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# Optical Resolution of the Antitumor Agents Isophosphamide and Triphosphamide by Means of Diastereomeric Platinum(II) Complexes

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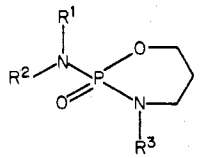
The optical resolution of the antitumor drugs isophosphamide (**2**) and and triphosphamide (**3**) by means of diastereomeric platinum(II) complexes of the type *cis*-$I_2Pt[(S)$-(+)-**7**$]$(**8**) and *cis*-$I_2[(S)$-(+)-**7**$]$(**9**) is reported. Here, **7**, the resolving agent, is an enantiomer of $Ph(MeO_2C)CHOPOCH_2CH_2CH_2O$ derived from commercially available (*S*)-(+)-mandelic acid and **8** and **9** are analogues of **3** and **2**, respectively, in which phosphorus is trivalent (i.e., $R_2NPOCH_2CH_2CH_2NR$ (**8**) and $HRNPOCH_2CH_2CH_2NR$ (**9**), where R = $ClCH_2CH_2$). The diastereomeric complexes are formed in the equilibration of *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$ with *cis*-$I_2Pt$(**8**)$_2$ (Scheme I) or *cis*-$I_2Pt$(**9**)$_2$ (Scheme II) which is catalyzed by a very small excess of (*S*)-(+)-**7**. Destruction of the diastereomers with excess $CN^-$ and oxidation of **9** to **2** and **8** to **3** by $N_2O_4$ and $O_3$, respectively, gave the enantiomers of **2** and **3** in overall yields of about 7% and better than 95% optical purity in the 11-step procedures. Although diastereomeric complexes of the type *trans*-$Cl_2Pt$(**8**)((−)-$PhCHMeNH_2$), *cis*-$Cl_2Pt$(**8**)$(MeOPOCHMeCH_2CH_2O)$ and *cis*-$Cl_2Pt$(**8**)((+)-$PhMeCHNHP(OMe)_2$) could not be separated, those of *cis*-$Cl_2Pt$(**8**)$[(S)$-(+)-**7**$]$ and *cis*-$I_2Pt$-(**8**)$(MeOPOCHMeCH_2CH_2O)$ are separable.

## Introduction

The potent antitumor properties of the phosphamides **1**,[2] **2**,[3] **3**,[3,4] and **4**[5] have stimulated intense interest during the past



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1**, cyclophosphamide | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ | H |
| **2**, isophosphamide | $CH_2CH_2Cl$ | H | $CH_2CH_2Cl$ |
| **3**, triphosphamide | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ |
| **4**, sulfophosphamide | $CH_2CH_2OSO_2Me$ | H | $CH_2CH_2Cl$ |

5 years in their stereochemical properties and the relationship of these properties to their biological behavior. The conformation of the ring in **1**,[6] **2**,[7] and **3**[8] in the solid state has been found from X-ray crystallographic studies to be chair form, slightly flattened at phosphorus, with nearly planar nitrogens and with an axial phosphoryl oxygen. More recently, $^1H$ NMR spectroscopic studies of **1** in solution revealed a rapid conformational equilibrium between two chair forms.[9] Additional $^1H$ NMR investigations and IR studies allowed the conclusion to be drawn that there is a considerable bias toward the axial P=O conformer in hydrogen-bonding solvents such as water and chloroform.[10]

The presence of a chiral center at phosphorus in **1**–**4** permits testing of the idea that metabolic selection for a particular enantiomer in each of these drugs may occur. A method of resolving cyclophosphamide (**1**) has been reported in which diastereoisomerism is induced on the ring nitrogen by formation of an optically active amino alcohol precursor to **1** from $ClCH_2CH_2CH_2OH$ using two different optically active amines.[11,12] In another strategy the endocyclic nitrogen of commercially available racemic **1** was functionalized with an optically active silicon reagent to afford diastereomers.[13] In the former approach the optically active center of the resolving agent was cleaved from the endocyclic nitrogen of the separated diastereomers by hydrogenolysis in 10–12% overall yield, while in the latter studies it was released by solvolysis in about 14% overall yield. The absolute configurations of (+)-**1** and (−)-**1** are *R*[14] and *S*,[15] respectively, as determined from anomalous dispersion of X-rays.

Two routes have been reported from different laboratories for the resolution of isophosphamide (**2**) using the optically active intermediate $Cl_2P(O)N(CH_2CH_2Cl)CPhMeH$.[16,17] Upon reaction of this compound with $HO(CH_2)_3NH(CH_2)_2Cl$, the exocyclic nitrogen of **2** becomes functionalized with the optically active resolving moiety, which is then cleaved hydrogenolytically from the separated diastereomers. The overall yields in these procedures, however, are quite low (<0.5%). In a more recent report,[12] enantiomers of **2** were realized in 10% overall yield by hydrogenating the separated diastereomers of **5** to form the intermediate (+)-**6** and (−)-**6**. The enantiomers of **6** were then selectively functionalized at the endocyclic nitrogen with a $ClCH_2CH_2$ group with retention

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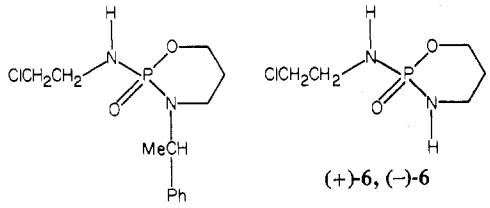


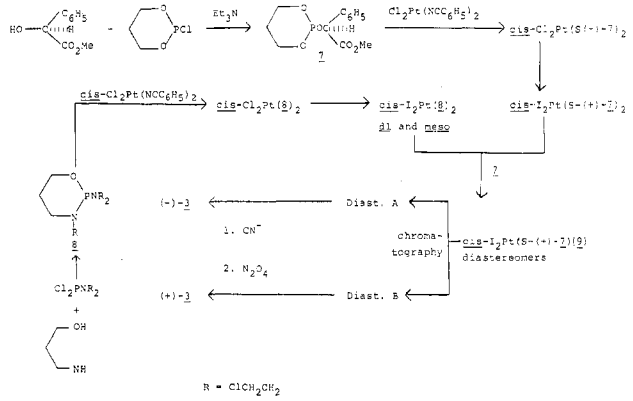
5 (+)-6, (−)-6

of configuration at phosphorus.[12] In a two-step transformation of the enantiomers of **2**, an overall yield of 3% of enantiomeric sulfosphamide (**4**) was reported.[12] Absolute configurational assignments for (+)-**2** (*R*), (−)-**2** (*S*), (+)-**4** (*R*), and (−)**4** (*S*) were arrived at by synthesizing the respective enantiomers of **4** and **2**, which stem from one of the enantiomers of **5**, by transformations involving no bond cleavages at phosphorus.[12] The absolute configuration of **5** was determined by converting one of its enantiomers to the corresponding enantiomer of **1** (whose absolute configuration is known) by reactions which occur stereoretentively at phosphorus.[12]

Two quite different methods for the resolution of triphosphamide (**3**) were simultaneously reported very recently by Stec et al.[12] and by us.[18] By reacting (−)-**1** with $ClC(O)CH_2Cl$ followed by reduction of the carbonyl function with $B_2H_6$, the Polish workers[12] were able to synthesize (+)-**3** in about 4% overall yield and assign its absolute configuration as *S* on the basis of the known *S* configuration of (−)-**1**. Starting with (+)-(*S*)-mandelic acid, we synthesized the resolving agent *cis*-$I_2Pt[(S)\text{-}(+)\text{-}7]_2$ as shown in Scheme I.[18] Upon reaction of this complex with *cis*-$I_2Pt(\mathbf{8})_2$, the diastereomeric complex *cis*-$I_2Pt[(S)\text{-}(+)\text{-}7](\mathbf{8})$ was synthesized from which (−)-**3** and (+)-**3** could be obtained in about 7% overall yields as outlined in this scheme.

Reported efforts to determine the presence or absence of metabolic selectivity for the enantiomers of the phosphamides **1**–**4** have been restricted to cyclophosphamide (**1**). In an earlier study[19] involving human patients, it was concluded from optical rotation measurements on urine samples that (+)-**1** was metabolized much more preferentially than (−)-**1**. More recent work from the same laboratories[20] included LIS $^{31}P$ NMR investigations of these samples, and the conclusion was reached that the optical rotation measurements were adversely affected by chiral metabolites from sources other than **1**. In the latter investigation it was found that the plasma half-life and urinary output of all three forms of the drug are actually quite similar and that the plasma–protein binding is not significantly different for the enantiomers. The 4-keto derivative of **1** (a metabolite) did appear to have a higher concentration in the urine upon administration of (+)-**1** compared to (±)-**1**, however.[20] Regarding the relative therapeutic effects of the enantiomers, the data were deemed inconclusive, although stereoselective uptake of another metabolite, 4-hydroxy-**1**, by neoplastic cells could not be ruled out.[20] In vivo and in vitro experiments with L1210 mouse leukemia revealed no outstanding differences in therapeutic value between (+)-**1**[21] and (−)-**1**, although in another investigation (−)-**1** possessed about twice the therapeutic index of the (+) enantiomer against the ADJ/PC6A mouse plasma cell tumor.[19] Interestingly, in vitro and in vivo metabolism of the enantiomers of **1** and of its intermediate metabolites by liver microsomes has been found to be stereoselective in the mouse, rat, and rabbit, and moreover there are marked species differences in the extent

**Scheme I**



and direction of this stereoselectivity.[22]

The strategy for the resolution of **3** outlined in Scheme I is potentially applicable to the resolution of a variety of trivalent phosphorus esters which are chiral at phosphorus. Thus in the penultimate step of this scheme, a trivalent-phosphorus ester of the type $P(OR^1)(NR^2_2)(NR^2R^3)$ is liberated in solution when the diastereomeric complex is destroyed by cyanide ion.[23] Attempts to resolve trivalent-phosphorus esters have been few[24-26] and have been of rather limited utility. Thus one of the methods (reaction 1) yields esters of low optical

$$R^1PhPCl + R^2EH \xrightarrow{Me_2NR^*} R^1PhP^*ER^2 \quad E = O, S \qquad (1)$$

purity.[25] Moreover, this route is likely to be restricted to $R^1R^2PER^3$ systems since starting materials of the type $(R^1O)(R^2O)PCl$, for example, are difficult to purify. The other two approaches (reactions 2 and 3) necessitate the

$$O{=}P^*Ph(OEt)H \xrightarrow{Me_3SiCl} P^*Ph(OEt)OSiMe_3 \quad (2)^{24}$$

$$O{=}P^*Ph(t\text{-}Bu)SeH \xrightarrow{MeI} O{=}P^*Ph(t\text{-}Bu)SeMe \xrightarrow{CF_3SO_3Me} [MeOP^*Ph(t\text{-}Bu)SeMe]^+ \xrightarrow{EtS^-} P^*Ph(t\text{-}Bu)OMe \quad (3)^{26}$$

synthesis of an optically active precursor which in the case of reaction 2[27a] provides a starting material of low optical purity (<3%). Recently a phosphorus(III) amide was resolved by using an optically active phosphine as the starting material as shown in reaction 4. The product in this approach is limited

$$MeP^*Ph(CH_2Ph) \xrightarrow[(2)EtBr]{(1)EtN_3} {}^{+}MeP^*Ph(CH_2Ph)(NEt_2) \xrightarrow{\text{electrolysis}} MeP^*Ph(NEt_2) \quad (4)$$

to one $NR_2$ substituent, however, since electrolytic cleavage is efficient only for benzyl substituents.

The resolution of trivalent group 5 derivatives via diastereomeric platinum(II)[28,29] or palladium(II)[30] complexes has

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been restricted to tertiary phosphines[28,30] and a tertiary arsine.[29,31] While tertiary phosphines have been resolved by other methods,[32-36] the two classical approaches involve reduction of a phosphoryl linkage[32] or a phosphonium salt.[33] Such reductions of phosphorus ester analogues thus far have apparently not been successful, presumably because the ester derivatives are more difficult to reduce and are quite susceptible to undesirable side reactions. Of the more recently reported tertiary phosphine resolutions,[34-36a] two involve a step in which an alkyllithium reagent is introducted[34,35] (which is expected to displace the OR group from a phosphorus ester), two start with chloro- or dichlorophosphines[34,35] (which as mentioned earlier are not very viable starting materials among the ester analogues), and a third route begins with a resolved tertiary thiophosphine which must later be reduced.[36a] Interestingly, in two of the reaction sequences, a metal complex is formed (i.e., with Cu(I)[34] and Ni(II)[36a]) which incorporates the phosphorus moiety as a trivalent ligand. However, in neither case is the complex diastereomeric. In recent reports[36b,c] advantage was taken of the displacement of an alkoxy substituent by an alkyllithium reagent:

$$\mathrm{RPhPO((-)men) + R'Li \rightarrow RPhP^{*}R' + LiO((-)men)} \quad (5)$$

$$\mathrm{RPhPO((-)men) + Me_2NLi \rightarrow RPhP^{*}NMe_2 + LiO((-)men)} \quad (6)$$

(men = menthyl).

In this paper we give details of the resolution of triphosphamide (**3**) via a diastereomeric platinum(II) complex as reported in a recent communication from our laboratories,[18] and the utility of this technique in resolving isophosphamide (**2**) is also demonstrated.

## Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1$H NMR spectra were obtained with a Varian A-60 spectrometer with $Me_4Si$ as an internal reference. $^{31}$P NMR spectra were obtained with a Bruker HX-90 spectrometer using external $H_3PO_4$ as a reference. Downfield and upfield shifts are positive and negative, respectively. Thin-layer chromatography was carried out with the use of Baker-flex (silica gel IB-F) precoated plates, and spots were visualized by exposure to iodine vapors. Column chromatography was done with Baker 40-140 or 60–200 mesh silica gel and was followed by TLC. Optical rotations were measured with a Perkin-Elmer 141 Polarimeter at 25 °C. Ozone was generated by a Welsbach F23 laboratory ozonator.

All solvents were reagent grade and were dried over molecular sieves before use. (*R*)-(+)-α-Phenylethylamine, (*S*)-(+)-mandelic acid and tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$) were used as supplied by Aldrich Chemical Co. and tris[((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium(III) (EuOpt-I, Eu(tfc)$_3$) was purchased from Willow Brook Laboratories. Samples of racemic triphosphamide and isophosphamide were kindly supplied by Mead Johnson Co. Aziridine was obtained as a gift from Dow Chemical Co. and Cordova Chemicals.

The following starting materials were prepared according to literature reports: bis(benzonitrile)dichloroplatinum,[37] 2,7,8-trioxa-1-phosphabicyclo[3.2.1]octane,[38] 2-bis((β-chloroethyl)amino)-1-((β-chloroethyl)amino)-1,3,2-azaoxaphosphorinane (**8**),[23] 2-((β-chloroethyl)amino)-1-((β-chloroethyl)amino)-1,3,2-azaoxaphosphorinane (**9**),[23] *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinane (**10**),[39,40] *cis*-$Cl_2Pt(\mathbf{8})_2$,[23] *cis*-$Cl_2Pt(\mathbf{9})_2$,[23] tri-(-)-menthyl phosphite[41] ($\delta^{31}$P = +144.0), dimethyl phosphorochloridite,[42] 2-chloro-1,3,2-dioxaphosphorinane,[39] and methyl mandelate.[43]

The complexes $Cl_2Pt(CH_2{=}CH_2)L$ where L = (+)-PhCH(Me)$NH_2$ and (-)-$PhCH_2CH(CH_3)NH_2$ were made following a literature preparation.[44] For the preparation of di-(-)-menthyl phenylphosphonite, a literature procedure was followed.[45] A white solid was obtained after evaporation of benzene (mp 60–63 °C), and a sample of this material was recrystallized from benzene (mp 62–63.5 °C, lit.[45] mp 66–68 °C; $[\alpha]^{25}_{589}$ −79.2° (*c* 2.674, $CHCl_3$), $[\alpha]^{20}_{589}$ −59.49° (*c* 2.62, chloroform[43]); $^1$H NMR ($CDCl_3$) δ 0.5–2.6 (m, 36 H, alkyl protons), 3.4–4.1 (m, 2 H, HCOP), 7.2–7.8 (m, 5 H, $C_6H_5$); $^{31}$P NMR ($CHCl_3$–$CD_3CN$) 159.6 ppm).

**(*S*)-(+)-2-((Carbomethoxy)phenyl)methoxy)-1,3,2-dioxaphosphorinane (7).** To a solution of 3.89 g (23.3 mmol) of methyl mandelate and 3.20 mL (23.3 mmol) of triethylamine in 20 mL of toluene cooled to 3 °C was added dropwise a solution of 3.28 g (23.3 mmol) of 2-chloro-1,3,2-dioxaphosphorinane in 30 mL of toluene while the temperature was kept at 3–5 °C. After being stirred for 1 h at 5 °C, the reaction mixture was allowed to reach 25 °C. Triethylamine hydrochloride was then filtered off and washed with 25 mL of toluene. Solvent was evaporated at room temperature, and the crude product (6.0 g) of about 80% purity (as judged by $^{31}$P NMR spectroscopy) was used without further purification ($[\alpha]^{25}_{589}$ 44.9°, $[\alpha]^{25}_{578}$ 46.9°, $[\alpha]^{25}_{546}$ 53.9° (*c* 1.272, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 1.2–1.7 (*m*, 1 H) and 1.9–2.8 (m, 1 H, $CCH_2C$), 3.4–4.9 (m, 4 H, $CH_2OP$), 3.7 (s, 3 H, $CH_3OOC$), 5.53 (d, 1 H, HC*, $^3J_{HC^*OP}$ = 10 Hz), 7.3–7.7 (m, 5 H, $C_6H_5$); $^{31}$P NMR ($C_6D_6$) 129.3 ppm (main signal of three peaks)). The specific rotations of the (*S*)-(+)-methyl mandate used were $[\alpha]^{25}_{589}$ −172.6° (*c* 1.642 $CHCl_3$), $[\alpha]^{25}_{589}$ −174.3° (*c* 1.234, $CHCl_3$),[46] and $[\alpha]^{20}_{589}$ −174.2° (*c* 4.05, $CHCl_3$).[47]

***cis*-$Cl_2$Pt[(*S*)-(+)-7]$_2$.** To a solution of 3.415 g (7.20 mmol) of dichlorobis(benzonitrile)platinum(II) in 50 mL of methylene chloride was added dropwise a solution of **7** in 5 mL of methylene chloride at 5 °C. After 30 min of stirring, at room temperature, the solvent was evaporated, and the crude reaction mixture was kept under vacuum in order to remove as much benzonitrile as possible (approximately 3 h). The yellowish solids remaining were dissolved in a minimum amount of methylene chloride, and after filtration the solution was subjected to column chromatography on 200 g of silica gel. Benzonitrile was first eluted with $CH_2Cl_2$ (1 L). The complex $Cl_2Pt(C_6H_5CN)_2$ was next removed with $CH_2Cl_2$–$Me_2CO$ (40:1, 1 L). Then $CH_2Cl_2$–$Me_2CO$ (20:1, 1 L) followed by $CH_2Cl_2$–$Me_2CO$ (10:1, 1 L) eluted the product in 63% yield (on the basis of (*S*)-(+)-methyl mandelate) as a colorless oil soluble in $CH_2Cl_2$ and $CHCl_3$ but insoluble in $C_6H_{14}$ and $Et_2O$ ($[\alpha]^{25}_{589}$ 79.2°, $[\alpha]^{25}_{578}$ 82.9°, $[\alpha]^{25}_{546}$ 96.1° (*c* 4.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) δ 1.7–2.4 (m, 4 H, $CCH_2C$), 3.75 (s, 6 H, $CH_3$), 3.8–4.9 (m, 8 H, $CH_2OP$), 6.4 (br d, 2 H, CH, $^3J_{POCH}$


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= 11.5 Hz), 7.3–7.7 (m, 10 H, $C_6H_5$); $^{31}P$ NMR ($C_6D_6$) 69.1 ppm ($^1J_{PPt}$ = 5742 Hz).

By use of racemic **7**, the analogous platinum(II) complex was obtained in 67% yield as white solid ($^1H$ NMR ($CDCl_3$) same as that of *cis*-$Cl_2Pt[(S)$-(+)-**7**$]_2$ except for a resonance which could be assigned to the meso isomer at $\delta$ 3.78 (s, 6 H, $CH_3OCO$)); $^{31}P$ NMR ($C_6D_6$) 69.1 ppm ($^1J_{PPt}$ = 5742 Hz)).

***cis*-$I_2Pt[(S)$-(+)-**7**$]_2$.** Halogen methathesis[48] of (*S*)-(+)-*cis*-$Cl_2Pt(7)_2$ gave the yellow, crystalline diiodide complex which was purified by chromatography on silica gel with $CH_2Cl_2$ in 61% overall yield based on (*S*)-(+)-methyl mandelate and using the crude precursor complex from which only $C_6H_5CN$ and $Cl_2Pt(C_6H_5CN)_2$ had been removed by chromatography ($[\alpha]^{25}_{589}$ 62.0°, $[\alpha]^{25}_{546}$ 75.9° (*c* 2.0, $CH_2Cl_2$); $^1H$ NMR $\delta$ ($CDCl_3$) 1.6–2.6 (m, 4 H, $CCH_2C$), 3.7 (s, 6 H, $CH_3OCO$), 3.8–5.0 (m, 8 H, $CH_2OP$), 6.4 (br d, 2 H, HC*, $^3J_{PH}$ = 12.4 Hz), 7.2–7.7 (m, 10 H, $C_6H_5$); $^{31}P$ NMR ($C_6D_6$) 75.1 ppm ($^1J_{PPt}$ = 5473 Hz)). With use of racemic **7**, the corresponding diiodoplatinum(II) complex was obtained in 76% yield ($^1H$ NMR ($CHCl_3$) identical with that of *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$; $^{31}P$ NMR ($C_6D_6$) 75.2 (meso, $^1J_{PPt}$ = 5473 Hz), 75.1 ppm (*dl*, $^1J_{PPt}$ = 5473 Hz)).

***dl*- and *meso*-*cis*-$I_2Pt(8)_2$.** A mixture of these complexes was obtained as a yellow solid in 96% yield from the corresponding dichlorides[23] by halogen metathesis[48] ($^1H$ NMR ($CD_2Cl_2$) $\delta$ 1.5–2.3 (m, 4 H, $CCH_2C$), 2.8–4.7 (m, 32 H, $CH_2N$, $CH_2Cl$, $CH_2O$)), and the *dl* and meso diastereomers were separated by silica-gel chromatography using a 10:1 $MeC_6H_5$–$CHCl_3$ eluant mixture ($^{31}P$ NMR ($CH_2Cl_2$–$C_6D_6$) 70.9 (*dl*, $^1J_{PPt}$ = 5071 Hz), 73.6 ppm (meso, $^1J_{PPt}$ = 4989 Hz); TLC $R_f$ = 0.38 (*dl*, $CCl_4$–$Me_2CO$ 5:1), $R_f$ = 0.46 (meso, $CCl_4$–$Me_2CO$ 5:1), $R_f$ = 0.30 (*dl*, $C_6H_6$–$CHCl_3$ 5:1), $R_f$ = 0.21 (meso, $C_6H_6$–$CHCl_3$ 5:1).

**Diastereomeric *cis*-$I_2Pt(8)[(S)$-(+)-**7**$]$.** A suspension of 5.73 g (5.79 mmol) of *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$ and 6.16 g (5.79 mmol) of *cis*-$I_2Pt(8)_2$ (as the *dl* or meso diastereomer or a mixture of both) in 30 mL of benzene, to which 1.0 mol % of **7** was added, was refluxed for 7 h. After evaporation of the solvent, the products were chromatographed on silica gel with $CH_2Cl_2$ to give a 22% yield (based on the reactants) of faster running diastereomer A as yellow needles ($[\alpha]^{25}_{589}$ 42.2°, $[\alpha]]^{25}_{578}$ 44.0°, $[\alpha]^{25}_{546}$ 51.7° (*c* 2.15, $CH_2Cl_2$); $^1H$ NMR ($CD_2Cl_2$) $\delta$ 1.6–2.1 (m, 4 H, $CCH_2CO$), 3.0–5.0 (m, 20 H, $CH_2O$, $CH_2N$, $CH_2Cl$), 3.7 (s, 3 H, $CH_3O_2C$), 6.4 (d, 1 H, HC, $^3J_{PH}$ = 12.2 Hz), 7.2–7.7 (m, 5 H, $C_6H_5$); $^{31}P$ NMR ($CH_2Cl_2$–$C_6D_6$) 72.6 ($^1J_{PPt}$ = 4677 Hz, **8**), 74.4 ppm ($^1J_{PPt}$ = 5846 Hz; **7**); TLC $R_f$ = 0.30 ($CH_2Cl_2$)) and an identical yield of diastereomer B ($[\alpha]^{25}_{589}$ 11.85°, $[\alpha]^{25}_{578}$ 12.1°, $[\alpha]^{25}_{546}$ 12.8° (*c* 5.205, $CH_2Cl_2$); $^1H$ NMR ($CD_2Cl_2$) $\delta$ 1.6–2.2 (m, 4 H, $CCH_2C$), 3.2–5.2 (m, 20 H, $CH_2O$, $CH_2N$, $CH_2Cl$), 3.7 (s, 3 H, $CH_3O_2C$), 6.4 (d, 1 H, CH, $^3J_{PH}$ = 12.5 Hz), 7.3–7.6 (m, 5 H, $C_6H_5$); $^{31}P$ NMR ($CH_2Cl_2$–$C_6D_6$) 71.5 ($^1J_{PPt}$ = 4690 Hz, **8**), 73.6 ppm ($^1J_{PPt}$ = 5859 Hz, **7**); TlC $R_f$ = 0.22 ($CH_2Cl_2$)).

Diastereomer B (531 mg, 0.52 mmol) was suspended in 12 mL of benzene. A benzene solution of 0.0052 mmol (1 mol %) of (*S*)-(+)-**7** was added and the mixture refluxed for 7 h. After evaporation of the solvent, examination of the $^{31}P$ spectrum revealed approximately 14% *cis*-$I_2Pt(8)_2$, 68% starting material, and 18% *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$. From the residue, 52 mg of *l*-*cis*-$I_2Pt(8)_2$ ($[\alpha]^{25}_{589}$ −76.7°, $[\alpha]^{25}_{578}$ −82.3°, $[\alpha]^{25}_{546}$ −100.7° (*c* 1.62, $CH_2Cl_2$)) and 421 mg of starting material ($[\alpha]^{25}_{589}$ 11.7°, $[\alpha]^{25}_{578}$ 12.0°, $[\alpha]^{25}_{546}$ 12.6° (*c* 5.095, $CH_2Cl_2$)) were recovered by column chromatography using $CH_2Cl_2$ as eluant.

**(+)-3.** To 0.922 g (18.8 mmol) of NaCN suspended in 20 mL of methanol at −50 °C was added dropwise a solution of 2.42 g (2.35 mmol) of diastereomer B in 20 mL of $CH_2Cl_2$. The yellow color of the diiodoplatinum complex solution began to disappear immediately. The white suspension was stirred at −50 °C for 1–2 h after which approximately 60 mL of $CH_2Cl_2$ was added. From this suspension, the inorganic salts were filtered off and the solution was cooled to −70 °C. Gaseous $N_2O_4$ was then introduced in 20-mL portions from a syringe until the reaction mixture (which was kept under nitrogen) became red. After being stirred for 15 min, the reaction mixture was poured into 50 mL of 5% aqueous $NaHCO_3$ and about 0.1 g of solid $Na_2SO_3$ was added. The layers were separated and washed with water, and the $CH_2Cl_2$ layer dried over anhydrous $Na_2SO_4$. The organic solution was then evaporated, leaving a yellow oil which was chromatographed on 80 g of silica gel by using chloroform as an eluant. Fractions containing (+)-**3** were collected, evaporated, and kept under vacuum (0.02 torr) until constant weight was reached. This reaction gave a 64.4% yield (489.5 mg) of (+)-**3** as a colorless oil ($[\alpha]^{25}_{589}$ 30.1°, $[\alpha]^{25}_{578}$ 31.4°, $[\alpha]^{25}_{546}$ 35.4°, $[\alpha]^{25}_{500}$ 42.9° (*c* 3.535, MeOH); $^{31}P$ NMR ($C_6D_6$) 12.4 ppm; $^{13}C$ NMR ($C_6D_6$) 66.48 (d, $CH_2O$, $^2J_{CP}$ = 7.33 Hz), 50.34 (d, $NCH_2CH_2Cl$, $^2J_{CP}$ = 2.44 Hz), 49.31 (d, $N(CH_2CH_2Cl)_2$, $^2J_{CP}$ = 4.89 Hz), 47.57 (s, $ClCH_2CH_2N$), 42.32 (s, $(ClCH_2CH_2)_2N$), 41.48 (d, $NCH_2CH_2O$), $^2J_{CP}$ = 3.66 Hz), 26.04 ppm (d, $NCH_2CH_2CH_2O$, $^3J_{CP}$ = 3.66 Hz); TLC $R_f$ = 0.53 ($CH_2Cl_2$–acetone 2:1)).

**(−)-3.** The same procedure as described for (+)-**3** was followed. From 2.66 g (2.59 mmol) of diastereomer A, 491.4 mg of (−)-**3** representing a 64.6% yield was obtained ($[\alpha]^{25}_{589}$ −29.7°, $[\alpha]^{25}_{578}$ −31.0°, $[\alpha]^{25}_{546}$ −34.5°, $[\alpha]^{25}_{500}$ −41.5° (*c* 3.535, MeOH); $^{31}P$ and $^{13}C$ NMR spectra identical with those of (+)-(**3**)).

***cis*-$I_2Pt(9)_2$.** This yellow complex was synthesized from the corresponding chloride[23] by halogen metathesis[48] in 99% yield after recrystallization from $CH_2Cl_2$–$Et_2O$ ($^1H$ NMR ($CDCl_3$) $\delta$ 1.7–2.3 (m, 4 H, $CH_2CH_2CH_2$), 2.8–4.2 (m, 20 H, $CH_2Cl$, $CH_2N$), 4.2–4.9 (m, 4 H, $CH_2O$); $^{31}P$ NMR ($C_6D_6$) 70.5 (*dl*, $^1J_{PPt}$ = 4881 Hz), 68.2 ppm (meso, $^1J_{PPt}$ = 4931 Hz)).

**Diastereomeric *cis*-$I_2Pt(9)[(S)$-(+)-**7**$]$.** To a solution of 3.775 g (4.02 mmol) of *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$ and 3.98 g (4.02 mmol) of *cis*-$I_2Pt(9)_2$ in 160 mL of benzene was added a benzene solution containing 0.0804 mmol of (*S*)-(+)-**7**. The reaction mixture was refluxed for 1 h after which the solvent was evaporated. The residual yellow oil was chromatographed on 280 g of silica gel (60–200 mesh) with $CH_2Cl_2$. Unreacted *cis*-$I_2Pt(9)_2$ was first eluted followed by diastereomer A and then B of the title complex. The separation of these diastereomers was monitored by $^{31}P$ NMR spectroscopy. Thus the −3.8 and −6.1 ppm upfield satellite peaks of diastereomers A and B, respectively, were chosen as an indication of the presence of these diastereomers. The yields of diastereomers from the collected pure fractions were 25 and 19%, respectively. Further elution of the column yielded unreacted *cis*-$I_2Pt[(S)$-(+)-**7**$]_2$ which was combined with the unreacted *cis*-$I_2Pt(9)_2$ and refluxed for 1 h in 100 mL of benzene in the presence of 0.04 mmol of **7**. Chromatography and recrystallization from $CH_2Cl_2$–$Et_2O$ gave a total yield of 76.9% of diastereomer A as almost colorless crystals ($[\alpha]^{25}_{598}$ 76.0° (*c* 1.7, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.8–2.1 (m, 4 H, $CCH_2C$), 3.3–3.8 and 4.6–4.9 (m, 16 H, $CH_2O$, $CH_2N$, $CH_2Cl$), 3.8 (s, 3 H, $CH_3O_2C$), 6.4 (d, 1 H, CH, $^3J_{PH}$ = 6.0 Hz), 7.3–7.7 (m, 5 H, $C_6H_5$); $^{31}P$ NMR ($C_6D_6$) 76.6 [(*S*)-(+)-**7**, $^1J_{PPt}$ = 5865 Hz], 66.7 ppm (**9**, $^1J_{PPt}$ = 4469 Hz)) and a total yield of 41.7% of diastereomer B as slightly yellowish crystals ($[\alpha]^{25}_{589}$ −32.8 (*c* 1.54, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.8–2.1 (m, 4 H, $CCH_2C$), 3.3–3.8 and 4.6–4.9 (m, 16 H, $CH_2O$, $CH_2N$, $CH_2Cl$), 3.8 (s, 3 H, $CH_3O_2C$), 6.4 (d, 1 H, CH, $^3J_{PH}$ = 6.0 Hz), 7.3–7.7 (m, 5 H, $C_6H_5$); $^{31}P$ NMR ($C_6D_6$) 74.8 [(*S*)-(+)-**7**, $^1J_{PPt}$ = 5899 Hz], 66.1 ppm (**9**, $^1J_{PPt}$ = 4530 Hz)).

**(−)-2.** To 1.0 g (20.4 mmol) of NaCN suspended in 20 mL of MeOH at −70 °C was added dropwise a solution of 0.9791 g (1.015 mmol) of diastereomer A from the preceding preparation of 20 mL of $CH_2Cl_2$. The yellow color of the complex soon disappeared, leaving a white suspension. Ozone was bubbled into the solution at −70 °C for 15 min after which the solution was purged with $O_2$. After reaching room temperature, the reaction mixture was brought to a volume of 150 mL with $CH_2Cl_2$ and poured into a separatory funnel containing 50 mL of a 5% aqueous $NaHCO_3$ solution and 0.05 g of $Na_2SO_3$. The organic layer was separated, extracted with 20 mL of $H_2O$, and evaporated to a yellow oil. Chromatography of the oil on 60 g of silica gel with $Me_2CO$ gave a 22% yield of (−)-**2** as a colorless oil ($[\alpha]^{25}_{589}$ −37.8° (*c* 1.158, $C_6H_6$)). $^{31}P$ (($C_6D_6$) 11.1 ppm) and $^{13}C$ (($CDCl_3$) 67.3 (d, $CH_2O$, $^2J_{CP}$ = 6.1 Hz), 50.2 (d, $ClCH_2CH_2N$(ring), $^2J_{CP}$ = 3.7 Hz), 47.7 (s, $ClCH_2CH_2N$(ring)), 45.5 (d, $ClCH_2CH_2N$(exo), $^2J_{CP}$ = 4.9 Hz), 43.2 (s, $ClCH_2CH_2N$(exo)), 42.1 (d, $CH_2N$(ring), $^2J_{CP}$ = 3.7 Hz), 26.3 ppm (d, $NCH_2CH_2CH_2O$, $^3J_{CP}$ = 4.1 Hz)) NMR spectra are identical with those of the commercially available racemic mixture.

**(+)-2.** The procedure for this enantiomer was identical with that given in the preceding preparation, giving a 22% yield ($[\alpha]$ 35.7° (*c* 0.54, $C_6H_6$); $^{31}P$ and $^{13}C$ NMR spectra identical with those of the commercially available racemic mixture).

**Attempted Synthesis of Separable Diastereomeric $X_2Pt(8)L$ Complexes. A. Reaction of $Cl_2Pt(CH_2{=}CH_2)L$ with 8.** In addition to the title complexes where L = (+)-$PhCH(CH_3)NH_2$ and (−)-$PhCH_2CH(CH_3)NH_2$, which were made according to a literature

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procedure,[44] the compounds where L = (+)-$PhCH_2CH(CH_3)NHCH_3$ ($[\alpha]^{25}_{589}$ 16.7° ($CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.87 (d, 3 H, $CH_3C$, $^3J_{HH}$ = 7.2 Hz), 2.93 (br s, 6 H, $(CH_3)_2N$), 4.55 (s, 4 H, $H_2C{=}CH_2$, satellites $^2J_{HPt}$ = 66 Hz), 4.72 (q, 1 H, HC, $^3J_{HH}$ = 7.2 Hz), 7.3–7.8 (m, 5 H, $C_6H_5$)) and (+)-$PhCH(CH_3)N(CH_3)_2$ ($[\alpha]^{25}_{589}$ 1.39° ($CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (d, 3 H, $CCH_3$, $^3J_{HH}$ = 6.5 Hz), 2.7–3.2 and 2.92 (m, s, 5 H, $CH_2$, $NCH_3$), 3.35–3.8 (m, 1 H, CH), 4.56 (s, satellites $^2J_{HPt}$ = 66.5 Hz, 4 H, $CH_2{=}CH_2$), 7.32 (s, 5 H, $C_6H_5$)) were made in an analogous manner.

The reaction of **8** (0.01 mol in a freshly prepared $MeC_6H_5$–$CH_2Cl_2$ solution[23]) with $Cl_2Pt(CH_2{=}CH_2)$[(+)-$PhCH(CH_3)NH_2$] (4.15 g, 0.01 mmol, in 150 mL of $CH_2Cl_2$) was accomplished at room temperature in 24 h after dropwise addition of the ligand solution to the stirred solution of the complex. Chromatography of the residue left after evaporation on 250 g of silica gel using $CHCl_3$–$C_6H_6$ (1:1) gave *trans*-$Cl_2Pt$(**8**)$_2$ as pale yellow crystals in 32% yield (mp 138–140 °C; soluble in most organic solvents except ether and aliphatic hydrocarbons; $^1H$ NMR ($CDCl_3$) $\delta$ 1.65–2.15 (m, 2 H, $CCH_2C$), 3.15–4.1 (m, 14 H, $CH_2N$, $CH_2Cl$), 4.2–4.7 (m, 2 H, $CH_2O$); $^{31}P$ NMR ($CDCl_3$) 100.0 ppm; TLC $R_f$ = 0.67 (same eluant)) and *trans*-$Cl_2Pt$(**8**)[(+)-$PhCH(CH_3)NH_2$] as a yellow glass in 24% yield (soluble in most organic solvents except aliphatic hydrocarbons; $[\alpha]^{25}_{589}$ 14.0° ($CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.67 and 1.55–2.1 (d, m, 5 H, $CH_3$, $CCH_2C$, $^3J_{HH}$ = 7.0 Hz), 3.0–4.1 (m, 15 H, CH, $CH_2N$, $CH_2Cl$), 4.25–4.65 (m, 2 H, $CH_2O$), 7.36 (s, 5 H, $C_6H_5$); $^{31}P$ NMR ($CDCl_3$) 68.1 ppm ($^1J_{PPt}$ = 4791 Hz)) as major products. All attempts to separate diastereomers of the latter complex failed.

A similar reaction of **8** with $Cl_2Pt(CH_2{=}CH_2)$[(−)-$PhCH_2CH(CH_3)NH_2$] (except that addition was carried out at −30 °C and the mixture was allowed to stand overnight at −20 °C and then 2 h at room temperature) gave on chromatography of the residue left after evaporation a 27% yield of *trans*-$Cl_2Pt$(**8**)$_2$ and a 22% yield of *trans*-$Cl_2Pt$(**8**)[(−)-$PhCH(CH_3)NH_2$] as a glassy material ($[\alpha]^{25}_{589}$ −15.2° ($CH_2Cl_2$); soluble in a variety of organic solvents except aliphatic hydrocarbons; $^1H$ NMR ($CDCl_3$) $\delta$ 1.38 (d, 3 H, $CH_3$, $^2J_{HH}$ = 6.4 Hz), 1.68–2.18 (m, 2 H, $CCH_2C$), 2.75–3.02 (br d, 2 H, $C_6H_5CH_2$, $^2J_{HH}$ = 6.3 Hz), 3.2–4.15 (m, 15 H, CH, $CH_2N$, $CH_2Cl$), 4.3–4.7 (m, 2 H, $CH_2O$), 7.28 (s, 5 H, $C_6H_5$); $^{31}P$ NMR ($CDCl_3$) 68.7 ppm ($^1J_{PPt}$ = 4768.5 Hz); TLC $R_f$ = 0.64 (same eluant)). All attempts to separate the diastereomers of this complex failed.

By halogen metathesis,[48] 0.9 g of this product was transformed into the corresponding diiodide. Extraction of the complex from the residue left upon evaporation was accomplished with $CH_2Cl_2$. Evaporation of the $CH_2Cl_2$ left a residue which was chromatographed on 100 g of silica gel with $CHCl_3$–$C_6H_6$ (1:1). The diiodo complex was isolated as an orange-yellow glassy mass in 62% yield ($[\alpha]^{25}_{589}$ −19.9° ($CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (d, 3 H, $CH_3$, $^3J_{HH}$ = 6.0 Hz), 1.77–2.2 (m, 2 H, $CCH_2C$), 2.7–3.0 (m, 2 H, $PhCH_2$), 3.0–4.6 (m, 17 H, CH, $CH_2Cl$, $CH_2N$, $CH_2O$), 7.31 (s, 5 H, $C_6H_5$). All attempts to separate diastereomers failed.

The reaction of **8** with $Cl_2Pt(CH_2{=}CH_2)$[(+)-$PhCH_2CH$-MeNHMe] was carried out by dropwise addition of a solution of **8** (0.01 mol in $MeC_6H_5$–$CH_2Cl_2$) to a stirred solution of the complex (4.4 g, 0.01 mol) in 150 mL of $CH_2Cl_2$. After the mixture was stirred overnight at room temperature, the solvent was evaporated and the residue chromatographed on 250 g of silica gel with $CHCl_3$–$C_6H_6$ (1:1). The only product isolated according to $^{31}P$ NMR spectroscopy and TLC analysis was *trans*-$Cl_2Pt$(**8**)$_2$ in 49% yield.

**B. Reaction of $Cl_2Pt(C_6H_5CN)_2$, 8, and $POCH(CH_2O)CH_2CH_2O$.** In the reaction of an equimolar mixture of $Cl_2Pt(C_6H_5CN)_2$, **8**, and the title caged phosphite in racemic form[49] at 0 °C in toluene, the main product formed was a meso–*dl* mixture of *cis*-$Cl_2Pt$(**8**)$_2$ as shown by $^{31}P$ NMR spectroscopy and TLC.

**C. Reaction of *dl*- and *meso-cis*-$Cl_2Pt$(8)$_2$ and *trans*-$Cl_2Pt$(8)$_2$ with $MeOPOCHMeCH_2CH_2O$.** Addition of an equimolar amount of the title phosphite in racemic form to NMR tubes containing the title complexes in $CD_3CN$ resulted in the formation of colorless solutions within a few minutes at room temperature. $^{31}P$ NMR spectra were immediately observed in which no uncoordinated phosphite or **8** could be detected but three signals associated with **8** (99.3 ppm ($^1J_{PPt}$ = 3290 Hz, $^2J_{PPtP}$ = 23.3 Hz), 101.0 ppm ($^1J_{PPt}$ = 3216 Hz, $^2J_{PPtP}$ = 24.4 Hz), 100.3 ppm ($^1J_{PPt}$ = 3229 Hz, $^2J_{PPtP}$ = 25.5 Hz)) and an unresolved multiplet for the phosphite (70–73 ppm ($^1J_{PPt} \simeq$ 5900 Hz)) were observed in a 2:1 ratio. After 12 h the peaks of **8** moved downfield (109.8 ppm ($^1J_{PPt}$ = 3578 Hz, $^2J_{PPtP}$ = 21.1 Hz), 108.4 ppm ($^1J_{PPt}$ = 3662 Hz, $^2J_{PPtP}$ = 21.1 Hz), 108.2 ppm ($^1J_{PPt}$ = 3635 Hz, $^2J_{PPtP}$ = 20.0 Hz)) and the multiplet associated with the phosphite ligand moved upfield, resolving into two signals (31.8 ppm ($^1J_{PPt}$ = 5174 Hz, $^2J_{PPtP}$ = 21.1 Hz) and 32.3 ppm ($^1J_{PPt}$ = 5156 Hz, $^2J_{PPtP}$ = 20.0 Hz)). Since none of these reactions produced the desired diastereomers of $Cl_2Pt$(**8**)($MeOPOCHMeCH_2CH_2O$), further efforts to characterize these interesting transformations will be described in a future publication.

**D. Equilibration of $Cl_2Pt(8)_2$ and $Cl_2PtL_2$.** Refluxing an equimolar mixture of *trans*-$Cl_2Pt(8)_2$ and *cis*-$Cl_2Pt(MeOPOCHMeCH_2CH_2O)_2$ in $CHCl_3$ for 24 h followed by evaporation of the solvent and chromatography on silica gel with $CHCl_3$–$Me_2CO$ (20:1) gave a complex in 82% yield (as judged by $^{31}P$ spectroscopy) whose solubility and spectral properties are consistent with a 50:50 mixture of *dl* and meso diastereomers of *cis*-$Cl_2Pt$(**8**)($MeOPOCHMeCH_2CH_2O$) ($^{31}P$ NMR ($CD_3CN$) 74.6 (**8**, $^1J_{PPt}$ = 4797 Hz, $^2J_{PPtP}$ = 16.6 Hz), 73.3 (**8**, $^1J_{PPt}$ = 4870 Hz, $^2J_{PPtP}$ = 15.5 Hz), 65.9 (phosphite ligand, $^1J_{PPt}$ = 6053 Hz, $^2J_{PPtP}$ = 16.6 Hz), 66.2 ppm (phosphite ligand, $^1J_{PPt}$ = 6062 Hz, $^2J_{PPtP}$ = 15.5 Hz)). Separation of the diastereomers was not achieved.

Reaction of *cis*-$Cl_2Pt(8)_2$ with *cis*-$Cl_2PMeOPOCHMeCH_2CH_2O)_2$ in refluxing $CHCl_3$ for 4 days produced no products. Changing the solvent to refluxing $MeC_6H_5$ caused the formation of some *cis*-$Cl_2Pt$(**8**)($MeOPOCHMeCH_2CH_2O$), but separation was hindered by the coformation of several other products.

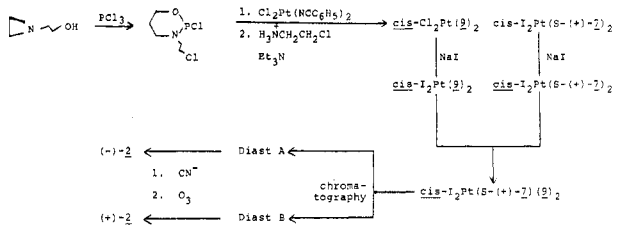
The complex *cis*-$Cl_2Pt(MeOPOCHMeCH_2CH_2O)_2$ was prepared by adding dropwise a solution of 600 mg (4.00 mmol) of $MeOPOCHMeCH_2CH_2O$ in 5 mL of $CH_2Cl_2$ to a solution of 948.5 mg (2.00 mmol) of $Cl_2Pt(C_6H_5CN)_2$ in 20 mL of $CH_2Cl_2$ at room temperature. After 3 h of stirring, the solvent was evaporated and the residue chromatographed on 30 g of silica gel with $CH_2Cl_2$ to remove $C_6H_5CN$ and then with $CH_2Cl_2$–$Me_2CO$ (40:1) to remove the unreacted platinum complex, and then the product *cis*-$Cl_2Pt(MeOPOCHMeCH_2CH_2O)_2$ in 74% yield was obtained as white crystals (mp 164.5–166 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.2 (d, 3 H, $CH_3C$, $^3J_{HH}$ = 6 Hz), 1.8–2.3 (m, 2 H, $CCH_2C$), 3.9 (d, 3 H, $CH_3OP$, $^3J_{PH}$ = 13 Hz), 4.1–5.1 (m, 3 H, $HCOPOCH_2$); $^{31}P$ NMR ($CDCl_3$) 58.8 ($^1J_{PPt}$ = 5787 Hz), 68.7 ppm ($^1J_{PPt}$ = 5791 Hz)).

After equimolar mixtures of *trans*-$Cl_2Pt(8)_2$ and *trans*-$Cl_2PtL_2$ (L = [(−)-menO]$_2$PPh or [(−)-men]$_3$P) had been refluxed in benzene for 72 h, the only reaction detected was the isomerization of *trans*-$Cl_2Pt(8)_2$ to a *dl*–meso mixture of the cis isomer. The *trans*-$Cl_2PtL_2$ complexes were prepared by following the procedure for *cis*-$Cl_2Pt$-[(*S*)-(+)-**7**]$_2$ given earlier. The *trans*-$Cl_2Pt$([(−)-menO]$_2$PPh)$_2$ complex was obtained in 90% yield as yellow needles (mp 123–136 °C dec; very soluble in hexane, $C_6H_6$, $Et_2O$, and $CH_2Cl_2$ but insoluble in MeCN; $[\alpha]^{25}_{589}$ −121.0°, $[\alpha]^{25}_{578}$ −126.2°, $[\alpha]^{25}_{546}$ −143.8° (*c* 5.075, $C_6H_6$); $^1H$ NMR ($CDCl_3$) $\delta$ 0.3–4.0 (m, 72 H, alkyl protons), 4.5–5.0 (m, 4 H, HCOP), 7.3–8.0 (m, 10 H, $C_6H_5$); $^{31}P$ NMR ($CHCl_3$–$CH_3CN$) 106.0 ppm ($^1J_{PPt}$ = 3325 Hz)). The *trans*-$Cl_2Pt$([(−)-menO]$_3$P)$_2$ complex was obtained in 67% yield as yellow crystals (mp 154.5–155.5 °C; very soluble in hexane; $[\alpha]^{25}_{589}$ −147.6°, $[\alpha]^{25}_{578}$ −154.3°, $[\alpha]^{25}_{546}$ −176.8° (*c* 5.44, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 0.6–2.7 (m, 108 H, alkyl protons), 4.3–5.9 (m, 6 H, HCOP); $^{31}P$ NMR ($C_6D_6$) 80.1 ppm ($^1J_{PPt}$ = 3945 Hz)).

When *trans*-$Cl_2Pt(8)_2$ was allowed to reflux for 2 days in benzene with an equimolar quantity of *cis*-$Cl_2Pt$[(+)-$PhMeCHNHP(OMe)_2]_2$, the presence of a 40:60 ratio of diastereomers of *cis*-$Cl_2Pt$(**8**)[(+)-$PhMeCHNHP(OMe)_2$] was detected ($^{31}P$ NMR ($C_6D_6$) 71.8 (**8**, meso or *dl*, $^1J_{PPt}$ = 5116 Hz, $^2J_{PPtP}$ = 0), 71.5 (**8**, *dl* or meso, $^1J_{PPt}$ = 5114 Hz, $^2J_{PPt}$ = 0), 68.3 (L, meso or *dl*, $^1J_{PPt}$ = 5307 Hz, $^2J_{PPt}$ = 0), 68.7 ppm (L, *dl* or meso, $^1J_{PPt}$ = 5304 Hz, $^2J_{PPtP} \simeq$ 0 Hz). No separation of the diastereomers could be effected, however. The ligand (+)-$PhMeCHNHP(OMe)_2$ was made by adding dropwise a solution of 468 mg (3.64 mmol) of $(MeO)_2PCl$ in 3 mL of $C_6H_6$ to a solution of 441 mg (3.64 mmol) of (*R*)-(+)-$PhMeCHNH_2$ and 0.51 mL (3.64 mmol) of $Et_3N$ in 20 mL of $C_6H_6$ cooled to 3 °C. After it had been stirred for 1 h at 5 °C, the reaction mixture was allowed to reach

(49) Kainosho, M.; Nakamura, A. *Tetrahedron*, **1969**, *25*, 4071.

**Scheme II**



25 °C after which the $Et_3NHCl$ was filtered and washed with $C_6H_6$. Solvent was evaporated, giving the crude ligand which was used without further purification ($^1H$ NMR ($C_6H_6$) $\delta$ 1.35 (d, 3 H, $CH_3C$, $^3J_{HH}$ = 7 Hz), 3.25 (d, 3 H, $CH_3OPOCH_3$, $^3J_{HP}$ = 11 Hz), 3.30 (d, 3 H, $CH_3OPOCH_3$), $^3J_{HP}$ = 11 Hz), 3.52 (dq, 1 H, HC, $^3J_{HP}$ = 9.5 Hz, $^3J_{HCCH} \simeq {}^3J_{HCNH} \simeq$ 7 Hz)). The complex *cis*-$Cl_2Pt[(+)$-$PhMeCHNHP(OMe)_2]_2$ was made by following the procedure for *cis*-$Cl_2Pt[(S)$-$(+)$-$7]_2$ given earlier, in 51% yield as colorless crystals ($[\alpha]^{25}_{589}$ −6.7°, $[\alpha]^{25}_{578}$ −7.1°, $[\alpha]^{25}_{546}$ −8.8° (*c* 5.88, $C_6H_6$); soluble in $CCl_4$, $C_6H_6$, $CHCl_3$, and $Me_2CO$ but insoluble in hexane and $Et_2O$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.47 (br d, 6 H, $CH_3C$, $^3J_{HH}$ = 7 Hz), 3.1 (br d, 6 H, $CH_3OPOCH_3$, $^3J_{PH}$ = 14 Hz), 3.83 (br d, 6 H, $CH_3OPOCH_3$, $^3J_{PH}$ = 13.5 Hz), 4.0–4.6 (m, 2 H, HC), 5.7 (br dd, 2 H, HN $^2J_{HP}$ = 25 Hz, $^3J_{HH}$ = 9 Hz), 7.3 (m, 10 H, $C_6H_5$); $^{31}P$ NMR ($C_6D_6$) 68.8 ppm ($^1J_{PPt}$ = 5183 Hz)).

Refluxing an equimolar mixture of *trans*-$Cl_2Pt(8)_2$ and *cis*-$Cl_2Pt(7)_2$ (wherein **7** is racemic) in benzene for 62 h gave a 79% yield of the *cis*-$Cl_2Pt(7)(8)$ complex which in the $^{31}P$ NMR spectrum showed the presence of diastereomers in a 50:50 ratio ($^{31}P$ NMR ($C_6D_6$) 75.9 (**8**, $^1J_{PPt}$ = 4785 Hz, $^2J_{PPtP} \simeq$ 15 Hz), 75.2 (**8**, $^1J_{PPt}$ = 4798 Hz, $^2J_{PPtP} \simeq$ 15 Hz), 67.5 (**7**, $^1J_{PPt}$ = 6037 Hz, $^2J_{PPtP} \simeq$ 15 Hz), 67.1 ppm (**7**, $^1J_{PPt}$ = 6052 Hz, $^2J_{PPtP}$ = 15 Hz)). Although these complexes appeared to be separable on TLC, it was decided to use the diiodide derivatives of the starting complexes so that crystallinity and purity of the products could be enhanced and because *cis*-$I_2Pt(8)_2$ is more reactive than the *cis*-dichloro analogue and easier to prepare than the *trans*-dichloro analogue.

**E. Equilibrium of *cis*-$I_2Pt(8)_2$ and *cis*-$I_2PtL_2$.** Refluxing an equimolar mixture of the title complexes where L is MeOPOCHMeCH$_2$CH$_2$O in $C_6H_6$ for 12 h afforded a 55% yield of a 50:50 mixture of the diastereomers of *cis*-$I_2Pt$(**8**)-(MeOPOCHMeCH$_2$CH$_2$O) according to the $^{31}P$ spectrum ($^{31}P$ NMR ($CD_3CN$) 74.4 (**8**, $^1J_{PPt}$ = 4635 Hz, $^2J_{PPtP} \simeq$ 0 Hz), 73.6 (**8**, $^1J_{PPt}$ = 4696 Hz, $^2J_{PPtP} \simeq$ 0 Hz), 72.1 (MeOPOCHMeCH$_2$CH$_2$O, $^1J_{PPt}$ = 5795 Hz), 73.2 ppm (MeOPOCHMeCH$_2$CH$_2$O, $^1J_{PPt}$ = 5814 Hz)). The diastereomers do appear to be separable according to TLC but since the resolving ligand *S*-(+)-**7** is easier to synthesize in resolved form than (+)- or (−)-MeOPOCHMeCH$_2$CH$_2$O,[50] further resolution work was carried out with it (vide supra). The complex *cis*-$I_2Pt$-(MeOPOCHMeCH$_2$CH$_2$O)$_2$ was made from the corresponding *cis*-dichloride (vide supra) by halogen metathesis,[48] giving orange crystals in 84% yield ($^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (br d, 6 H, $CH_3C$, $^3J_{HH}$ = 6.5 Hz), 1.5–2.3 (m, 4 H, $CCH_2C$), 3.9 (br d, 6 H, $CH_3OP$, $^3J_{PH}$ = 14.4 Hz), 4.0–5.1 (m, 6 H, $CH_2OPOCH$); $^{31}P$ NMR ($(CD_3)_2CO$) 72.3 ppm ($^1J_{PPt}$ = 5557 Hz)).

## Discussion

**Optical Resolution of Triphosphamide (3) and Isophosphamide (2).** The reaction sequences for the resolution of **3** and **2** summarized in Schemes I and II, respectively, are the same except for the oxidizing agent in the last step and the method of synthesizing the trivalent phosphorus forms of the drugs (**8** and **9**).[23] These changes permitted higher yields and purer products in the respective reactions in Scheme II. Interestingly, ozonolysis at a higher temperature (0 °C compared to −70 °C) in an aqueous peroxide medium (rather than an organic solvent) has been used to synthesize the 4-keto and 4-hydroperoxy derivatives of cyclophosphamide (**1**).[51] Under the milder conditions employed in the present work, no evidence for oxidation at the 4-position of **2** could be detected by $^{13}C$ NMR spectroscopy.

Noteworthy is the observation that a catalytic amount of (*S*)-(+)-**7** gave better than 70% of the diastereomeric *cis*-$I_2Pt(8)[(S)$-$(+)$-$7]$ in typical runs of 7 or 8 h in refluxing benzene, whereas without the catalyst only a 44% yield was realized in 48 h under the same conditions. That equilibrium is reached in the catalyzed equilibration is shown by repetition of the experiment using only diastereomer A in which an almost identical composition of this diastereomer, *cis*-$I_2Pt(8)_2$, and *cis*-$I_2Pt[(S)$-$(+)$-$7]_2$ is produced. No precedent for the catalysis of a similar equilibrium of platinum complexes could be found in the literature. Our results are suggestive of the formation of a reactive five-coordinate intermediate platinum(II) complex. Catalyzed equilibrations of pure *meso*-*cis*-$I_2Pt(8)_2$ and *dl*-*cis*-$I_2Pt(8)_2$ with *cis*-$I_2Pt[(S)$-$(+)$-$7]_2$ under the same conditions in separate experiments revealed that the meso diastereomer reacts somewhat faster than the *dl*.

The optical purities of resolved **2** and **3** were judged to be about 95% or better by $^{31}P$ NMR spectroscopy in the presence of an optically active shift reagent. Thus a 1:1 molar ratio of (+)-**3** to EuOpt-I shift reagent as a 0.2 M solution in $C_6D_6$ exhibited two well-defined peaks at −107.2 and −108.7 ppm. Under the same conditions, the enantiomers gave only the −108.7 ppm peak for (+)-**3** and the −107.2 ppm peak for (−)-**3**. Using $Eu(hfc)_3$, as has been done by others for evaluating the optical purity of resolved **2**,[17] we found that at ratios of shift reagent to (+)-**2** of ≥2 in $CDCl_3$, narrow $^{31}P$ peaks at −69.9 and −72.0 ppm of equal intensity appear. Under the same conditions, only the peak at −69.9 and −72.0 ppm could be seen for (−)-**2** and (+)-**2**, respectively. The optical rotations for (+)-**3** (30.1°, MeOH), (−)-**3** (−29.7°, MeOH), (+)-**2** (35.7°, $C_6H_6$), and (−)-**2** (−37.8°, $C_6H_6$) compare well with those obtained by others recently for three of these enantiomers[12] [(−)-**3** (−28.6°, MeOH), (+)-**2** (39.0°, MeOH), and (−)-**2** (−38.8°, MeOH)]. The (+) enantiomer of **3** was not reported in the latter publication.[12]

As can be seen from the Experimental Section, numerous attempts were made to synthesize separable platinum(II) complex diastereomers containing **8** as a ligand. Although (+)- and (−)-MeOPOCHMeCH$_2$CH$_2$O could function as resolving ligands in such diastereomers, these enantiomers are more tedious to prepare[50] than (*S*)-(+)-**7**, which is made in three steps in 99% optical purity. While it would have been possible to utilize *trans*-$Cl_2Pt(8)_2$ in the equilibrium step with *cis*-$Cl_2Pt[(S)$-$(+)$-$7]_2$, the former complex is not prepared in high yield, and its cis isomer is not as reactive. Use of the diiodide derivatives offers the advantage that *cis*-$I_2Pt(8)_2$ (to which both dichloro isomers are easily converted in better than 90% yield) is reactive toward *cis*-$I_2Pt[(S)$-$(+)$-$7]_2$ (which is also made from the dichloro derivative in better than 90% yield). Moreover the diiodides are crystalline and quite easily purified. Use of $^{31}P$ NMR spectroscopy has shown that in a $(CD_3)_2CO$ solution of NaI, *trans*-$Cl_2Pt(8)_2$ appears to be immediately converted to a meso–*dl* mixture of *trans*-$I_2Pt(8)_2$ (96.2 ppm ($^1J_{PPt}$ = 3216 Hz), 96.1 ppm ($^1J_{PPt}$ = 3218 Hz)). This complex on standing in solution, however, isomerizes to the cis isomer.

**Assignment of Meso and *dl* Configurations to *cis*-$X_2Pt(8)_2$.** By catalyzed equilibration of purified diastereomer A of *cis*-$I_2Pt(8)[(S)$-$(+)$-$7]$, it was found that only one $^{31}P$ signal for *cis*-$I_2Pt(8)_2$ could be detected (70.1 ppm, $^1J_{PPt}$ = 5071 Hz) which is assigned to the *dl* diastereomer. The fact that the equilibration did not result in the formation of diastereomer

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A in quantities detectable by $^{31}P$ spectroscopy or TLC implies that no racemization of **8** occurs under these conditions.

Conversion of one of the purified diastereomers of *cis*-$Cl_2Pt(\mathbf{8})_2$ ($^{31}P$ 74.1 ppm, $^1J_{PPt}$ = 5190 Hz) to the corresponding *cis*-diiodo complex in the usual way[48] showed that according to the $^{31}P$ NMR spectrum, the latter complex was the meso diastereomer (73.6 ppm, $^1J_{PPt}$ = 4989 Hz). Thus the *cis*-dichloro precursor must also be a meso diastereomer.

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**Registry No.** (–)-**2**, 66849-33-0; (+)-**2**, 66849-34-1; (–)-**3**, 72282-84-9; (+)-**3**, 72282-85-0; (+)-**7**, 75045-93-1; *cis*-$Cl_2Pt$[(*S*)-(+)-**7**]$_2$, 72316-66-6; *cis*-$I_2Pt$[(*S*)-(+)-**7**]$_2$, 72316-69-9; *meso-cis*-$I_2Pt(\mathbf{7})_2$, 75082-09-6; *dl-cis*-$I_2Pt(\mathbf{7})_2$, 75082-10-9; *meso-cis*-$Cl_2Pt(\mathbf{7})_2$, 75082-11-0; *cis*-$I_2Pt(\mathbf{8})$[(*S*)-(+)-**7**] (isomer 1), 72316-68-8; *cis*-$I_2Pt(\mathbf{8})$[(*S*)-(+)-**7**] (isomer 2), 72376-60-4; *cis*-$Cl_2Pt(\mathbf{7})(\mathbf{8})$ (isomer 1), 75045-95-3; *cis*-$Cl_2Pt(\mathbf{7})(\mathbf{8})$ (isomer 2), 75082-12-1; *cis*-$I_2Pt(\mathbf{9})$[(*S*)-(+)-**7**] (isomer 1), 75045-96-4; *cis*-$I_2Pt(\mathbf{9})$[(*S*)-(+)-**7**] (isomer 2), 75109-25-0; *dl-cis*-$I_2Pt(\mathbf{9})_2$, 72316-67-7; *meso-cis*-$I_2Pt(\mathbf{8})_2$, 72346-74-8; *l-cis*-$I_2Pt(\mathbf{8})_2$, 75109-26-1; *meso-cis*-$Cl_2Pt(\mathbf{8})_2$, 74858-59-6; *dl-cis*-$Cl_2Pt(\mathbf{8})_2$, 75082-13-2; *trans*-$Cl_2Pt(\mathbf{8})_2$, 75082-14-3; *trans*-$Cl_2Pt(\mathbf{8})$[(+)-PhCH(CH$_3$)NH$_2$], 75045-97-5; *trans*-$Cl_2Pt(\mathbf{8})$[(–)-PhCH$_2$CH(CH$_3$)NH$_2$], 75045-98-6; *trans*-$I_2Pt(\mathbf{8})$[(–)-PhCH$_2$CH(CH$_3$)NH$_2$], 75045-99-7; *cis*-$Cl_2Pt(\mathbf{8})$(MeOPOCHMeCH$_2$CH$_2$O) (isomer 1), 75046-00-3; *cis*-$Cl_2Pt(\mathbf{8})$(MeOPOCHMeCH$_2$CH$_2$B) (isomer 2), 75082-15-4; *cis*-$Cl_2Pt(\mathbf{8})$[(+)-PhMeCHNHP(OMe)$_2$], 75059-71-1; *cis*-$I_2Pt(\mathbf{8})$(MeOPOCHMeCH$_2$CH$_2$O) (isomer 1), 75046-01-4; *cis*-$I_2Pt(\mathbf{8})$(MeOPCHMeCH$_2$CH$_2$O) (isomer 2), 75082-16-5; *meso-cis*-$I_2Pt(\mathbf{9})_2$, 75046-02-5; *meso-cis*-$Cl_2Pt(\mathbf{9})_2$, 74858-58-5; *dl-cis*-$I_2Pt(\mathbf{9})_2$, 75109-27-2; *dl-cis*-$Cl_2Pt(\mathbf{9})_2$, 74892-36-7; $Cl_2Pt(CH_2{=}CH_2)$[(+)-PhCH(CH$_3$)N(CH$_3$)$_2$], 75046-03-6; $Cl_2Pt(CH_2{=}CH_2)$[(+)-PhCH(CH$_3$)NH$_2$], 53274-62-7; $Cl_2Pt(CH_2{=}CH_2)$[(–)-PhCH$_2$CH(CH$_3$)NH$_2$], 75082-17-6; $Cl_2Pt(CH_2{=}CH_2)$[(+)-PhCH$_2$CH(CH$_3$)NH(CH$_3$)], 75082-18-7; *cis*-$Cl_2Pt$(MeOPOCHMeCH$_2$CH$_2$O)$_2$, 75046-04-7; *trans*-$Cl_2Pt$([(–)-menO]$_2$PPh)$_2$, 75046-07-0; *trans*-$Cl_2Pt$([(–)-menO]$_3$P)$_2$, 75046-08-1; *cis*-$Cl_2Pt$[(+)-PhMeCHNHP(OMe)$_2$]$_2$, 75046-05-8; *cis*-$I_2Pt$(MeOPOCHMeCH$_2$CH$_2$O)$_2$, 75046-06-9; di-(–)-menthyl phenylphosphonite, 58359-50-5; methyl mandelate, 21210-43-5; 2-chloro-1,3,2-dioxaphosphorinane, 6362-89-6; $Cl_2Pt(C_6H_5CN)_2$, 15617-19-3; $(MeO)_2PCl$, 3743-07-5; (R)-(+)-PhMeCHNH$_2$, 3886-69-9; (+)-PhMeCHNHP(OMe)$_2$, 75045-94-2.

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# Metal Atom Reactions with Fluorocarbons. 9. Preparation and Spectral Analyses of (Perfluoroalkyl)- and (Perfluoroaryl)palladium Halides

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Oxidative insertion of palladium atoms into pefluoroalkyl and -aryl halide C–X bonds has yielded stable $C_6F_5PdBr$ and $CF_3PdI$. These formally two-coordinate nonligand-stabilized organometallics have been isolated and characterized. Their tendency to form bridging telomers in solution in order to fill open coordination sites and their unusual bonding and thermal stabilities are discussed. Their chemistry with a host of added ligands, including dienes, sulfides, amines, and phosphines, has yielded a number of new $Ar_f$ and $R_fPdX(L)_2$ complexes. Spectra of these complexes are reported and compared. For the $CF_3PdI$ and $CF_3PdI(L)_2$ systems a $d_\pi \rightarrow \sigma^*$ back-bonding scheme to explain the robust character of the C–Pd bond is *not* supported by the spectroscopic data. An ionic–covalent resonance interaction appears more appropriate and is encouraged by the presence of $PEt_3$ and $C_5H_5N$ ligands.

## Introduction

Formal two-coordinate organopalladium complexes RPdX, ArPdX, and RCOPdX have been proposed as intermediates in a variety of important catalysis schemes.[2-7] Generally, it had been assumed that coordinatively unsaturated species such as these were too short-lived to detect or isolate and that it would be necessary to trap them with stabilizing ligands to yield $RPdX(L)_2$. However, there are now several examples in palladium chemistry where RPdX or $R_2Pd$ species possessing very unusual R groups (or Ar groups) have been isolated.[8] Pracejus and co-workers[9] have prepared $Pd(CH_2CN)_2$ which is stable in air and decomposes thermally at 220 °C.

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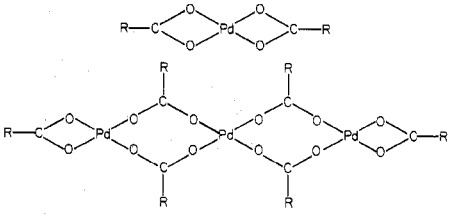
(8) We are only referring to $\sigma$-bonded C–Pd species here. Of course it should be noted that palladium dihalides ($PdX_2$) are well-known two-coordinate palladium compounds that fill open coordination sites through extensive halide bridging and are actually best described as polymers in the solid state. Also, the work of Wilkinson and co-workers on the preparation of carboxylates of palladium [$Pd(OCOR)_2$ where R = $CH_3$, $CH_3CH_2$, $C_6H_5$, $CF_3$, and $C_6F_5$] are examples of formally two-coordinate Pd–O bonded species. Extensive bridging also occurs in these cases:



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