one equiv of HPIP to precipitate Pt(HPIP)I_2 (reaction B). The reaction of $PtLI_2$ with $AgNO_3$ led to formation of [Pt(HPIP)$(H_2O)_2$]$(NO_3)_2$ in solution (reaction C), which was further converted into [Pt^{II}(HPIP)Cl_2] by treatment with 1:1 HCl (reaction D). Reaction of [Pt^{II}(HPIP)Cl_2] with Ag_2SO_4 formed [Pt^{II}(HPIP)$(OSO_3)H_2O$] (reaction E). The reaction of [Pt^{II}(HPIP)$(OSO_3)H_2O$] with one or two equiv of the corresponding sodium salts of monocarboxylic acids of the type NaL (reaction F) or dicarboxylic acids of the type Na_2L (reaction G) in methanol produced [Pt^{II}(HPIP)LL] and [Pt^{II}(HPIP)L] complexes 1–16 and 17–18 respectively.

Characterization of Platinum Complexes

All complexes were characterized by elemental analysis, and by IR, ^{13}CNMR, and ^{195}Pt NMR spectroscopic techniques. The theoretical

Pt^{II} Complexes



SCHEME 1 HPIP = homopiperazine. L = acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, nonanoat decanoate, undecanoat, laurate, tridecanoat, myristate, pentadecanoat, palmitate, or heptadecanoate. L = oxalate or tartronate.

elemental data presented in Table II are in good agreement with the actual elemental findings.

The IR, ^{13}C NMR, and ^{195}Pt NMR spectroscopic data shown in Table III confirmed the general structure of [Pt(HPIP)L_2] (Fig. 1), and [Pt(HPIP)L] (Fig. 2) complexes. In the IR spectra of all complexes, prominent changes were observed [25]. Broad absorptions between 3190–3150 and 2920–2870 cm^{-1} in the IR spectra of all the complexes were attributed to the coordinated N—H bond of HPIP. The carboxyl groups in all the complexes displayed a band in the range of 1580–1610 cm^{-1} corresponding to the $\nu_{as}(COO^-)$ band. The $\nu_s(COO^-)$ band appeared in the range of 1360–1390 cm^{-1}. The Pt—N and Pt—O stretching frequencies in all the complexes showed peaks in the range of 520–525 and 420–425 cm^{-1}, respectively.

The proton-decoupled ^{13}C NMR spectra showed a signal in the range of 180–190 ppm for the carbonyl carbons of coordinated carboxylate ligands. This suggests that the two carboxylate carbons are magnetically equivalent in these complexes. These values are also close to the values for carboxylate carbons reported for other platinum carboxylate complexes [26]. The ^{13}C NMR shifts of the free acids and platinum complexes are shown in Table III. The values of the complexation shifts ($\Delta C = \delta$[complex] $- \delta$[ligand) for all the complexes fell between 1.8 and 2.5.

TABLE II Elemental analysis of platinum^{II}(HPIP) carboxylate

Complex no. complex name	*Observed (calculated)*		
	%C	*%H*	*%N*
1. [Pt^{II}(HPIP)(acetate)$_2$]	26.05 (26.15)	4.27 (4.40)	6.49 (6.77)
2. [Pt^{II}(HPIP)(propionate)$_2$]	30.12 (29.93)	4.90 (5.02)	6.08 (6.35)
3. [Pt^{II}(HPIP)(butyrate)$_2$]	32.98 (33.26)	5.53 (5.58)	5.81 (5.97)
4. [Pt^{II}(HPIP)(valerate)$_2$]	35.95 (36.21)	5.90 (6.07)	5.65 (5.63)
5. [Pt^{II}(HPIP)(hexanoate)$_2$]	38.62 (38.85)	6.37 (6.52)	5.35 (5.33)
6. [Pt^{II}(HPIP)(heptanoate)$_2$]	41.53 (41.22)	6.83 (6.92)	4.87 (5.06)
7. [Pt^{II}(HPIP)(octanoate)$_2$]	43.47 (43.36)	7.34 (7.28)	4.73 (4.82)
8. Pt^{II}(HPIP)(nonanoate)$_2$]	46.04 (45.31)	7.57 (7.60)	4.85 (4.60)
9. [Pt^{II}(HPIP)(decanoate)$_2$]	47.4 (47.08)	7.20 (7.90)	4.10 (4.39)
10. [Pt^{II}(HPIP)(undecanoate)$_2$]	49.00 (48.72)	8.24 (8.12)	4.46 (4.21)
11. [Pt^{II}(HPIP)(laureate)$_2$]	49.78 (50.21)	8.23 (8.36)	3.86 (4.04)
12. [Pt^{II}(HPIP)(tridecanoate)$_2$]	51.49 (51.59)	8.48 (8.59)	3.67 (3.88)
13. [Pt^{II}(HPIP)(myristate)$_2$]	52.73 (52.87)	8.62 (8.81)	3.61 (3.73)
14. [Pt^{II}(HPIP)(pentadecanoate)$_2$]	54.00 (54.05)	9.00 (8.74)	3.60 (3.58)
15. [Pt^{II}(HPIP)(palmitate)$_2$]	55.15 (55.14)	9.17 (9.19)	3.47 (3.47)
16. [Pt^{II}(HPIP)(heptadecanoate)$_2$]	56.43 (56.17)	9.39 (9.36)	3.64 (3.36)
17. [Pt^{II}(HPIP)(oxalate)]	21.58 (21.92)	3.17 (3.13)	6.95 (7.30)
18. [Pt^{II}(HPIP)(tartronate)]	23.58 (23.23)	3.17 (3.33)	6.95 (6.77)

HPIP = homopiperazine.

The ^{195}Pt NMR spectra further confirmed the structure of the platinum complexes. In methanol, the signal ranged from -1900 to -2050 ppm. Such chemical shifts are characteristic of square planar platinum(II) complexes having two nitrogens and two oxygen donors [27].

TABLE III IR ^{13}C NMR and ^{195}Pt NMR spectroscopic data for platinum(II) complex

Complex		*IR*[a] *cm*$^{-1}$				$^{13}C(>C=O)$[f]		
No.	*νN—H*	$\nu_a C{=}O$	$\nu_s C{-}O$	*Pt—N*	*Pt—O*	*Complex*	*ΔC*	^{195}Pt *NMR, ppm*
1.	2927, 3188	1604	1373	520	422	182.1	3.5	−1915[b]
2.	2969, 3163	1593	1384	521	423	181.5	2.4	−1912[b]
3.	2955, 3161	1594	1374	523	422	181.8	1.9	−1905[b]
4.	2956, 3158	1586	1376	525	421	182.5	2.0	−1903[b]
5.	2928, 3158	1586	1376	524	422	182.4	2.6	−1912[b]
6.	2927, 3152	1585	1368	524	421	182.9	2.9	−1915[b]
7.	2923, 3152	1591	1370	522	422	182.3	1.9	−1915[b]
8.	2950, 3175	1590	1380	520	425	182.4	2.8	−1914[b]
9.	2948, 3170	1588	1375	522	422	182.6	2.5	−1916[b]
10.	2945, 3168	1580	1373	523	421	182.8	2.4	−1912[b]
11.	2930, 3175	1578	1378	525	424	182.6	2.6	−1917[b]
12.	2945, 3182	1580	1378	523	424	182.4	2.5	−1913[b]
13.	2960, 3180	1570	1380	525	425	182.8	2.0	−1920[b]
14.	2970, 3175	1575	1375	522	425	182.7	2.2	−1925[b]
15.	2960, 3165	1570	1365	520	423	181.9	2.3	−1920[c]
16.	2965, 3158	1560	1360	525	420	182.6	2.5	−1932[c]
17.	2972, 3178	1575	1376	523	424	182.0	1.9	−2050[d]
18.	2980, 3174	1572	1370	524	425	182.4	2.5	−2040[d]

[a] Recorded in KBr pellets.
[b,c,d] Recorded in acetone, methanol, and DMF, $\Delta C = \delta$[complex]δ[ligand].

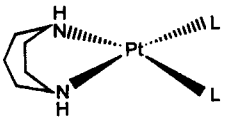


FIGURE 1 L = acetate, propionate, butyrate, velarate, hexanoate, heptanoate, octanoate, nonanoate, decanoate, undecanoate, laurate, tridecanoate, myristate, pentanoate, myristate, and heptadecanoate in complexes 1 – 16 respectively.

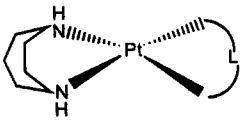


FIGURE 2 L = oxalate and tartronate in complexes 17 and 18, respectively.

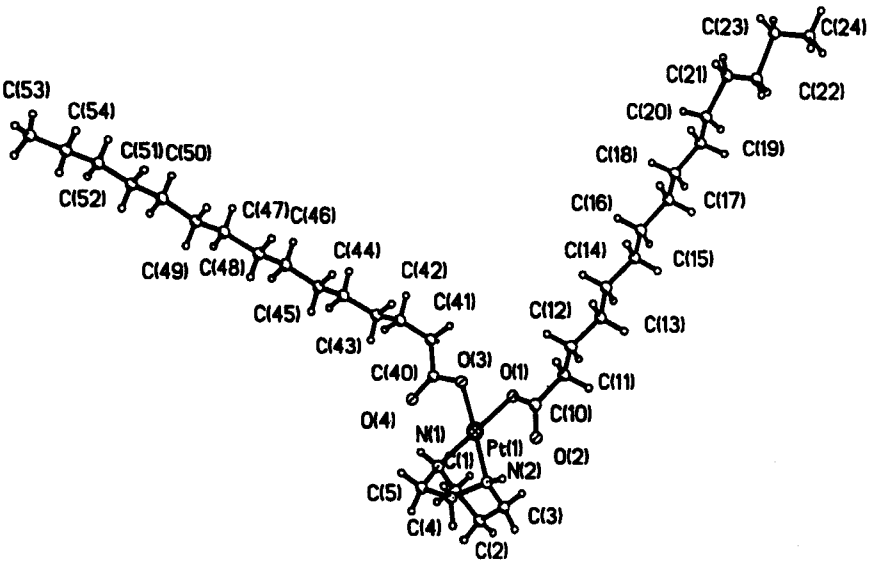


FIGURE 3 ORTEP representation of the structure of $[Pt^{II}(HPIP)(pentadecanoate)_2]$ with atom-numbering scheme.

Crystal Structure

The crystal structure of the $[Pt^{II}(HPIP)(pentadecanoate)_2]$ molecule is shown in Figure 3, which also defines the labeling of the atoms of the compound. Bond lengths and bond angles are given in Table IV, and atomic coordinates and equivalent isotopic displacement parameters are given in Table V.

TABLE IV Bond lengths [Å] and [°] for [Pt^{II}(HPIP)(pentadecanoate)$_2$]

Pt(1)—N(2)		1.997(10)
Pt(1)—O(3)		2.001(10)
Pt(1)—N(1)		2.007(10)
Pt(1)—O(1)		2.038(10)
N(2)—Pt(1)—O(3)	178.3(4)	
N(2)—Pt(1)—N(1)	76.3(4)	
O(3)—Pt(1)—N(1)	102.6(4)	
N(2)—Pt(1)—O(1)	101.8(4)	
O(3)—Pt(1)—O(1)	79.4(4)	
N(1)—Pt(1)—O(1)	177.6(4)	
C(5)—N(1)—Pt(1)	105.9(8)	
C(1)—N(1)—Pt(1)	112.1(7)	
C(3)—N(2)—Pt(1)	110.8(9)	
C(4)—N(2)—Pt(1)	105.8(8)	
C(10)—O(1)—Pt(1)	125.9(9)	
C(40)—O(3)—Pt(1)	125.6(10)	

In the [Pt^{II}(HPIP)(pentadecanoate)$_2$] molecule, the coordination around the platinum is square planar but slightly distorted, with the angles ranging from 76.3° to 102.6°. The distortion is caused by the limited bite distances of the chelating ligands. Two adjacent corners of the slightly distorted square plane of the platinum are occupied by the amino nitrogen of the HPIP ligand, whereas the remaining *cis* corners are used to bind unidentate pentadecanoate ions. The average Pt—N bond distance, 2.02(10) Å, is not significantly different from those observed in Pt(II) complexes. For instance, this length is 1.99(2) Å in [Pt^{II}(mhpip)(methylmalonate)]·H_2O [17b], 2.027(6) Å in [Pt^{II}(HPIP)Cl_2] [28], 2.05(2) Å in [Pt^{II}(1*R*,2*R*-DACH)(oxalate)], 2.03(2) Å in [Pt^{II}(1*R*,2*R*-DACH)(malonate)] [29], and 2.01(8) Å in [$Pt^{II}(NH_3)_2$(1,1-cyclobutanedicarboxylate)] [30]. The average Pt—O bond length of 2.019(10) Å is comparable with the Pt—O bond lengths observed in the following Pt(II) complexes: [Pt^{II}(mhpip)(methylmalonate)·$2H_2O$ [17b], 2.02(2) Å; [Pt^{II}(*cis*-1,4-DACH)(malonate)], 2.024(5) Å [31]; [Pt^{II}(*trans*-1,2-DACH)(acetate)$_2$], 2.01(3) Å [32]; and [$Pt^{II}(NH_3)_2$(1,1-cyclobutanedicarboxylate), 2.029(9) Å [30]. The bites of the bidentate HPIP ligand impose an N1—Pt—N2 angle of 76.3(4)°, which agrees well with the angles of 77.8(8)° observed in [Pt^{II}(mhpip)(methylmalonate)·H_2O, [17b] 76.9° in [Pt(HPIP)Cl_2] [28], 83.8(7)° in [Pt^{II}(1*R*,2*R*-DACH)(oxalate)], 83.8(7)° in [Pt^{II}(1*R*,2*R*-DACH)(malonate)] [29], and 83.5(5)° in [Pt(*trans-l*-1,2-DACH)(CBDCA)] [33]. The O—Pt—O bond angle of 79.4(4)° is normal compared with those in other platinum(II)dicarboxylate complexes, *e.g.*, 88.5(7)° [Pt^{II} (mhpip)(methylamalonate)]·$2H_2O$ [17b], 90.3(6)° in [Pt^{II}(1*R*,2*R*-DACH)(malonate)] [29] and 90.0(2)° in [Pt(*cis*-1,4-DACH)(malonate)] [31]. Bonding of platinum with the amino nitrogen of HPIP is

TABLE V Atomic coordinates and equivalent isotropic displacement parameters [Å^2] for [Pt^{II}(HPIP)(pentadecanoate)$_2$]

Atom	*x*	*y*	*z*	$U_{(eq)}$[a]
Pt(1)	14668(1)	4126(1)	−11892(1)	47(1)
N(1)	15139(4)	4970(7)	−12723(9)	41(3)
C(1)	15490(5)	5432(10)	−11725(12)	52(4)
C(2)	15839(6)	4649(12)	−11136(15)	71(5)
C(3)	15618(6)	3744(11)	−10728(15)	68(4)
N(2)	15264(4)	3328(7)	−11734(11)	49(3)
C(4)	15434(6)	3320(11)	13068(13)	65(5)
C(5)	15364(5)	4332(11)	−13646(16)	66(4)
O(1)	14213(3)	3251(7)	−10991(9)	53(3)
O(2)	14661(4)	1919(7)	−10800(10)	69(3)
C(10)	14288(5)	2357(12)	−10648(14)	56(4)
C(11)	13914(5)	1902(10)	−9949(16)	63(4)
C(12)	13570(5)	2530(11)	−9355(14)	62(4)
C(13)	13198(6)	1990(11)	−8670(17)	74(5)
C(14)	12830(6)	2654(13)	−8064(17)	86(5)
C(15)	12461(6)	2099(12)	−7428(18)	84(5)
C(16)	12102(6)	2720(14)	−6800(20)	102(6)
C(17)	11721(7)	2121(15)	−6200(20)	111(7)
C(18)	11352(7)	2726(16)	−5550(20)	18(7)
C(19)	10965(9)	2095(19)	−5040(30)	147(9)
C(20)	10593(9)	2640(30)	−4440(30)	189(13)
C(21)	10098(17)	2030(50)	−4190(50)	310(40)
C(22)	10150(20)	1530(40)	−3370(50)	280(30)
C(23)	9617(17)	1060(40)	−3150(60)	270(30)
C(24)	9684(18)	330(50)	−2320(50)	330(30)
O(3)	14075(3)	4934(7)	−12106(10)	64(3)
O(4)	14334(4)	6181(7)	−13315(12)	76(3)
C(40)	14021(6)	5745(13)	−12770(16)	69(5)
C(41)	13532(7)	6173(12)	−12770(20)	87(6)
C(42)	13280(10)	6380(30)	−13940(40)	218(18)
C(43)	13205(8)	5872(15)	−15110(20)	110(7)
C(44)	12960(10)	6130(20)	−16310(30)	171(12)
C(45)	12848(9)	5658(19)	−17510(30)	129(8)
C(46)	12579(14)	5990(20)	−18690(40)	216(18)
C(47)	12444(12)	5600(20)	−19840(30)	171(11)
C(48)	12178(11)	6060(20)	−21010(40)	170(13)
C(49)	12058(13)	5720(20)	−22190(40)	186(13)
C(50)	11782(11)	6120(20)	−23330(50)	202(17)
C(51)	11632(15)	5730(30)	−24520(40)	212(16)
C(52)	11373(11)	6040(30)	−25640(40)	197(17)
C(54)	11063(15)	6060(30)	−27960(50)	260(20)
C(53)	11240(20)	5710(40)	−26810(40)	330(30)

[a] $U_{(eq)}$ is defined as one third of the trace orthogonalized U_{ij} tensor.

considerably strained, and in compensation, the bond angles N2—Pt—O1 and N1—Pt—O3 are expanded to 101.8(4)° and 102.6(4)°, respectively. HPIP is in a boat conformation and forms five- and six-membered chelating rings with platinum. The observed Pt—N1—C5 and Pt—N1—C1 bond angles

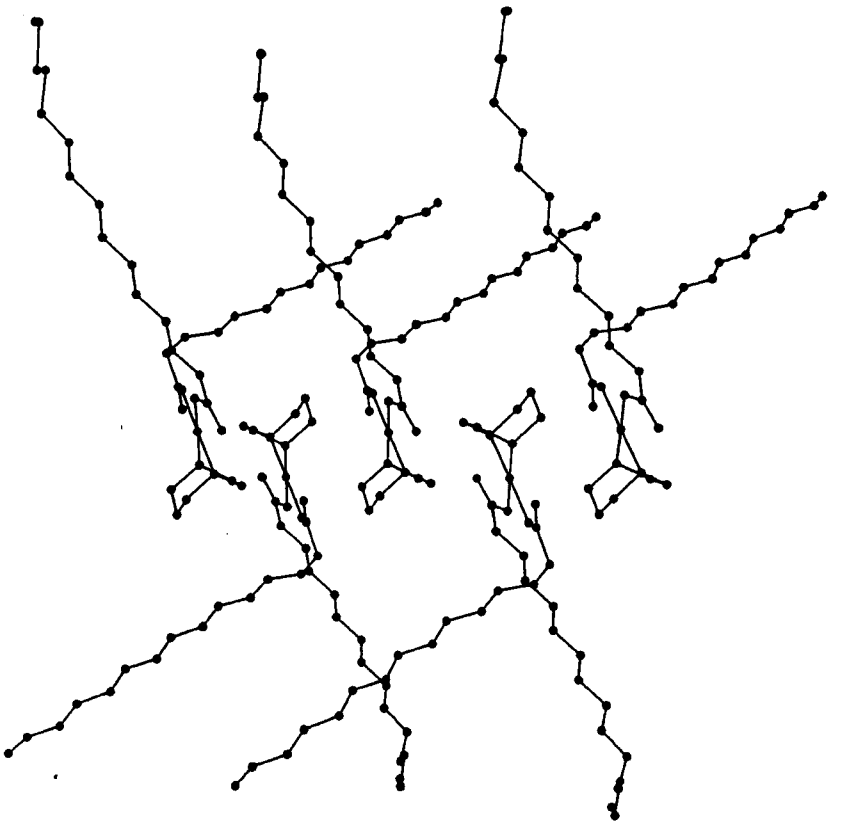


FIGURE 4 A stereoscopic view of molecule packing in [Pt^{II}(HPIP)(pentadecanoate)$_2$]. Hydrogen bonds are indicated by dashed lines.

were 105.9(8)° and 112.1(7)°, respectively. In [Pt^{II}(mhpip)(methylmalonate)]·H_2O, [17b] these bond angles were observed to be 104.3(14)° and 105.5(14)° and in [Pt^{II}(hpip)C12] [28] 107.7(4)° and 109.0(4)°, respectively. As shown by the stereoscopic view of the molecular packing in Figure 4, the molecules in the crystal are held together by a system of weak N—H—O hydrogen bonds.

CONCLUSIONS

In summary, we have synthesized and characterized a series of new lipophilic cisplatin analogs in the form of [Pt^{II}(HPIP)carboxylate]

complexes. We have also determined the crystal structure of one of the complexes, [Pt^{II}(HPIPX)(pentadecanoate)$_2$], by X-ray crystallography.

Acknowledgement

This work was supported by American Cancer Society Grant DPH No. 148.

Supplementary Material

Observed and calculated structural factors as well as anisotropic parameters and hydrogen coordinates of the new lipophilic complexes are available from ARK.

References

[1] B. Rosenberg, L. Van Camp, J. E. Troska and V. H. Mansour, *Nature (London)* **222**, 385 (1969).
[2] I. H. Krakoff, M. Nicolini (Eds.), *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy: Clinical Application of Platinum Complexes*, Martinus Nijhoff Boston, MA, p. 351 (1988).
[3] P. J. Loehrer Sr., S. D. Williams and L. H. Einhorn, *J. Natl. Cancer Inst.* **80**, 1373 (1988).
[4] P. J. Loehrer and L. H. Enihorn, *Ann. Intern. Med.* **100**, 704 (1984).
[5] I. H. Krakoff, *Cancer Treat. Rep.* **63**, 1523 (1979).
[6] J. B. Vermorken and H. M. Pinedos, *Nth. J. Med.* **25**, 270 (1982).
[7] D. D. Vonhoff, R. Schlsky and R. Reichert, *Cancer Treat. Rep.* **63**, 1527 (1979).
[8] A. Eastman and S. Illenye, *Cancer Treat. Rep.* **68**, 1189 (1984).
[9] (a) J. H. Burchenal, K. Kalaher, K. Dew and L. Lokys, *Cancer Treat Rep.* **63** (9–10) 1493 (1979); (b) J. H. Burchenal, K. Kalaher, K. Dew, L. Lokys and G. Gale, *Biochemie* **60**, 961 (1978); (c) J. H. Burchenal, K. Kalaher, T. O'Toole and J. Chishoim, *Cancer Res.* **37**, 3455 (1977).
[10] (a) K. R. Harrap, *Cancer Treat. Rev.* **12**, 2133 (1985); (b) C. Magioni, G. Bolis, S. Pecorelli, K. Bragman, A. Epis, G. Favalli, A. Gambino, F. Landoni, M. Presti, W. Tori, W. Vassena, F. Zanaboni and S. Marsoni, *J. Natl. Cancer Inst.* **81**, 1464 (1989); (c) A. H. Calvert, S. J. Harland, D. R. Newell, Z. H. Siddik and K. R. Harrap, *Cancer Treat. Rev.* **12** (suppl. A) 51 (1981); (d) B. W. Booth, R. B. Weiss, A. H. Korzan, W. C. Wood, R. W. Carey and L. P. Panasci, *Cancer Treat. Rep.* **69**, 919 (1985).
[11] J. M. Extra, M. Espie, F. Calvo, C. Ferme, L. Mignot and M. Marti, *Cancer Chemother. Pharmacol.* **25**, 299 (1990).
[12] G. Gregoniadis *et al.* (Eds.), *Receptor-Mediating Targeting of Drugs*, Plenum Press, New York, p. 427 (1985).
[13] E. Mayhew, D. Papahadjopoulos and M. J. Ostro (Eds.), *Liposomes*, Marcel Deckker, New York, p. 289 (1983).
[14] J. N. Weinstein and L. D. Leserman, *Pharmacol Ther.* **24**, 207 (1984).
[15] G. Poste, R. Kirch, P. Bugelski and P. S. Sunkara (Eds.), *Novel Approach to Cancer Chemotherapy*, Academic, Orlando, FL (1984).
[16] (a) J. Freis, W. H. Mueller, P. Magerstedt and H. J. Schmoll, *Arch. Int. Pharmacodyn. Ther.* **258**, 180 (1980); (b) V. I. Kaledin, N. A. Matlenko, V. P. Nikolin, V. V. Gruntenko and V. G. Budker, *J. Natl. Cancer Inst.* **41**, 1602 (1982); (c) M. B. Yatvin, H. Muhlensiepen, W. Proschen, J. N. Weinstein and L. E. Feinendegen, *Cancer Res.* **258**, 180 (1982).

[17] (a) A. R. Khokhar, S. Al-Baker and G. J. Lumetta, *J. Coord. Chem.* **18**, 291 (1988); (b) A. R. Khokhar, S. Al-Baker, T. Brown and R. Perez-Soler, *J. Med. Chem.* **34**, 325 (1991); (c) A. R. Khokhar, Q. Xu and S. Al-Baker, *J. Coord. Chem.* **24**, 77 (1991); S. Al-Baker, R. Perez-Soler, and A. R. Khokhar, *J. Inorg. Biochem.* **47**, 99 (1992); (e) S. Al-Baker, R. Perez-Soler and A. R. Khokhar, *J Coord. Chem.* **29**, 1 (1993); (f) Mohammad S. Ali, Kenton H. Whitmire, Zahid H. Siddik and Abdul R. Khokhar, *J. Bioinorg. Chem.* **77**, 231–238 (1999).

[18] (a) R. Perez-Soler, A. R. Khokhar and G. Lopez-Berestein, *Cancer. Res.* **47**, 6462 (1987); (b) A. R. Khokhar, S. Al-Baker and R. Perez-Soler, *Anticancer Drug Des.* **3**, 177 (1988); (c) A. R. Khokhar, S. Al-Baker, I. H. Krakoff and R. Perez-Soler, *Cancer Chemother. Pharmacol.* **23**, 219 (1989).

[19] R. Perez-Soler, G. Lopez-Berestein, J. Lauthersztain, S. Al-Baker, K. Francis, D. MaciasKiger, M. N. Raber and A. R. Khokhar, *Cancer Res.* **50**, 4254 (1990).

[20] TEXSAN: Single Crystal Analysis Software, Version 5.0; Molecular Structure Corporation: The Woodlands, TX (1989).

[21] The scattering factors are part of the SHELX-93 package and can be found in the International Tables for X-ray Crystallography; Tables 4.2.6.8 and 6.1.1.4. Kluwers Academic Publishers: Dordrecht, The Netherlands, Vol. C (1992).

[22] SHELXTL-PLUS PC Version 4.2; Siemens Crystallographic Research Systems; Madison, WI (1990).

[23] G. M. Sheldrick, SHELXL-93; University of Gottingen: Gottingen, Germany (1993).

[24] S. C. Dhara, *Ind. J. Chem.* **8**, 193 (1970).

[25] K. Nakamato, *Infrared and Raman Spectra of Inorganic Coordination Compounds*, 4th edn., John Wiley and Sons, New York, p. 383 (1986).

[26] (a) A. R. Khokhar, S. Al-baker, T. Brown and R. Perez-Soler, *J. Med. Chem.* **34**, 321 (1991); (b) S. Al-Baker, R. Perez-Soler and A. R. Khokhar, *J. Inorg. Biochem.* **47**, 99 (1992); (c) S. Al-Baker, R. Perez-Soler and A. R. Khokhar, *J. Coord. Chem.* **29**, 1(1993).

[27] (a) J. H. Price, A. N. Williamson, R. F. Schramm and B. B. Wayland, *Inorg. Chem.* **11**, 1280 (1972); (b) P. Bita, G. O. Morton, T. S. Dunne, E. F. Delos Santos, Y. Lin, S. R. Boone, R. C. Haltiwanger and C. G. Pierpont, *Inorg. Chem.* **29**, 645 (1990); (c) A. R. Khokhar, S. Al-Baker, I. H. Krakoff and R. Perez-Soler, *Cancer. Chemother. Pharmacol.* **23**, 219 (1989).

[28] E. C. H. Ling, W. A. Gregory and T. W. Hambley, *J. Am. Chem. Soc.* **116**, 2673 (1994).

[29] M. Bruck, R. Bau, M. Noji, K. Inagaki and Y. Kidani, *Inorg. Chim. Acta* **92**, 279 (1984).

[30] S. Neidle, I. M. Ismail and P. J. Sadler, *J. Inorg. Biochem.* **13**, 205 (1980).

[31] J. D. Hoeschele, H. D. H. Showalter, A. J. Kraker, W. L. Elliott, B. J. Robert and J. W. Kampf, *J. Med. Chem.* **37**, 2630 (1994).

[32] F. D. Rochon, R. Melanson, J. P. Meacquet, F. Belanger-Gariepy and A. L. Beauchamp, *J. Inorg. Chim. Acta, Chim.* **108**, 17(1985).

[33] P. Bitha, G. O. Morton, T. S. Dunne, E. F. Delos Santos, Y. Lin, S. R. Boone, R. Haltiwanger and C. G. Pierpont, *Inorg. Chem.* **29**, 645 (1990).