# Studies on the Oral Anticancer Drug JM-216: Synthesis and Characterization of Isomers and Related Complexes

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The complex *cis,trans,cis*-[$PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)$] (JM-216) is currently undergoing clinical evaluation as an antitumor agent. In support of characterization and analysis of this complex a study of its isomers and other complexes [$PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}NH_2)$] ($m = 0-4$) has been undertaken. The complexes have been obtained by a variety of synthetic routes which now extend the scope for the preparation of platinum(IV) antitumor complexes. As platinum(IV) complexes are very stable to substitution in the absence of catalysis, use has been made of both light and base catalysis to promote substitution. Oxidative addition to platinum(II) using hypervalent iodine reagents has also been used. The stereochemistry of the complexes has been confirmed by spectroscopic studies, primarily NMR including natural abundance $^{15}N$ NMR spectroscopy.

## Introduction

The preparation of platinum(IV) carboxylate complexes has been described recently.[1,2] Compounds of this type containing *cis* amine ligands have shown potential as antitumor agents suitable for oral administration.[3] One compound of this class, *cis,trans,cis*-[$PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)$] (JM-216), is currently undergoing clinical evaluation in USA, Europe, and Japan.[4] As part of the chemical studies of this compound, its isomers and related complexes have been synthesized and characterized.

Previous studies of platinum(IV) bis(amine) antitumor complexes have been largely based on hydroxo complexes obtained by oxidation of platinum(II) complexes with hydrogen peroxide and chloro complexes obtained by oxidation of the platinum(II) compounds with chlorine or treatment of the hydroxo compounds with chloride under strongly acidic conditions.[5] The recent reporting of the carboxylation of hydroxo-complexes has extended the range of platinum(IV) complexes, but the examples given are limited to *cis,trans,cis* stereochemistry.[2]

The oxidation of platinum(II) complexes with hydrogen peroxide has been shown to proceed with the addition of *trans* hydroxide ligands and retention of the stereochemistry of the platinum(II) complex.[6,7] For the *trans*-ammine complexes [$PtCl_2(OH)_2(NH_3)_2$], it has been found that rearrangement of the anionic ligands may occur readily, leading to conversion of the *all-trans* complex to the *cis,cis,trans* isomer.[8] Complexes containing *trans* chloride ligands and a chelating carboxylate ligand can be obtained by oxidation of the platinum(II) carboxylate complex. One or both axial chloride ligands may then be replaced by reaction of this species with silver carboxylates.[9] The formation of a platinum(IV) complex containing *trans* chloride and *cis* sulfate and water ligands has also been reported as the product of reaction of the tetrachloro complex with silver sulfate, although no evidence was presented to confirm the stereochemistry of the product.[10] The scope of reactions for the preparation of complexes of the type [$PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}NH_2)$] ($m = 0-4$) is thus limited, and alternate routes are required to obtain further isomers.

There are six geometric isomers of [$PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)$] as shown in Figure 1 with the *all-cis* isomers existing as stereoisomers. The *fac* isomers of the trisacetato and trichloro complexes (Figure 2) also exist as stereoisomers. No attempt has been made in this study to separate the individual enantiomers for these compounds.

Here we report the use of a variety of reactions to obtain novel isomers of complexes [$PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}$-

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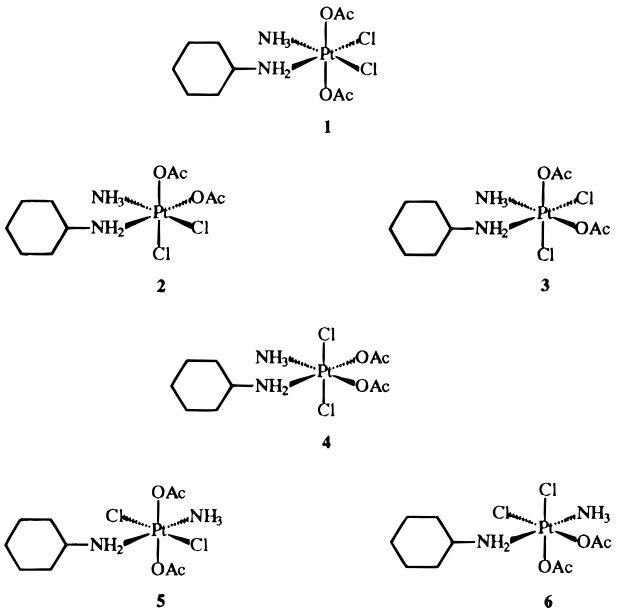


**Figure 1.** Isomers of $[PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)]$.

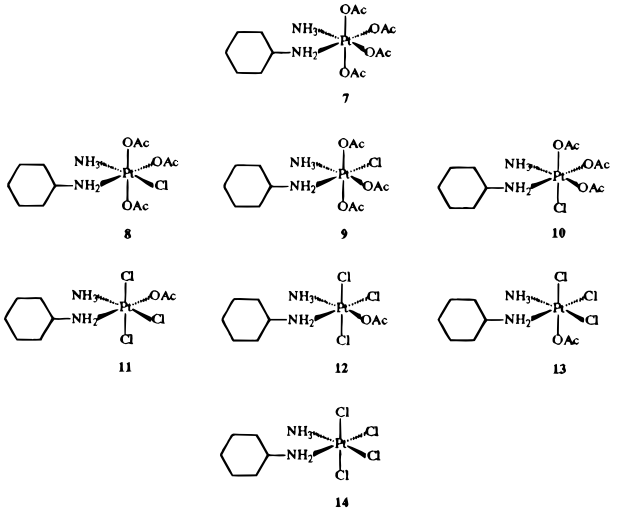


**Figure 2.** Complexes $[PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}NH_2)]$ ($m = 0$, 1, 3, or 4).

$NH_2)]$ ($m = 1-3$). Carboxylation of *trans*-hydroxo complexes has been used to obtain *trans* acetate ligands. Oxidations with (diacetoxyiodo)benzene have been used to add acetate ligands in *cis* positions. Light catalysis has been used to promote substitution in platinum(IV) complexes. This can lead to isomerization or substitution if suitable alternate ligands are available. Base catalysis has also been used to achieve stereoselective substitution in platinum(IV) complexes.

NMR spectroscopy using both $^{13}C$ and $^{15}N$ nuclei has been used to characterize these complexes and, in particular, to confirm their stereochemistry.

## Results and Discussion

**Characterization.** The stereochemistry of the isomers of $[PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)]$ has been determined with reference to that of the *cis,trans,cis* complex for which a single crystal X-ray diffraction study has been published.[11] In the $^{13}C$ NMR spectra a *trans* pair of acetate or chloride ligands creates a symmetry plane which results in equivalence of the C2 and C6 (and C3 and C5) carbons of the cyclohexylamine ring. Equivalence of the acetate ligands arises when these are *trans* to one another or *trans* to the chloride ligands. The *trans,cis,-cis* isomer **4** is therefore defined by the observation of two resonances for the acetate methyl groups but single resonances for C2 and C6 (and C3 and C5) of the cyclohexylamine ring (Table 1). The two *trans* amine isomers **5** and **6** are distinguished by their high symmetry but cannot be differentiated from each other by their $^{13}C$ spectra. Similarly, the two *all-cis* isomers **2** and **3** are identified by the lack of equivalences in their $^{13}C$ spectra but cannot be differentiated from one another.

**Table 1.** $^{13}C$ NMR Data for Complexes $[PtCl_2(OAc)_2NH_3(c\text{-}C_6H_{11}NH_2)]$

| | acetate[a] $\delta$ | | cyclohexylamine[a] $\delta$ | | | |
|---|---|---|---|---|---|---|
| complex | $O_2CCH_3$ | $O_2CCH_3$ | C1 | C2,C6 | C3,C5 | C4 |
| **1** | 182.6 (29) | 23.09 (35) | 56.15 (~10) | 33.85 (16) | 26.07 | 26.43 |
| **2** | 182.0 (24) | 23.45 (32) | 57.68 | 34.05 (17) | 26.11 | 26.36 |
| | 181.7 (29) | 23.88 (29) | | 33.64 (15) | 25.98 | |
| **3** | 182.7 (21) | 24.17 (29) | 56.06 (11) | 33.73 (19) | 26.31 | 26.38 |
| | 182.1 (28) | 24.02 (34) | | 33.40 (13) | 26.18 | |
| **4** | 182.9 (17) | 24.17 | 57.56 | 33.40 (17) | 26.02 | 26.43 |
| | | 24.37 | | | | |
| **5** | 181.7 (28) | 23.40 (35) | 55.60 (<8) | 33.93 (13) | 26.16 | 26.50 |
| **6** | 181.2 (29) | 23.86 (34) | 55.00 (<6) | 33.87 (12) | 26.16 | 26.50 |

[a] $^{13}C-^{195}Pt$ coupling constants are indicated in parentheses.

The *trans* amine isomers are distinguished by their vibrational spectra using the Pt−Cl bands. For **6** these occur at 358 ($\nu_{sym}$) and 301 ($\nu_{asym}$) $cm^{-1}$ in the IR spectrum and at 359 + 367 (probably one band split by solid state effects) and 301 $cm^{-1}$ in the Raman spectrum, consistent with *cis* chloride ligands.[12] For **5** there is only a single strong band at 356 $cm^{-1}$ in the IR spectrum as expected for *trans* chloride ligands. This assignment is also consistent with the chromatographic behavior of the complexes.

The two *all-cis* isomers present a more complex problem for structural assignment which has been resolved by $^{15}N$ NMR spectroscopy. The high solubility (*ca.* 100 g $L^{-1}$) of these complexes in polar aprotic solvents such as *N,N*-dimethylformamide permits satisfactory INEPT spectra to be obtained overnight using a high-field (500 MHz) instrument. The complexes **1** and **4** provide the basic data on the chemical shift and $^{15}N-^{195}Pt$ coupling constants for nitrogen *trans* to chloride and acetate, respectively. The resonances for the amine and cyclohexylamine are assigned by the proton coupling observed in the DEPT spectrum ($NH_3$ quartet $^1J_{N-H}$ 75 Hz, $c\text{-}C_6H_{11}NH_2$ triplet $^1J_{N\text{-}H}$ 74 Hz for both complexes). The data (Table 3) for **1** and **4** show a clear shift of *ca.* −16 ppm with a larger $^{15}N-^{195}Pt$ coupling constant for nitrogen *trans* to acetate compared with nitrogen *trans* to chloride. The data for **2** and **3** then confirm their stereochemistries as cyclohexylamine *trans* to acetate and chloride, respectively.

The $^{13}C$ NMR spectra for the trisacetato complexes **8**, **9**, and **10** and trichloro-complexes **11**, **12,** and **13** distinguish the *fac* isomers by their lack of symmetry and hence inequivalent cyclohexylamine ring carbon atoms (Table 2). Distinction between the two *mer* isomers in each case is not possible by $^{13}C$ NMR spectroscopy alone and again the $^{15}N$ spectra are required to identify the ligands *trans* to each amine. From the data in Table 3 it can be seen that complexes **9** and **12** are related to **1** and have cyclohexylamine *trans* to chloride, while **8** and **11** have cyclohexylamine *trans* to acetate.

HPLC has also been used to characterize these complexes and to assist in following the course of the reactions. The

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**Table 2.** $^{13}C$ NMR Spectral Data for Complexes $[PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}NH_2)]$ ($m$ = 0, 1, 3 or 4)

| | acetate[a] $\delta$ | | cyclohexylamine[a] $\delta$ | | | |
|---|---|---|---|---|---|---|
| complex | $O_2CCH_3$ | $O_2CCH_3$ | C1 | C2, C6 | C3, C5 | C4 |
| **7** | 182.2 (17, eq) | 23.74 (29, eq) | 56.55 | 33.28 (17) | 26.20 | 26.36 |
| | 181.3 (27, ax) | 23.20 (29, eq) | | | | |
| | 181.2 (20, eq) | 22.32 (38, ax) | | | | |
| **8** | 182.3 (28, ax) | 23.50 (29, eq) | 57.21 (8) | 33.58 (16) | 25.95 | 26.36 |
| | 181.0 (23, eq) | 22.62 (35, ax) | | | | |
| **9** | 182.1 (22, eq) | 23.90 (29, eq) | 56.01 (12) | 33.51 (17) | 26.27 | 26.38 |
| | 182.0 (28, ax) | 22.89 (37, ax) | | | | |
| **10** | 182.7 (16, eq) | 24.10 (29, eq) | 56.50 (11) | 33.40 (~17) | 26.14 | 26.34 |
| | 182.1 (17, eq) | 23.77 (28, eq) | | 33.30 (~17) | 26.07 | |
| | 180.8 (29, ax) | 23.18 (35, ax) | | | | |
| **11** | 182.9 (23) | 24.38 (29) | 58.43 (9) | 33.85 (16) | 26.00 | 26.37 |
| **12** | 182.8 (22) | 24.24 (28) | 56.64 (8) | 33.67 (17) | 26.09 | 26.36 |
| **13** | 182.4 (30) | 24.08 (33) | 56.69 | 34.57 (18) | 25.98 | 26.36 |
| | | | | 33.82 (12) | 26.16 | |
| **14** | | | 57.20 (8) | 34.36 (15) | 26.02 | 26.38 |

[a] $^{13}C-^{195}Pt$ coupling constants indicated in parentheses; eq = equatorial, ax = axial, see Figure 2.

**Table 3.** $^{15}N$ NMR Spectral Data for Complexes $[PtCl_m(OAc)_{(4-m)}NH_3(c\text{-}C_6H_{11}NH_2)]$ ($m$ = 1−3)

| complex | ammine[a] $\delta$ | cyclohexylamine[a] $\delta$ |
|---|---|---|
| **1** | −402.8 (254) | −370.7 (245) |
| **4** | −419.6 (267) | −386.3 (262) |
| **2** | −404.9 (246) | −382.7 (271) |
| **3** | −418.9 (270) | −369.7 (241) |
| **8** | −408.0 (254) | −387.4 (272) |
| **9** | −422.7 (278) | −372.8 (248) |
| **11** | −399.8 (234) | −380.0 (271) |
| **12** | −414.1 (277) | −369.9 (234) |

[a] $^{15}N-^{195}Pt$ coupling constants indicated in parentheses.

**Table 4.** Relative Retention of Complexes on Reverse Phase HPLC

| complex | relative retention | complex | relative retention |
|---|---|---|---|
| **7** | 0.45 | **2** | 0.90 |
| **9** | 0.61 | **1** | 1.00 |
| **10** | 0.61 | **13** | 1.07 |
| **3** | 0.74 | **11** | 1.10 |
| **8** | 0.80 | **14** | 1.17 |
| **12** | 0.84 | **6** | 2.38 |
| **4** | 0.86 | **5** | 3.00 |

relative retention times versus **1** for reverse phase conditions are given in Table 4. The complexes are eluted in order of decreasing polarity. Thus *trans* isomers elute much later than *cis* isomers and the *all-trans* isomer **5** has the longest retention time of these complexes. Retention is increased by replacing acetates with chloride ligands. Comparing the behavior of isomers it can be seen that complexes with ammonia *trans* to chloride elute after those with ammonia *trans* to acetate.

**Synthesis.** The complex **1** is prepared by the acetylation of the corresponding hydroxo complex with acetic anhydride.[2] Treatment of the *trans*-amine hydroxo complex $[PtCl_2(OH)_2NH_3(c\text{-}C_6H_{11}NH_2)]$ with acetic anhydride in the dark yields **5**. This reaction in itself provides evidence that the hydroxo complex has *all-trans* stereochemistry, which is otherwise difficult to establish, and that the complex has not undergone isomerization to a *cis,cis,trans* form as described for *trans*-$[PtCl_2(OH)_2(NH_3)_2]$ complexes. However, if the reaction is carried out in light the product obtained is the *cis,cis,trans* isomer **6**. HPLC analysis of the mixture during the course of the reaction indicated that the initial product was **5** which subsequently rearranged to **6**, i.e., isomerization of the acetato rather than the hydroxo complex. No mechanism was described for the isomerization of *trans*-$[PtCl_2(OH)_2(NH_3)_2]$, but it was noted that it was prevented by the addition of hydrogen peroxide during recrystallization of *all-trans*-$[PtCl_2(OH)_2(NH_3)_2]$.[8] No indication was given that precautions were taken to prevent exposure to light, and therefore it seems likely that in that case also photoinduced reduction initiates the isomerization and that the addition of hydrogen peroxide prevents this by trapping the intermediate before rearrangement can take place.

Hypervalent iodine compounds are versatile reagents which have been widely applied in organic chemistry.[13,14] However, they have been little used in inorganic chemistry. For the oxidation of platinum(II) complexes we have found that (diacetoxyiodo)benzene can give somewhat cleaner reactions than manganese(III) or lead(IV) acetates. As for many other oxidative additions to platinum(II) an intermediate species is formed by attack of the platinum complex on the oxidizing agent with the second *trans* ligand being acquired in a subsequent step.[15] This may either be a solvent molecule or another added ligand if the solvent is a poorly coordinating one. To obtain diacetate products we have investigated dichloromethane, chlorobenzene, acetone, and *N,N*-dimethylacetamide as noncoordinating solvents. (In ethanol ethoxide products are formed.) Only minor differences in the product distribution were noted between the solvents. For reaction of *cis*-$[PtCl_2(NH_3)(c\text{-}C_6H_{11}NH_2)]$ with (diacetoxyiodo)benzene a mixture of products is formed with three species predominating. The major product is **2**, but significant amounts of **8** and **13** are also formed. Evidently the lifetime of the five-coordinate intermediate is sufficient for it to rearrange to give the *cis* addition product in contrast to the more normal *trans* oxidative addition reaction. The evidence of halide exchange suggests that the lifetime of the intermediate is sufficient for it also to participate in intermolecular exchange reactions. Reaction of *trans*-$[PtCl_2(NH_3)(c\text{-}C_6H_{11}NH_2)]$ with (diacetoxyiodo)benzene in dichloromethane gives good yields of **4**, further emphasizing the rearrangement of the intermediate prior to coordination of the second acetate ligand.

In contrast with the reactions of (diacetoxyiodo)benzene, the reaction of (dichloroiodo)benzene with *cis*-$[Pt(OH)_2NH_3(c\text{-}C_6H_{11}NH_2)]$ and subsequent treatment with acetic anhydride generates a mixture in which **4** is the dominant species, i.e., the product of *trans* oxidative addition. Since ligand exchange products are still formed, this suggests a thermodynamic preference for the initial intermediate, so that there is a reduced tendency to isomerization.

A study of the photolysis of amminehaloplatinum(IV) complexes in water has been previously reported.[16] Although an

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initial reduction to platinum(III) arising from ligand to metal charge transfer was believed to occur, platinum(II) products were rarely observed, with ligand substitution by water predominating. Substitution *trans* to chloride was found to be favored, with chloride *trans* to OH or $H_2O$ being photostable.

We have made use of this photochemistry to obtain substitution products of *cis*-[$PtCl_4(NH_3)$(*c*-$C_6H_{11}NH_2$)]. As for oxidative addition reactions, an added ligand can compete with a poorly donating solvent. To obtain acetate products the photolysis was carried out in ethanol containing potassium acetate. The course of the reaction was followed by HPLC. The initial products show little selectivity with respect to the different chloride ligands in the molecule. The favored product is **13**, which is obtained by substitution of either of the axial chloride ligands, while substitution of the equatorial ligands yields **11** and **12**. Further substitution continues with loss of a second chloride ligand, generating **2**, **3**, and **4**. A third chloride is then lost, in each case forming **8**. The absence of **1** and triacetate isomers other than **8** is in agreement with the previous conclusion that chloride *trans* to hydroxide or water is photostable. The final yield of **8** in these reactions is poor (<40%) suggesting that other products are formed which elute at the solvent front or which do not elute at all during HPLC. Solvated platinum(II) complexes would be expected to give this behavior.

Although the reactions described above give sources for all complexes [$PtCl_m(OAc)_{(4-m)}NH_3$(*c*-$C_6H_{11}NH_2$)] ($m = 1-3$), poor yields and the unwieldy preparative HPLC isolation procedure led us to explore alternative routes to the some of these complexes. Base-catalyzed solvolysis of platinum(IV) complexes has received little attention in comparison with the work on cobalt(III) complexes.[17] The reactions of platinum(IV) acidoamine complexes with hydroxide were found to be very slow and complicated by reduction to platinum(II).[18] However, given the potential for stereospecific substitution we have explored this possibility. We have found that **1** reacts readily with base leading to chloride substitution.[19] When the reaction is carried out in an aqueous solvent the products are hydroxo-complexes formed by deprotonation of the coordinated water ligand. By carrying out the reaction with approximately 1 equiv of hydroxide the selective substitution of one chloride ligand can be achieved. Treatment of the product [PtCl(OH)-$(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (**15**) with acetic anhydride yields **8,** indicating that it is the chloride *trans* to cyclohexylamine which is lost. As for the oxidative addition reactions of platinum, if a ligand is present at sufficient concentration it may compete effectively with a poorly coordinating solvent for binding to the metal. This has been exploited for the formation of **9**. The reaction was carried out in *N*,*N*-dimethylacetamide using lithium chloride as the source of incoming ligand. Triethylamine was used as the base. Reaction of **7** under these conditions gave substitution of the acetate group *trans* to cyclohexylamine with the formation of **9** in good yield. It should be noted that treatment of **14** with base (hydroxide or carbonate) gave a mixture of products including a significant amount of reduction to platinum(II), consistent with the previous work in this area.[18]

## Conclusion

Platinum(IV) complexes are inert to substitution in the absence of catalysis, e.g., by light. We have demonstrated that this need not be a barrier to the synthesis of the full range of isomers of complexes [$PtX_mZ_{(4-m)}LL'$] ($m = 1-3$). In the absence of crystals suitable for X-ray diffraction studies we have demonstrated that multinuclear NMR spectroscopy may be used to assign structures to these complexes and that significant structural information may be inferred from reverse phase HPLC data.

The antitumor activity of platinum(II) complexes is known to be dramatically influenced by stereochemistry with only a few examples of active *trans* isomers while there are many active *cis* complexes.[20-23] The different isomers of the complexes [$PtCl_2(OAc_2)NH_3$(*c*-$C_6H_{11}NH_2$)] may be expected to have different pharmacokinetics and metabolism on administration to animals, and this may result in significant variations in their antitumor properties. This is currently being investigated.[24]

## Experimental Section

**General Methods.** Organic solvents were obtained from Merck Ltd. (BDH). Organic reagents were obtained from Aldrich Chemical Co. and used without further purification. (Dichloroiodo)benzene was prepared by passing dry chlorine into a solution of iodobenzene in chloroform cooled in an ice−salt bath.[25]

IR spectra were recorded as KBr disks using a Perkin-Elmer 1720X spectrometer. Raman spectra were obtained using Innova 70 CRL $Ar^+$ and 90 CRL $Kr^+$ lasers with a Spex Ramalog 5 instrument and Spex Datamate data acquisition unit. $^1H$ and $^{13}C$ NMR spectra were recorded for solutions in $CD_3OD$ using a Jeol GSX 270 instrument. $^{15}N$ NMR spectra were recorded using solutions in freshly distilled *N*,*N*-dimethylformamide using a Bruker AMX 500 spectrometer operating at 50.70 MHz for $^{15}N$. Chemical shifts are reported in ppm downfield from external nitromethane. Elemental microanalyses were performed at the University of Strathclyde.

For analytical HPLC, samples were chromatographed on Hypersil ODS 5 $\mu$m (250 × 4.8 mm) using aqueous acetonitrile solutions (range 10%−50% v/v) as eluent and UV detection. For preparative HPLC, samples dissolved in 50% aqueous acetonitrile were chromatographed on PLRP-S 100 Å 5 $\mu$m (300 × 30 mm) with aqueous acetonitrile eluent (*ca*. 30% v/v) using a Waters Prep 2000 chromatograph. The eluent composition was adjusted slightly to optimize the separation for each sample. Samples were recovered by evaporation to dryness under reduced pressure with the exclusion of light. The solids were washed with diethyl ether and dried *in vacuo*.

**Preparation of Complexes. *cis,trans,cis*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (1), (*OC*-6-43)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV).** This was prepared as described by Giandomenico *et al*.[2]

***all-cis*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (2), (*OC*-6-42)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV).** A suspension of *cis*-[$PtCl_2(NH_3)$(*c*-$C_6H_{11}NH_2$)] (2 g, 5.2 mmol) in dichloromethane (50 mL) was treated with (diacetoxyiodo)benzene (2 g, 6.2 mmol) and the mixture stirred at room temperature for 20 h. The solution was evaporated under reduced pressure to yield an oil which was triturated with diethyl ether to yield a solid. This was purified by preparative HPLC. Yield 0.5 g (20%). Anal. Calcd for $C_{10}H_{22}N_2Cl_2O_4Pt$: C, 24.01; H, 4.43; N, 5.60; Cl, 14.18. Found: C, 24.16; H, 4.67: N, 5.57: Cl, 14.2. IR $\nu_{max}$ 698 ($\delta$ O−C−O) 343 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (3H, $^4J_{Pt-H} = 2.3$ Hz, OCOC$H_3$) 2.08 (3H, $^4J_{Pt-H} = 3.2$ Hz, OCOC$H_3$).

***trans,cis,cis*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)]·$H_2O$ (4), (*OC*-6-14)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV) Mono-**

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**hydrate.** The complex *trans*-[$PtCl_2(NH_3)$(*c*-$C_6H_{11}NH_2$)] was prepared as previously described.[24] This compound (1 g, 2.6 mmol) was suspended in dichloromethane (20 mL) and treated with (diacetoxyiodo)benzene (1 g, 3.1 mmol). The mixture was stirred at room temperature for 20 h and a pale yellow solid collected by filtration and washed with dichloromethane. The solid was recrystallized from *N*,*N*-dimethylacetamide and water, and the product was recovered as a monohydrate. Yield 0.3 g (22%). Anal. Calcd for $C_{10}H_{24}N_2Cl_2O_5Pt$: C, 23.18; H, 4.67; N, 5.41; Cl 13.69. Found: C, 23.07; H, 4.60; N, 5.30; Cl, 14.2. IR $\nu_{max}$ 3537 ($\nu$ O−H) 703, 690 ($\delta$ O−C−O) 354 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.07 (3H, OCOC$H_3$) 2.08 (3H, OCOC$H_3$).

***all-trans*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (5), (*OC*-6-12)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV).** A suspension of *all-trans*-[$PtCl_2(OH)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (1 g, 2.4 mmol) in a mixture of acetic anhydride (5 mL) and diethyl ether (3 mL) was stirred in the dark for 3 days. The yellow product was collected by filtration and washed with diethyl ether. Yield 0.75 g (62%). Anal. Calcd for $C_{10}H_{22}N_2Cl_2O_4Pt$: C, 24.01; H, 4.43; N, 5.60; Cl, 14.18. Found: C, 24.02; H, 4.35; N, 5.53; Cl, 14.4. IR $\nu_{max}$ 712 ($\delta$ O−C−O), 356 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.01 (6H, $^4J_{Pt-H}$ = <3 Hz, OCOC$H_3$).

***cis,cis,trans*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (6), (*OC*-6-22)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV).** The complex was prepared as previously described.[24] A suspension of *all-trans*-[$PtCl_2(OH)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (2 g, 4.8 mmol) in acetic anhydride (10 mL) was stirred at ambient temperature for 5 days without protection from daylight. The cream-colored product was collected by filtration and washed with diethyl ether. Yield 1.72 g (72%). Anal. Calcd for $C_{10}H_{22}N_2Cl_2O_4Pt$: C, 24.01; H, 4.43; N, 5.60; Cl, 14.18. Found: C, 24.16; H, 4.33; N, 5.52; Cl, 14.1. IR $\nu_{max}$ 695 ($\delta$ O−C−O) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (6H, OCOC$H_3$).

***cis*-[$Pt(OAc)_4NH_3$(*c*-$C_6H_{11}NH_2$)] (7), (*OC*-6-32)-Tetrakis(acetato-*O*)amminecyclohexylamineplatinum(IV).** An aqueous suspension of *cis*-[$PtCl_2(NH_3)$(*c*-$C_6H_{11}NH_2$)] (4.5 g, 11.8 mmol) was stirred with silver nitrate (3.92 g, 23.1 mmol) overnight with protection from light. The suspension was filtered to remove AgCl and the filtrate passed down a column of Amberlite IRA-400 resin (OH form, 100 mL) to remove nitrate. The eluent was treated with activated charcoal and filtered, hydrogen peroxide (30% w/v; 8 mL, 70 mmol) was added to the eluent, and the mixture heated at 80 °C for 30 min. The solution was allowed to cool and evaporated under reduced pressure to low volume using additions of ethanol to minimize foaming. [Caution: Solutions containing residual hydrogen peroxide should not be reduced to dryness]. The solution was treated with acetone to yield white *cis*-[$Pt(OH)_4NH_3$(*c*-$C_6H_{11}NH_2$)]. This was washed with diethyl ether and dried *in vacuo*. Yield 2.95 g (66%). A sample (0.6 g) was stirred in acetic anhydride for 16 h at room temperature. Evaporation of the solution yielded an oil which was dissolved in acetone to precipitate the white crystalline product. This was recrystallized from ethanol and diethyl ether. Yield 0.3 g (35%). Anal. Calcd for $C_{14}H_{28}N_2O_8Pt$: C, 30.72; H, 5.16; N, 5.12. Found: C, 31.03; H, 5.19; N, 5.09. IR $\nu_{max}$ 706, 687 ($\delta$ O−C−O) $cm^{-1}$. $^1H$ NMR $\delta$ 2.03 (6H, $^4J_{Pt-H}$ = 3.2 Hz, OCOC$H_3$) 2.06 (3H, OCOC$H_3$) 2.10 (3H, OCOC$H_3$).

**[$PtCl(OH)(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)]·$H_2O$ (15), (*OC*-6-52)-Bis(acetato-*O*)amminechloro(cyclohexylamine)hydroxoplatinum(IV) Monohydrate.** A solution of **1** (5 g, 10 mmol) in 75/25 acetonitrile/water (800 mL) was treated with KOH (1 M, 12 mL). The mixture was stirred for 3 h in the dark at room temperature and then evaporated under reduced pressure until precipitation was initiated. The white product was washed with acetone and dried *in vacuo*. Yield 2.1 g (44%). Anal. Calcd for $C_{10}H_{25}N_2ClO_6Pt$: C, 24.03; H, 5.04; N, 5.60; Cl, 7.09. Found: C, 24.13; H, 5.00; N, 5.52; Cl, 7.35. IR $\nu_{max}$ 712 ($\delta$ O−C−O) 562 (Pt−OH) 331 ($\nu$ Pt−Cl) $cm^{-1}$.

***mer*-[$PtCl(OAc)_3NH_3$(*c*-$C_6H_{11}NH_2$)] (8), (*OC*-6-43)-Tris(acetato-*O*)amminechloro(cyclohexylamine)platinum(IV).** A suspension of **15** (0.5 g) in acetic anhydride (3 mL) was stirred at room temperature for 16 h. The solution was evaporated under reduced pressure and the resultant oil triturated with diethyl ether to yield the white crystalline product. Yield 0.5 g (92%). Anal. Calcd for $C_{12}H_{25}N_2ClO_6Pt$: C, 27.51; H, 4.81; N, 5.35; Cl, 6.77. Found: C, 27.72; H, 4.85; N, 5.44; Cl, 7.07. IR $\nu_{max}$ 702 ($\delta$ O−C−O) 341 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (6H, $^4J_{Pt-H}$ = 3 Hz, OCOC$H_3$) 2.06 (3H, $^4J_{Pt-H}$ = <2.5 Hz, OCOC$H_3$).

***mer*-[$PtCl(OAc)_3NH_3$(*c*-$C_6H_{11}NH_2$)] (9), (*OC*-6-34)-Tris(acetato-*O*)amminechloro(cyclohexylamine)platinum(IV).** Triethylamine (0.7 mL) and **7** (1.1 g) were added to a solution of lithium chloride in *N*,*N*-dimethylacetamide (2 M, 5 mL). The mixture was stirred at room temperature for 50 min and then diluted with acetone to precipitate excess lithium chloride. The solution was filtered and evaporated to an oil which was purified by preparative chromatography. Yield 0.55 g (52%). Anal. Calcd for $C_{12}H_{25}N_2ClO_6Pt$: C, 27.51; H, 4.81; N, 5.35; Cl, 6.77. Found: C, 27.64; H, 4.99; N, 5.20; Cl, 6.76. IR $\nu_{max}$ 706, 698 ($\delta$ O−C−O) 343 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (6H, $^4J_{Pt-H}$ = 3.2 Hz, OCOC$H_3$) 2.09 (3H, $^4J_{Pt-H}$ = <2.1 Hz, OCOC$H_3$).

***fac*-[$PtCl(OAc)_3NH_3$(*c*-$C_6H_{11}NH_2$)]·$H_2O$ (10), (*OC*-6-24)-Tris(acetato-*O*)amminechloro(cyclohexylamine)platinum(IV) Monohydrate.** This complex was obtained by preparative HPLC. Mixtures containing the complex were obtained in two ways: (i) stirring **14** and silver acetate (1 equiv) in acetone at 40 °C in the dark for 7 days and (ii) stirring **14** (3 g, 6.6 mmol) in ethanolic potassium acetate (0.5 M, 100 mL) for 3 days in the light. The solution was evaporated, redissolved in acetone, and filtered three times to remove KOAc/KCl before chromatography. Typical yield *ca.* 5%. Anal. Calcd for $C_{12}H_{27}N_2ClO_7Pt$: C, 26.60; H, 5.02; N, 5.17; Cl, 6.55. Found: C, 26.46; H, 4.88; N, 5.03; Cl, 6.86. IR $\nu_{max}$ 703, 693 ($\delta$ O−C−O) 357 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.05 (3H, OCOC$H_3$) 2.075 (3H, $^4J_{Pt-H}$ = 3 Hz, OCOC$H_3$) 2.09 (3H, OCOC$H_3$).

***cis*-[$PtCl_4NH_3$(*c*-$C_6H_{11}NH_2$)] (14), (*OC*-6-32)-Ammine(tetrachloro)cyclohexylamineplatinum(IV).** A solution of *cis,trans,cis*-[$PtCl_2(OH)_2NH_3$(*c*-$C_6H_{11}NH_2$)] was heated in dilute hydrochloric acid (1 M) at 80 °C for 2 h. The product precipitated on cooling (typical yield 50%). The complex may also be obtained by oxidation of *cis*-[$PtCl_2(NH_3)$(*c*-$C_6H_{11}NH_2$)] with chlorine at room temperature (typical yield 46%). Anal. Calcd for $C_6H_{16}N_2Cl_4Pt$: C, 15.91; H, 3.56; N, 6.14; Cl, 31.30. Found: C, 15.90; H, 3.44; N, 6.10; Cl, 31.4. IR $\nu_{max}$ 346 ($\nu$ Pt−Cl) $cm^{-1}$.

***all-cis*-[$PtCl_2(OAc)_2NH_3$(*c*-$C_6H_{11}NH_2$)] (3), (*OC*-6-32)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum(IV); *mer*-[$PtCl_3(OAc)NH_3$(*c*-$C_6H_{11}NH_2$)] (11), (*OC*-6-41)-(Acetato-*O*)amminetrichloro(cyclohexylamine)platinum(IV); *mer*-[$PtCl_3(OAc)NH_3$(*c*-$C_6H_{11}NH_2$)] (12), (*OC*-6-31)-(Acetato-*O*)amminetrichloro(cyclohexylamine)platinum(IV); *fac*-[$PtCl_3(OAc)NH_3$(*c*-$C_6H_{11}NH_2$)] (13), (*OC*-6-43)-(Acetato-*O*)amminetrichloro(cyclohexylamine)platinum(IV).** A solution of **14** in ethanolic potassium acetate (0.5 M, 100 mL) was stirred in daylight for 3 h. The mixture was evaporated to dryness and redissolved in acetone. This mixture was filtered to remove potassium chloride and excess potassium acetate. Evaporation, dissolution, and filtration was repeated twice more and the final residue was separated using preparative HPLC.

**3:** Yield *ca.* 4%. Anal. Calcd for $C_{10}H_{22}N_2Cl_2O_4Pt$: C, 24.01; H, 4.43; N, 5.60; Cl, 14.18. Found: C, 24.22; H, 4.25; N, 5.42; Cl, 14.4. IR $\nu_{max}$ 697 ($\delta$ O−C−O) 352 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.07 (3H,-OCOC$H_3$) 2.08 (3H, OCOC$H_3$).

**11**: Yield *ca.* 5%. Anal. Calcd for $C_8H_{19}N_2Cl_3O_2Pt$: C, 20.16; H, 4.02; N, 5.88; Cl, 22.31. Found: C, 20.30; H, 3.73; N, 5.77; Cl, 22.4. IR $\nu_{max}$ 694 ($\delta$ O−C−O) 349 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (3H, $^4J_{Pt-H}$ = 2.4 Hz, OCOC$H_3$).

**12**: Yield *ca.* 3%. Anal. Calcd for $C_8H_{19}N_2Cl_3O_2Pt$: C, 20.16; H, 4.02; N, 5.88; Cl, 22.31. Found: C, 20.36; H, 4.03; N, 6.03; Cl, 20.8. IR $\nu_{max}$ 695 ($\delta$ O−C−O) 349 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.05 (3H, OCOC$H_3$).

**13**: Yield *ca.* 10%. Anal. Calcd for $C_8H_{19}N_2Cl_3O_2Pt$: C, 20.16; H, 4.02; N, 5.88; Cl, 22.31. Found: C, 20.13; H, 3.96; N, 5.72; Cl, 22.2. IR $\nu_{max}$ 696 ($\delta$ O−C−O) 347 ($\nu$ Pt−Cl) $cm^{-1}$. $^1H$ NMR $\delta$ 2.04 (3H, $^4J_{Pt-H}$ = 3.2 Hz, OCOC$H_3$).

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