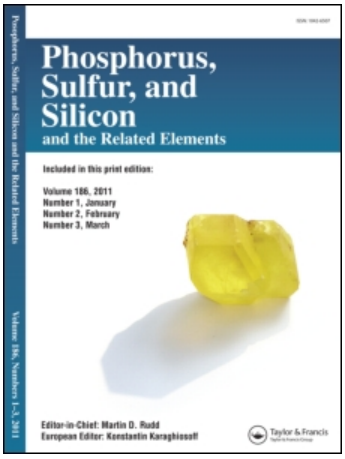

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PLATINUM(II) COMPLEXES OF P(III) CYCLOPHOSPHAMIDE DERIVATIVES

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PLATINUM(II) COMPLEXES OF P(III) CYCLOPHOSPHAMIDE DERIVATIVES

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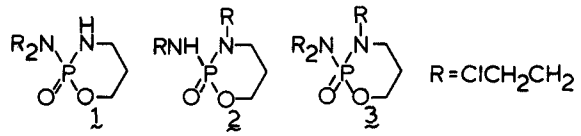
The syntheses of the P(III) analogues of cyclophosphamide, isophosphamide and triphosphamide are reported. These compounds (**4–6**, respectively) polymerize easily at room temperature but are sufficiently stable in solution to react with $Cl_2Pt(NCPh)_2$, forming *cis*-Cl_2Pt(**4**)$_2$, *cis*-Cl_2Pt(**5**)$_2$ and *cis*-Cl_2Pt(**6**)$_2$ (complexes **9–11**, respectively). Complex **10** can also be made by condensing *cis*-$Cl_2Pt[ClPN(CH_2CH_2Cl)CH_2CH_2CHO]_2$ with $ClCH_2CH_2NH_2$, while an alternate route to **9** and **11** is afforded by the condensation of *cis*-$Cl_2Pt[Cl_2PN(CH_2CH_2Cl)_2]_2$ with $H_2NCH_2CH_2CH_2OH$ and $ClCH_2CH_2NHCH_2CH_2CH_2OH$, respectively. Complexes **9–11** exist in two diastereomeric configurations and these can be separated in the cases of **9** and **11** by column chromatography. ^{31}P NMR spectral data for the complexes are discussed and the results of NCI antitumor screening are presented.

INTRODUCTION

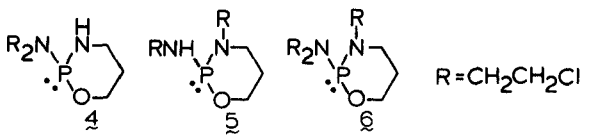
Cyclophosphamide (**1**) is effective against more varieties of human cancer than any of the approximately fifty compounds shown to have clinically-



cyclophosphamide isophosphamide triphosphamide

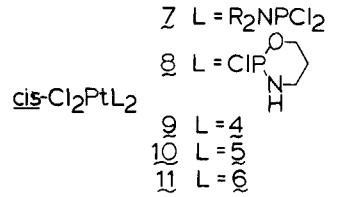
detectable antitumor activity.[1,2] It is therefore not surprising that more doses of this drug are administered to cancer patients than any other chemotherapeutic agent.[1] Also promising in this regard are the newer derivatives **2**[3] and **3**[4]. Of the more than five hundred platinum compounds tested by the National Cancer Institute, several have emerged with significant potential as chemotherapeutics for neoplastic diseases and *cis*-$Cl_2Pt(NH_3)_2$ has progressed to phase II clinical trials.

Because synergism has been observed when cyclophosphamide is used in combination with a platinum compound,[7] it is not unreasonable to suppose that complexation of the phosphamides



in trivalent form (**4–6**) to a *cis*-Cl_2Pt moiety might result in compounds displaying interesting cancerostatic activity. It is realized, of course, that the metabolic pathway utilized by such a complex could be quite different from that of the phosphamides since the latter have been found to undergo mixed function oxidose oxidation by liver microsomes.[1,2,8]

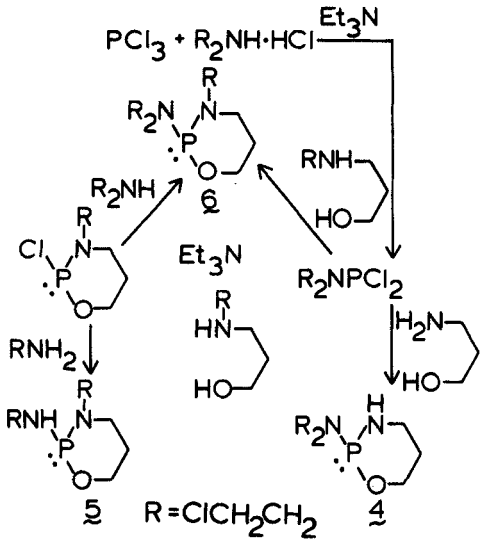
Here we report the synthesis of **4–6** and the platinum complexes **7–11**. Evidence for diastereomers of **9–11** is presented and preliminary results of cancer screening experiments are given.



DISCUSSION

P(III) Phosphamides

The syntheses of **4–6** were accomplished by means of the reactions summarized in Scheme I. Solutions of these compounds are unstable at room temperature but the substances do remain intact for several days in solutions frozen in liquid nitrogen. Their instability may arise from intra and/or



SCHEME I

intermolecular nucleophilic attack by a phosphorus lone pair on a chlorine-bearing carbon:

$$\text{—P:} + \text{ClCH}_2\text{CH}_2\text{—} \longrightarrow \text{—}\overset{+}{\text{P}}\text{CH}_2\text{CH}_2\text{—} + \text{Cl}^- \qquad \text{Rx. 1}$$

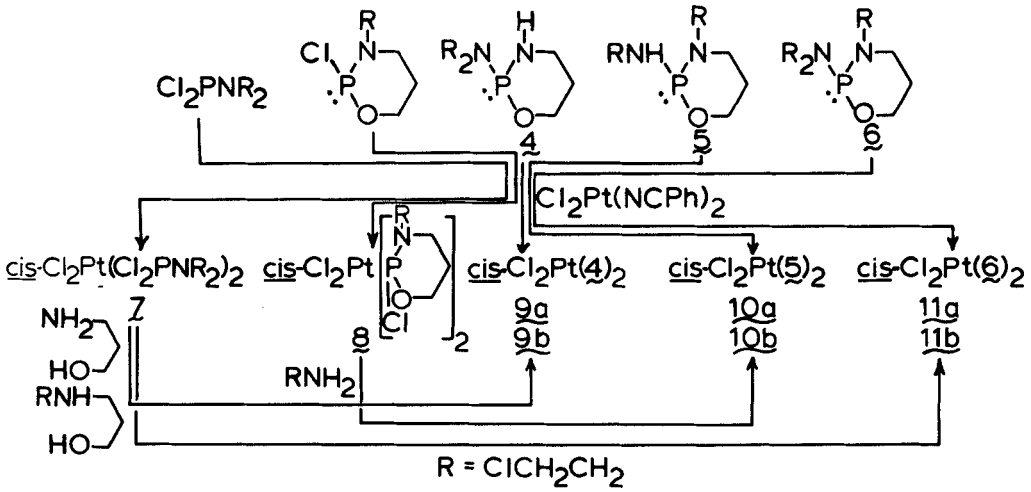
Although no yield could be ascertained in the synthesis of **4** because of the presence of several ^{31}P signals in the reaction mixture, a lower yield limit of 26% can be estimated from the preparation of the *cis*-$Cl_2Pt(\mathbf{4})_2$ diastereomers by Method B (see Experimental). As judged from the single ^{31}P absorptions in the fresh reaction mixtures of **5** and **6**, the yields of these ligands were probably nearly quantitative. This is further borne out by the single ^{31}P NMR absorption for triphosphamide (**3**) observed on oxidation of the reaction mixture of **6**, and the 73% yield of pure **3** realized on workup. Because of the unstable nature of **4**–**6**, evaluation of their antitumor properties was precluded.

Platinum Complexes 7–11

Using the transformations depicted in Scheme II, the platinum (II) complexes **7**–**11** of the P(III) phosphamides **4**–**6**, respectively, were synthesized. The low yield of **9** (5.0%) compared to those of **10** (39%) and **11** (45%) probably reflects the low yield of **4** realized in its preparation. The yield of **9** was substantially improved (26%) by reacting *cis*-$Cl_2Pt(Cl_2PNR_2)_2$ with 3-aminopropanol-1. The analogous reaction leading to **11** gave the product in 36% yield. Complex **10** was realized in 77% yield upon reaction of **8** with 2-chloroethylamine·HCl in the presence of Et_3N.

Owing to the chiral nature of the phosphorus ligand in **8**–**11**, *dl* and *meso* modifications are expected for the complexes. For **9** and **11** the diastereomers a and b can be separated by chromatography. In the case of **8**, it is probable that chloride exchange on the phosphorus is rapid on the NMR time scale[9] and this would prevent detection of diastereomeric complexes. Efforts to separate **10a,b** have thus far been unsuccessful.

From Table I it is seen that the diastereomers of **9**–**11** possess different ^{31}P chemical shifts and



SCHEME II

TABLE I

^{31}P NMR spectral data for *cis*-Cl_2PtL_2 complexes[a]

L	Complex Diastereomer	$\delta^{31}P$ (ppm)	$^1J^{195}Pt^{31}P$ (Hz)
$Cl_2PNR_2^b$		90.7[c]	5095.0[c]
$ClPNRCH_2CH_2CH_2O$		87.3	5427.2
$R_2NPNHCH_2CH_2CH_2O$ (4)	**9a**	68.5	5173.2
	9a	68.2	5121.0
$RNHPNRCH_2CH_2CH_2O$	**10a**	64.4	5064.9
	10b	62.9	4951.7
$R_2NPNRCH_2CH_2CH_2O$	**11a**	72.5	5229.0
	11b	74.2	5190.2

[a] In $CDCl_3$ except as indicated.
[b] R = $ClCH_2CH_2$
[c] In $(CD_3)_2CO$

$^1J^{195}Pt^{31}P$ coupling constants. Interestingly the $^1J^{195}Pt^{31}P$ values for the b diastereomers differ by 39–113 Hz. The "a" and "b" designations for the two modifications of **9** and **11** were made on the basis of the different R_f values on TLC; the higher value corresponding to "a". Since the "a" modifications of these complexes also possessed higher $^1J^{195}Pt^{31}P$ couplings, this criterion was used to label the a and b diastereomers of **10**. The assignment of the diastereomeric configurations in **9a,b**–**11a,b** is the subject of current efforts. It is of interest that the equilibration of **10a,b** and of **11a,b** led to *ca.* 80/20 ratios of **10b/10a** and **11a/11b**. Equilibration experiments with **9a,b** samples did not give consistent results.

The *cis* configuration of these complexes is supported by their colorless appearance and their relative insolubility in non-polar organic solvents.[10] Their $^1J^{195}Pt^{31}P$ values are also in the range for *cis*-$Cl_2Pt[P(OR)_3]_2$ complexes.[11]

In vivo screening carried out by the National Cancer Institute on L-1210 lymphoid leukemia mouse tumors showed that complexes **9a**, **9b**, **10a**, **10b**, **11a** and **11b** all showed T/C percentages between 87 and 104, thus failing the minimal percentage of 125 for activity in this system. No significant differences in T/C ranges were observed among the compounds. In hindsight, many possible reasons could be enumerated for the failure of these complexes to register significant activity in an antitumor screening experiment. Interesting, however, is the observation that these complexes are unable to function as well as the phosphamides **1**–**3** despite the fact that low valent transition metal-phosphorus bonds, like the phosphoryl link (O=P) possesses substantial multiple bond character.[12] The Pt-P bonds in the complexes apparently do not permit the P(III) phosphamide ligands to mimic effectively the phosphamides **1**–**3** in their metabolism.

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EXPERIMENTAL

All preparations were carried out in a dry nitrogen atmosphere. ^{31}P NMR spectra were obtained on solutions in 10 mm tubes with a Bruker HX-90 instrument operating at 36.434 mHz in the FT mode. The spectrometer was locked on the ^2H resonance of the deuterated solvent. The external standard was 85% H_3PO_4 contained in a 1 mm capillary held coaxially in the sample tube by a Teflon vortex plug. Positive shifts are those downfield of the standard. Proton spectra were obtained on a Varian HA-100 or A-60 instrument using TMS as an internal standard.

trans-dichlorobis(benzonitrile)platinum(II). This compound was prepared by a literature method.[13]

bis-(β-chloroethyl)amine. Solutions of this compound were made as needed from the commercially available hydrochloride by neutralizing a 5°C aqueous solution of the latter with NaOH and extracting the product into CH_2Cl_2. Such a solution can be stored in a refrigerator over molecular sieves.

N,N-bis(2-chloroethylamino)phosphorus dichloride. To a solution of 13.7 g (100 mmol) of PCl_3 in 100 mL of benzene was added 17.8 g (100 mmol) of N,N-*bis*(2-chloroethyl)amine hydrochloride. While stirring this suspension, 20.2 g (200 mmol) of triethylamine was added dropwise at room temperature. Following the termination of the ensuing exothermic reaction, the reaction mixture was stirred under reflux for 3 hrs. After cooling to room temperature the triethylamine hydrochloride was removed by filtration, washed with benzene and the solvent evaporated from the filtrate. The residue was distilled at 106° at 0.5 mm (yield, 21.6 g, 87.7%; δ^1H($CDCl_3$) 3.6–3.85 m; δ^{31}P($CDCl_3$) 162.2).

3-N-ethyleneimine propanol-1. To 28.6 g (665 mmol) of anhydrous aziridine was added 59.7 mL (57.2 g, 665 mmol) of methyl acrylate at room temperature with vigorous stirring. After heating at 78° for 7 hrs the 3-N-ethyleneimine methylpropanoate was distilled at 40° at 0.5 mm using a short-path condenser (yield 60.3 g, 80.2%). To 9.88 g (87.3 mmol) of this product in 150 mL of dry ether was added 1.453 g (38.3 mmol) of $LiAlH_4$ in 50 mL of dry ether at room temperature with stirring. After completion of the addition (30 min) the mixture was refluxed for 40 min, cooled to room temperature and hydrolyzed by slowly adding $Na_2SO_4 \cdot 10H_2O$. Separation of the ether layer and evaporation of the solvent left a clear viscous liquid which was distilled using a short path condenser at 53–5° at 0.5 mm (yield, 6.44 g, 73%).

3-N-β-chloroethylamine propanol-1. To 50 mL of concentrated HCl was added dropwise, with vigorous stirring, 10.1 g (100 mmol) of 3-N-ethyleneimine propanol-1. After the exothermic reaction had subsided, the hydrochloride was recovered by evaporating the water under vacuum. The residue was again dissolved in water and the solvent evaporated to remove most of the HCl. The residue was then dissolved in 50 mL of H_2O, cooled to ice temperature and neutralized with 30% aqueous NaOH. After extracting the amino alcohol with three 100 mL portions of CH_2Cl_2, the organic layer was dried with Na_2SO_4, concentrated to about 100 mL and stored in a refrigerator over molecular sieves (^{1}H NMR spectrum ($CDCl_3$) δ^1H $CH_2CH_2CH_2$ 1.73 quint, ^{3}JHH 6.5, 2H; δ^1H CH_2N 2.85 t, ^{3}JHH 6.9, 2H; δ^1H CH_2N 3.00, ^{3}JHH 5.9 t, 2H; δ^1H CH_2O CH_2Cl 3.72 t, ^{3}JHH 6.0, 4H; δ^1H O*H* N*H* 3.91 s, 2H). The product is unstable, polymerizing when stored at room temperature in a concentrated solution.

2-Chloro-1-β-chloroethylamino-1,3,2-aza-oxaphosphorinane. To a vigorously stirred solution of 20.2 g (200 mmol) of Et_3N in 200 mL of benzene at 5° was added dropwise and simultaneously a solution of 1.37 g (100 mmol) of PCl_3 in 100 mL of benzene and 100 mL of a CH_2Cl_2 solution containing 0.1 mol of 3-N-β-chloroethylamine propanol-1. The mixture was stirred for 15 min at room temperature, filtered, and the precipitate was washed with 100 mL of benzene. After evaporation of the solvent from the filtrate, the residue was distilled at 80° at 0.07 mm (yield 15.0 g, 74.0%; ^{1}H NMR spectrum ($CDCl_3$) δ^1H $CH_2CH_2CH_2$ 1.7–2.2 m, 2H; δ^1H CH_2N CH_2Cl 2.9–3.8 m, 6H; δ^1H CH_2O 3.9–4.5 m, 2H; δ^{31}P ($CDCl_3$) 158.7). The product contains *ca.* 3–4% of an unidentified impurity, as judged by a ^{31}P resonance at 163.0 ppm, which did not disappear on distillation.

2-(Bis-β-chloroethylamino)-1,3,2-aza-oxaphosphorinane, **4**. To a well stirred solution of 2.0 g (20 mmol) of Et_3N in 15 mL of toluene at −20° was added simultaneously a solution of 2.4 g (100 mmol) of N,N-*bis*(2-chloroethylamino)-phosphorus dichloride in 5 mL of toluene and a solution of 0.75 g (10 mmol) of 3-aminopropanol-1 in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 15 min, filtered, and the precipitate washed with 5 mL of toluene. After evaporation of the filtrate to 1 mL, 10 drops of C_6D_6 were added and the ^{31}P spectrum obtained (δ^{31}P 147.5, 133.9, 130.8, 127.6, 123.1, 105.3, and 97.7). The relative intensities of the peaks varied from one experiment to the other. A similar mixture was produced when Et_2O or CH_2Cl_2 was the solvent and when excess 3-aminopropanol-1 was used instead of Et_3N as the condensing agent.

Solutions must be stored in the cold. At room temperature they deposit polymeric gums, the mother liquors of which display several ^{31}P absorptions in the 0–56 ppm range with the most intense one at 55.2 ppm. Evidence for the presence of **4** in these solutions comes from its derivitization as the diastereomeric platinum complexes **10a,b** (*vide infra*).

2-β-Chloroethylamino-1-β-chloroethylamino-1,3,2-aza-oxaphosphorinane, **5**. To a stirred suspension of 1.15 g (100 mmol) of β-chloroethylamine hydrochloride in 15 mL of CH_2Cl_2 was added at room temperature 2.0 g (20 mmol) of Et_3N. The mixture was stirred for 15 min at room temperature and then cooled in a Dry-Ice bath. A solution of 2-chloro-1-β-chloroethylamino-1,3,2-aza-oxaphosphorinane (2.0 g, 10 mmol) in 5 mL of CH_2Cl_2 was added dropwise at −10°. After stirring the mixture at 0° for 15 min, it was filtered and the $Et_3N \cdot HCl$ precipitate washed with 5 mL of CH_2Cl_2 (^{31}P NMR spectrum (CH_2Cl_2 solution with added C_6D_6) δ^{31}P 118.5 ppm; ^{1}H NMR spectrum (CH_2Cl_2) δ^1H $CH_2CH_2CH_2$ 1.75–2.25 m, 2H; CH_2N CH_2Cl 3.0–3.9 m, 10H; CH_2O 4.2–4.7 m, 2H).

While stable in solution at liquid N_2 temperature, room temperature solutions deposit gums and register several peaks in the ^{31}P spectrum between 20–56 ppm which appear at the expense of the 118.5 signal.

Bis-(β-chloroethylamino)-1-β-chloroethylamino-1,3,2-aza-oxaphosphorinane, **6**. Method A: To a well-stirred solution of 2-chloro-1-β-chloroethylamino-1,3,2-aza-oxaphosphorinane (2.0 g, 10 mmol) in 20 mL of toluene at −20° was added 10 mL of a 1.0 M CH_2Cl_2 solution of *bis*-(β-chloroethyl)amine containing 1.0 g (10 mmol) of Et_3N. Following completion of the addition, the mixture was stirred for 15 min at room temperature. The precipitate ($Et_3N \cdot HCl$) was filtered, washed with 5 mL of toluene and the filtrate subjected to ^{31}P NMR spectroscopic examination after adding C_6D_6 (δ^{31}P 138.4). A repetition of the preparation in CH_2Cl_2 afforded a ^{1}H NMR spectrum in this solvent (δ^1H $CH_2CH_2CH_2$ 1.8–2.1 m, 2H; δ^1H CH_2N CH_2Cl 2.9–3.95 m, 14H; δ^1H CH_2O 4.25–4.8 m, 2H).

Stability characteristics of this compound are similar to those of **4** and **5**. New ^{31}P peaks in the 30–70 ppm range appear on standing at room temperature while the 138.4 absorption decreases.

Method B: The CH_2Cl_2 solution of 3-N-β-chloroethylamine propanol-1 was prepared as described above on a 0.05 molar scale and concentrated to 30 mL. This solution was added dropwise simultaneously with a solution of 12.1 g (50 mmol) of N,N-*bis*(2-chloroethyl)phosphorus dichloride in 20 mL of CH_2Cl_2, into a well stirred solution of Et_3N (10.1 g, 100 mmol) in 150 mL of toluene held at −20°. Following stirring for 30 min at 0° and 10 min at room temperature, the amine hydrochloride was filtered and washed with toluene (^{31}P NMR spectrum (CH_2Cl_2 with added C_6D_6) δ^{31}P 138.4).

Oxidation of ***6*** *to* ***3***. A solution of **6** was prepared on a 0.01 molar scale by Method A using CH_2Cl_2 in place of toluene. The solution was cooled to $-20°$, stirred and N_2O_4 passed through for 15 min. After warming back to room temperature and evaporation of the solvent, the residue consisting mainly of crude **3** (as shown by comparison of the ^{31}P NMR spectrum with an authentic sample)[14] was recrystallized from Et_2O to give pure **3** (yield, 2.13 g, 73%; mp 49–51° (51–52°)[14]; ^{31}P NMR spectrum ($CDCl_3$) $\delta^{31}P$ 13.3).

Cis-$Cl_2Pt[Cl_2PN(CH_2CH_2Cl)_1]_2$, *7*. A solution of

$$Cl_2PN(CH_2CH_2Cl)_2$$

(2.09 g, 8.6 mmol) and $Cl_2Pt(NCPh)_2$ (2.04 g, 4.30 mmol) in 20 mL of CH_2Cl_2 upon standing overnight at room temperature deposited 1.95 g of colorless crystalline product which was filtered and washed with CH_2Cl_2. Addition of 20 mL of Et_2O and refrigeration for 3 hrs caused an additional 2.9 g of crystals to form (total yield 90%; mp 170–2°; anal calcd for

$$C_8H_{16}Cl_8N_2P_2Pt$$

(found): C, 12.78 (12.94); H, 2.14 (2.14); N, 3.73 (3.54); Cl, 47.16 (46.92)).

Cis-$Cl_2Pt[\overline{ClPNRCH_2CH_2CH_2O}]_2$, *8*. To a solution of

$$Cl_2Pt(NCPh)_2$$

(2.36 g, 5.00 mmol) in 20 mL of CH_2Cl_2 was added 2.1 g (10.5 mmol) of $\overline{ClPNRCH_2CH_2CH_2O}$. After the exothermic reaction ceased, the solution was refrigerated overnight whereupon white crystals of product (2.2 g) were obtained on filtration. Addition of 20 mL of Et_2O and further refrigeration yielded an additional 0.7 g of product (total yield 86%; mp 172–4°; anal calcd for $C_{10}H_{20}Cl_4N_2O_2P_2Pt$ (found): C, 17.92 (17.48); H, 3.01 (2.98); N, 4.18 (3.94); Cl, 31.74 (32.28)).

Diastereomers of cis-$Cl_2Pt(3)_2$, ***9a,b***. Method A: To a 0° solution of **3**, prepared on a 0.01 molar scale in CH_2Cl_2 instead of toluene, was added 1.5 g (3.2 mmol) of $Cl_2Pt(NCPh)_2$. Following stirring overnight at room temperature and evaporation of the solvent, the ^{31}P NMR spectrum of the residue in $CDCl_3$ revealed the presence of **9a** ($\delta^{31}P$ 68.5) and **9b** ($\delta^{31}P$ 68.2) in an approximate ratio of 55/45. Chromatography of the mixture on 80 g of silicagel with 10/1 $CHCl_3$/acetone yielded 0.22 g of crsytalline **9a** (yield 2.7%; mp 153–4°; R_f on TLC with same solvent 0.70) and 0.19 g of crystalline **9b** (yield 2.3%; mp 145–6°; R_f on TLC 0.43) which were recrystallized from $CHCl_3$-*c*-C_6H_{12}. TLC with the same solvent revealed one spot for **9a** (anal calcd for $C_{14}H_{30}Cl_6N_4O_2P_2Pt$ (found): C, 22.24 (22.20); H, 4.00 (3.78); N, 7.41 (7.21); Cl, 28.13 (28.85)) and one spot for **9b** (anal found: C, 22.05; H, 3.71; N, 7.16; Cl, 28.05).

Method B: A solution of **7** was prepared by refluxing a solution of Cl_2PNR_2 (2.18 g, 9.00 mmol) and $Cl_2P(NCPh)_2$ (1.88 g, 4.00 mmol) in 25 mL of CH_2Cl_2 for 30 min and then adding it dropwise to a stirred solution of 3-aminopropanol-1 (0.75 g, 10 mmol) and Et_3N (2.0 g, 20 mmol) in 20 mL of CH_2Cl_2 at 0°. After stirring the reaction mixture at room temperature for 30 min it was evaporated and the residue extracted with 50 mL of boiling acetone. Filtration of the extract and evaporation of the solvent yielded a residue which was dissolved in 10 mL of $CHCl_3/Me_2CO$ (10/1). This solution chromatographed on 80 g of silicagel using the same solvent mixture as eluent to give 0.34 g of **9a** and 0.44 g of **9b** (total yield 25.9%).

Diasteriomers of cis-$Cl_2Pt(4)_2$, **10a,b**. Method A: To a 0° stirred solution of **5** freshly prepared in CH_2Cl_2 on a 0.005 molar scale was added 1.2 g (2.5 mmol) of $Cl_2Pt(NCPh)_2$. After stirring the reaction mixture at room temperature for 2 hrs, the residue on evaporation was subjected to TLC with $CHCl_3/Me_2CO$ (20/1) which showed only one spot (R_f 0.47). Chromatography on 80 g of silicagel with the same solvent system gave **12a,b** as a glassy foam. ^{31}P NMR spectroscopy ($CDCl_3$) revealed the presence of **10a** (^{31}P 69.9) and **10b** ($\delta^{31}P$ 62.9) in an approximately 30/70 ratio (^1H NMR spectrum ($CDCl_3$)

$$\delta^1H\ CH_2CH_2CH_2\ 1.75\text{–}2.2\ m,\ 2H;$$

$\delta^1H\ CH_2ClCH_2N$ 3.0–3.9 m, 10H; $\delta^1H\ CH_2O$ 4.1–4.7 m, 2H). Repeated attempts to separate the diastereomers chromatographically failed as did attempts to obtain a crystalline product from this method.

Method B: A solution of **8** was prepared by dissolving 1.00 g (0.00212 mol) of $Cl_2Pt(NCPh)_2$ and $\overline{ClPNRCH_2CH_2CH_2O}$ (0.860 g, 4.24 mmol) in 20 mL of CH_2Cl_2 and refluxing for 15 min. To this stirred solution at room temperature was added 0.51 g (4.4 mmol) of β-chloroethylamine hydrochloride and 0.90 g (9.0 mmol) of Et_3N. After stirring for 2 hrs at room temperature the reaction mixture was filtered, the filtrate evaporated and the residue chromatographed on 80 g of silicagel with $CHCl_3/Me_2CO$ (10/1) to give 1.23 g of the glassy foam **10** (yield 76.8%; ^{31}P NMR spectrum ($CDCl_3$) $\delta^{31}P$ **10a** 64.4; $\delta^{31}P$ **10b** 62.9; **10a/10b** = 45/55). Partial recrystallization of this product was accomplished from CH_2Cl_2—Et_2O giving 0.35 g of colorless crystals which from ^{31}P NMR analysis appeared to be **10a/10b** = 80/20 (anal calcd for

$$C_{14}H_{30}Cl_6N_4O_2P_2Pt$$

(found): C, 22.24 (22.13); H, 4.00 (3.17); N, 7.41 (7.17); Cl, 28.19 (27.77)).

Equilibration of ***10a*** *and* ***10b***. To a 0.1 g sample of the complex, wherein **10a/10b** = 45/55 was dissolved in 1 mL of $CDCl_3$, was added 5 drops of a freshly prepared CH_2Cl_2 solution of **5**. After heating at 55° for 3 hrs the ^{31}P NMR spectrum showed the presence of **10a/10b** in a 20/80 ratio. The same ratio was achieved under the same conditions using a $CDCl_3$ solution of a sample in which the **10a/10b** ratio was 80/20.

Diastereomers of cis-$Cl_2Pt(6)_2$, ***11a,b***. Method A: To a stirred 0° solution of **6** prepared from Cl_2PNR_2 and $HO(CH_2)_3NHR$ (as described above) on a 0.005 molar scale was added 1.18 g (2.50 mmol) of $Cl_2Pt(NCPh)_2$. After stirring over-night at room temperature the solvent was evaporated and the residue dissolved in $CDCl_3$ for ^{31}P NMR analysis. Two major signals were seen of which the one at 72.5 ppm corresponds to **11a** and the one at 74.2 ppm to **11b** with intensity ratios corresponding to **11a/11b** = 70/30. Chromatography of the mixture on 80 g of silicagel using $CHCl_3/Me_2CO$ (30/1) as eluent allowed separation of **11a** and **11b** in a total yield of 45.4%. Compound **11a** (0.68 g) was recrystallized from $CHCl_3$-Et_2O while **11b** (0.32 g) could be recrystallized from CH_2Cl_2-Et_2O. TLC with the same eluent showed one spot for both **11a** (R_f 0.67; mp 204–5° dec; anal calcd for $C_{18}H_{36}Cl_8N_4O_2P_2Pt$ (found): C, 24.53 (24.36); H, 4.12 (4.04); N, 6.36 (6.02); Cl, 32.19 (32.06)) and **11b** (R_f 0.57; mp 225–6° dec; anal found: C, 24.29; H, 4.02; N, 6.18; Cl, 31.25).

Method B: To a stirred suspension of **7** (0.880 g, 1.17 mmol) in 15 mL of CH_2Cl_2 at 5° was added dropwise a freshly prepared

5 mL CH_2Cl_2 solution of $HO(CH_2)_3NHR$ (2.5 mmol) containing 0.50 g (5.0 mmol) of Et_3N. After stirring for 1 hr at 5° and 2 hrs at room temperature, the mixture was filtered and the filtrate evaporated. Analysis of the residue by ^{31}P NMR spectroscopy ($CDCl_3$) revealed the ratio of **11a**/**11b** to be 55/45. Chromatography on 80 g of silica gel with $CHCl_3/Me_2CO$ (30/1) yielded 0.2 g **11a** and 0.125 g **11b** in a total yield of 36.4%.

Equilibration of 11a and 11b. To each of 30 mg samples of **11a** and **11b** in 1 mL of $CDCl_3$ was added 5 drops of a CH_2Cl_2 solution of **6**. After heating at 55° for 3 hrs, ^{31}P NMR analysis showed both tubes to contain a **11a**/**11b** ratio of *ca.* 80/20.

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