Transition Metal Chemistry of Main Group Hydrazides. Part 3:[1] Carboxylate Appended Phosphorus Hydrazides as Novel Functionalized Chelating Systems. Synthesis and Characterization of New Cyclometallaphosphohydrazides. X-ray Structure of a Palladium(II) Representative

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The synthesis of new bifunctional chelating agents (BFCAs) based on the phosphorus hydrazide ligand family for potential ^{109}Pd labeling of tumor-localizing biomolecules such as proteins/peptides is described. The new BFCAs were achieved in good yields (75–90%) by the reaction of the phosphorus hydrazide $PhP(S)(NMeNH_2)_2$ (**1**) with functionalized aldehydes to yield the Schiff-base products with the following chemical compositions as air-stable crystalline solids: $PhP(S)(NMeNH_2)(NMeNCHC_6H_4COOH)$, **2**; $PhP(S)(NMeNCHC_6H_4COOH)_2$, **3**; $PhP(S)(NMeNH_2)(NMeNCHC_6H_4CH{=}CHCOOH)$, **4**; $PhP(S)(NMeNCHC_6H_4CH{=}CHCOOH)_2$, **5**. The reactions of three of the new phosphorus hydrazides (**2–4**) with $PdCl_2(PhCN)_2$ resulted in the new Pd(II) metallacycles $PhP(S)(NMeNH_2)(NMeNCHC_6H_4COOH)\cdot PdCl_2$, **6**; $PhP(S)(NMeNCHC_6H_4COOH)_2\cdot PdCl_2$, **7**; and $PhP(S)(NMeNH_2)(NMeNCHC_6H_4CH{=}CHCOOH)\cdot PdCl_2$, **8**. The reactivity of **6** toward *n*-butylamine has been evaluated as a model for the preparation of new bioconjugates. The structural elucidation of all the new compounds has been carried out by analytical and complete NMR (^1H, ^{31}P) and IR spectroscopic data. As a representative example, the X-ray structure of one of the Pd(II) complexes, **8**, has been determined. Crystal data for **8**: monoclinic, space group $P2_1/c$, $a = 7.981(3)$ Å, $b = 21.566(4)$ Å, $c = 13.647(5)$ Å, $\beta = 104.4(2)°$, $Z = 4$. The structure was solved by direct methods and was refined to $R = 0.055$.

Introduction

Research in fundamental inorganic chemistry to generate new bifunctional chelating agents and studies of their reactivity with specific transition metals, as models for the corresponding reactions with metallic radioisotopes, has become the basis for the discovery of new and improved methods for the production of peptide/protein conjugates of radiometals.[3] Radiopharmaceuticals, like any other drug, tend to distribute uncharacteristically into various organs in the body and may cause excessive radiation damage to healthy cells. This has necessitated the development of targeting procedures so that the radiopharmaceutical biodistributes preferentially to a certain organ in the body or has greater affinity for certain parts in the body.[4] The radiometal conjugates of the protein/peptide bound ligating units are being considered as the most effective means of targeting radiopharmaceuticals for use in nuclear medicine. Certain peptides/proteins have been shown to have greater affinity for specific antigens in the body, and recent studies have shown that the radiometal conjugates of these molecular vectors (e.g., peptides/proteins) localize at desired sites in the body.[5] A need to develop more sophisticated targeting techniques has resulted in a considerable interest in the study of fundamental main group and transition metal chemistry of novel ligand systems to achieve the covalent attachment of proteins/peptides to the ligand backbone.

We are currently interested in the chemistry of Pd(II) with new bifunctional phosphorus–nitrogen ligand systems. The results from these studies may be used to generate the corresponding analogues with ^{109}Pd. Palladium-109 is a β-emitting radionuclide (1.02 MeV, 100%) that has many desirable nuclear properties for use in radioimmunotherapy (RIT).[6-8] Availability of enriched ^{108}Pd makes the production of high-yield ^{109}Pd by thermal neutron

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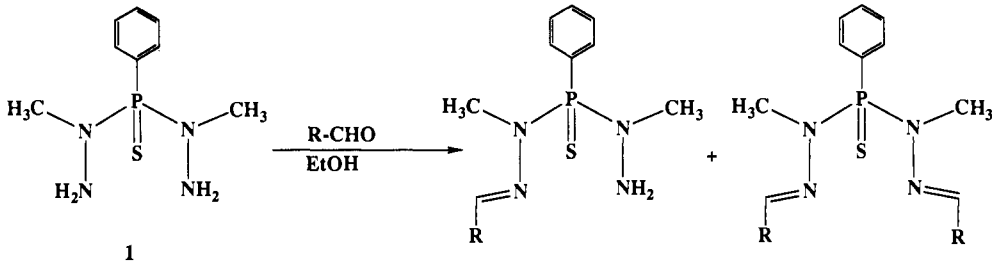
Scheme 1



1

R = C_6H_4COOH 2 3

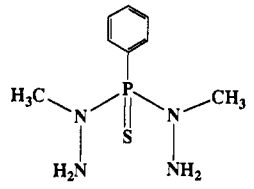
R = $C_6H_4CH{=}CHCOOH$ 4 5

irradiation (σ = 12 barn, resonance integral = 200 barn) plausible. The 1.02-MeV β emission classifies ^{109}Pd as a medium range β source for tumor therapy. Its decay to a 40-s half-life ^{109m}Ag which yields an 88-keV γ emission in 3.6% yield along with conversion and Auger electrons makes it suitable for imaging applications also.

Fawwaz et al.,[7] reported in 1984 that injection of ^{109}Pd labeled antimelanoma MAb into nude mice bearing human melanoma resulted in significant accumulation in tumors (~19% ID). Chen and Troutner[8] have also reported the use of a macrocyclic tetradentate bifunctional chelating agent (BFCA) to label proteins with ^{109}Pd. However, in both the earlier studies the radiolabeling yields were low, suggesting that a concerted effort in developing new chelating systems and radiolabeling methods is required to exploit or more fully explore the potential of using ^{109}Pd in radioimmunotherapy.

Most of the ^{109}Pd complexes used to date have been derived from a diverse range of macrocyclic amines or their carboxylate derivatives. However, the application of other ligating systems to produce stable ^{109}Pd complexes has remained largely unexplored.

As part of our ongoing efforts on the development of peptide/protein conjugates of diagnostically and therapeutically useful radiometals, we are presently interested in the chemistry of new multifunctional phosphorus hydrazides of type **1**. Recent studies



1

from our laboratory have shown that **1** can be used as (a) a chelate to early and late transition metals and metallic isotopes[1,9] and (b) a chemically flexible ligand framework because of the versatile reactivity of the terminal hydrazido groups in Schiff base and related reactions to generate a variety of functionalized ligating frameworks.[9] In this paper, we report the synthesis of carboxylate functionalized phosphorus hydrazides (Scheme 1) and demonstrate that they can be complexed with Pd(II) to produce stable carboxylate functionalized metal chelates. This paper also addresses the reactivities of the metal appended bifunctional chelates (BFCs) with primary amines to produce carboxylate–amine conjugates as possible models for the corresponding reactions of ^{109}Pd bound BFCAs with proteins/peptides.

Experimental Section

Unless otherwise stated, all reactions were carried out under anaerobic and anhydrous conditions using prepurified N_2 and conventional Schlenk techniques. Reagents such as 4-carboxybenzaldehyde, 4-formylcinnamic acid, $PhP(S)Cl_2$, and $PdCl_2$ were purchased from Aldrich Chemical Co. and were used without further purification. Phosphorous bis(hydrazide)-sulfide (BHPS) (**1**) was prepared by the reaction of $PhP(S)Cl_2$ with methylhydrazine.[9,10]

Nuclear magnetic resonance spectra were recorded on a Bruker WH-500 spectrometer. The ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from external standard $SiMe_4$. The ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external standard, and positive shifts lie downfield of the standard.

Synthesis of $C_6H_5P(S)(NMeNH_2)(NMeNCHC_6H_4COOH)$, 2. A solution of 4-carboxybenzaldehyde (1.3 g, 8.7 mmol) in ethanol (50 mL) was added dropwise to an ethanolic solution (100 mL) of **1** (1 g, 8.7 mmol) which had been cooled to −70 °C. The solution was allowed to warm to 25 °C and stirred for an additional 4 h. The thin layer chromatography analysis of the solution showed three spots (R_f = 0.3, 0.6, and 0.9). The solvent was removed *in vacuo* to obtain a white powdery residue. The three components were separated by flash chromatography (silica gel) with a solvent system of hexane–ethyl acetate–methanol in the ratio of 6:4:1. The eluants of each of the fractions were combined and evaporated to give the components as white crystalline powders. The component which showed an R_f of 0.6 was identified to be the mono-(carboxylate) derivative **2** whereas the component of R_f of 0.3 was the bis(carboxylate) compound **3**. The starting compound **1** showed an R_f of 0.9.

$C_6H_5P(S)(NMeNH_2)(NMeNCHC_6H_4COOH)$, **2**: white powder; yield 73%; mp 97 °C. ^{31}P NMR ($CDCl_3$): δ 82.34. ^{1}H NMR ($CDCl_3$): δ 2.9 (d, 3H, $^3J_{P-H}$ = 12.1 Hz), 2.41 (d, 3H, $^3J_{P-H}$ = 14.1 Hz), 7.57 (s, 1H, N=CH), 7.39–8.09 (m, 9H, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 40.16 (d, $^2J_{P-C}$ = 15.1 Hz), 31.99 (d, $^2J_{P-C}$ = 9.8 Hz), 143.1 (s, NC=H), 140.28, 136.58, 132.70, 132.34, 130.57, 130.31, 129.47, 128.28, 127.94, 126.31 (aromatic carbons). IR (KBr, cm^{-1}): 3216 (NH_2); 1670 (C=O); 603 (P=S). Anal. Calcd for $C_{16}H_{19}N_4O_2PS$: C, 53.03; H, 5.28; N, 15.46. Found: C, 53.44; H, 5.45; N, 15.31.

3: yield 12%; white powder; mp 103 °C. Anal. Calcd for $C_{24}H_{23}N_4O_4PS$: C, 58.29; H, 4.69; N, 11.33. Found: C, 58.35; H, 4.71; N, 11.30.

Unreacted phosphorus bis(hydrazide) sulfide (BHPS) **1** was recovered in 12% yield.

Synthesis of $C_6H_5P(S)(NMeNCHC_6H_4COOH)_2$, 3. A solution of 4-carboxybenzaldehyde (2.69 g, 17.4 mmol) in THF (50 mL) was added dropwise at 25 °C to a THF solution (100 mL) of **1** (2 g, 8.7 mmol). The mixture was stirred at RT for 6 h before the solvent was removed *in vacuo* to obtain a white crystalline powder of **3**. The final purification of **3** was achieved by boiling the solid in acetonitrile and cooling the solution to 0 °C to produce pure **3** (yield 89%), mp 103 °C. Anal. Calcd for $C_{24}H_{23}N_4O_4OPS$: C, 58.29; H, 4.69; N, 11.33. Found: C, 58.31; H,

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4.67; N, 11.29. ^{31}P NMR ($CDCl_3$): δ 80.04. ^{1}H NMR ($CDCl_3$): δ 3.21 (d, 6H, $^3J_{P-H}$ = 12.3 Hz), 7.67 (s, 2H, N=CH), 7.35–7.97 (m, 13H, aromatic protons). IR (KBr, cm^{-1}): 1647 (C=O); 605 (P=S). ^{13}C NMR (DMSO): 33.14 (d, $^2J_{P-C}$ = 9.75 Hz), 139.39 (s, NC=H), 171.7 (s, COOH), 126.07, 127.6, 127.7, 128.2, 129.8, 130.6, 130.9, 131.9, 133.1, 133.2, 136.4, 136.6 (aromatic carbons).

Synthesis of $C_6H_5P(S)(NMeNH_2)(NMeNCHC_6H_4CH$=CH—COOH), 4. To a methylene chloride (100 mL) solution of **1** (4.60 g; 20.0 mmol) was added dropwise at 0 °C a solution of 4-formylcinnamic acid (3.50 g; 19.9 mmol) also in methylene chloride (100 mL). The mixture was allowed to warm to 25 °C and stirred for 6 h before the solvent removed *in vacuo* to obtain a yellow powder. Unreacted **1** and the bis(cinnamic acid) adduct **5** were removed by washing the yellow powder with diethyl ether (2 × 25 mL). Recrystallization with dry acetonitrile gave pure **4** (89%), mp 68 °C. Anal. Calcd for $C_{18}H_{21}N_4O_2PS$: C, 55.66; H, 5.45; N, 14.43. Found: C, 55.37; H, 5.41; N, 14.37. ^{31}P NMR (DMSO): δ 81.37. ^{1}H NMR (DMSO): δ 2.82 (d, 3H, $^3J_{P-H}$ = 11.2 Hz), 3.4 (d, 3H, $^3J_{P-H}$ = 12.2 Hz), 7.34 (s, 1H, N=CH), 5.5–8.3 (m, 11H, aromatic and HC=CH protons). ^{13}C NMR (CH_3OD): δ 32.16 (d, $^3J_{P-C}$ = 10.1 Hz), 40.97 (d, $^3J_{P-C}$ = 14.98 Hz), 146.37 (s, NC=H), 170.31 (s, COOH), 119.64, 121.51 (>C=C<), 139.21, 139.13, 183.77, 138.68, 138.19, 138.09, 136.07, 135.92, 134.44, 134.36, 133.99, 133.92, 133.01, 132.93, 129.71, 129.53, 129.37, 129.09, 128.99, 128.80, 128.69, 128.02, 127.99. IR (KBr, cm^{-1}): 3179 (NH_2); 1671 (C=N); 608 (P=S); 1650 (C=O).

Synthesis of Pd(II) Complexes of 2–4. A solution of $PdCl_2(PhCN)_2$ (637 mg, 1.66 mmol) in CH_2Cl_2 (25 mL) was added dropwise at 25 °C to a CH_2Cl_2 solution of **2** (600 mg, 1.66 mmol). The reaction mixture was stirred for 2 h before the solvent removed *in vacuo* to obtain an orange solid **6**, which was repeatedly washed with dry hexane to remove the benzonitrile byproduct. Final purification of **6** was achieved through crystallization in acetonitrile (yield 73%); mp 134 °C dec. Anal. Calcd for $C_{16}H_{19}N_4O_2PSPdCl_2$: C, 35.68; H, 3.55; N, 10.40; Cl, 13.14. Found: C, 35.62; H, 3.61; N, 9.99; Cl, 13.01. ^{31}P NMR (DMSO): δ 84.38. ^{1}H NMR (DMSO): δ 2.43 (d, 3H, $^3J_{P-H}$ = 11.8 Hz), 3.24 (d, 3H, $^3J_{P-H}$ = 12.4 Hz), 7.61 (s, 1H, N=CH), 7.4–8.88 (m, 9H, aromatic protons). IR (KBr): 1673 (C=O); 3245 (NH_2); 553 (P=S).

The Pd(II) complexes of **3** and **4** were prepared following the procedure as described above by the interaction of the respective carboxylate functionalized phosphorus hydrazides with $PdCl_2(PhCN)_2$ in dichloromethane. Purification of the crude complexes **7** and **8** was effected through recrystallization in acetonitrile.

7: orange red crystals (75%); mp 195 °C dec. Anal. Calcd for $C_{24}H_{23}N_4O_4PSPdCl_2$: C, 42.99; H, 3.46; N, 8.36; Cl, 10.55. Found: C, 42.87; H, 3.45; N, 8.37; Cl, 10.13. ^{31}P NMR (DMSO): δ 82.79. ^{1}H NMR (DMSO): δ 3.25 (d, 3H, $^3J_{P-H}$ = 11.3 Hz), 3.61 (d, 3H, $^3J_{P-H}$ = 10.8 Hz), 8.81 (s, 1H, N=CH), 7.71 (s, 1H, N=CH), 7.4–8.9 (m, 13H, aromatic protons). IR (KBr): 1651 (C=O); 555 (P=S).

8: brown cubic crystals (69%), mp 168 °C dec. Anal. Calcd for $C_{18}H_{21}N_4O_2PSPdCl_2$: C, 38.22; H, 3.74; N, 9.91; Cl, 12.54. Found: C, 38.71; H, 3.75; N, 9.87; Cl, 12.23. ^{31}P NMR (DMSO): δ 83.62. ^{1}H NMR (DMSO): δ 2.86 (d, 3H, $^3J_{P-H}$ = 11.0 Hz), 3.64 (d, 3H, $^3J_{P-H}$ = 12.1 Hz), 7.43 (s, 1H, N=CH), 5.6–8.2 (m, 11H, aromatic and C=C protons). IR (KBr, cm^{-1}): 1647 (C=O); 3193 (NH_2); 557 (P=S).

Conjugation of 6 to *n*-Butylamine. To 500 mg of **6** (1.38 mmol) in 30 mL of methylene chloride was added 139 mg (1.38 mmol) of triethylamine. The mixture was stirred for 10 min after which 188 mg (1.38 mmol) of isobutyl chloroformate was added. The reaction mixture was stirred for 30 min, after which 125 mg (1.38 mmol) of *n*-butylamine was added dropwise in a solution of methylene chloride. Evaporation under reduced pressure gave a brown precipitate, which was extracted in chloroform and washed with brine and subsequently dried over $MgSO_4$. The brownish precipitate obtained was passed through celite to yield the pure product **9** (Scheme 3): yield 69%; brown powder. ^{31}P NMR ($CDCl_3$): δ 85.07. ^{1}H NMR ($CDCl_3$): δ 2.65 (d, 3H, NCH_3); 3.25 (d, 3H, NCH_3); 6.6–8.5 (m, Ar, and imine H); 0.97 (m, 3H, CH_3); 1.38 (m, 4H, $-CH_2-CH_2-$); 1.58 (m, 2H, $-HN-CH_2$). IR (KBr, cm^{-1}): 3195 (NH_2); 1648 (C=O); 557 (P=S). Anal. Calcd for $C_{20}H_{28}N_5Cl_2OPSPd$: C, 40.39; H, 4.74; N, 11.78; Cl, 11.92. Found: C, 39.31; H, 4.07; N, 11.53; Cl, 11.76.

X-ray Data Collection and Processing. Brown cubic shaped crystals of **8** were isolated from slow evaporation of acetonitrile solutions. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer with Mo Kα radiation and a graphite monochromator at 22(1) °C. Crystal data and details of the data collection are given in Table 1. The unit cell dimensions were obtained from a least-squares fit to setting angles of 25 reflections. The crystals of **8** exhibited no significant decay under X-ray irradiation.

Table 1. Crystallographic Data for $PhP(S)(NMeNH_2)(NMeNCHC_6H_4CH$=CHCOOH)·$PdCl_2$, **8**

formula	$C_{18}H_{20}N_4PSCl_2PdO_2$
fw	564.72
cryst syst	monoclinic
space group	$P2_1/c$
a, Å	7.981(3)
b, Å	21.566(4)
c, Å	13.647(5)
β, deg	104.4(20)
V, Å^3	2275.1(13)
Z	4
λ(Mo Kα), Å	0.70930
T, °C	22(1)
d_{calcd}, g cm^{-3}	1.649
μ, cm^{-1}	12.1
R^a	0.043
R_w^b	0.055

^{a} $R = \sum[|F_o| - |F_c|]/\sum|F_o|$. ^{b} $R_w = [\sum w(|F_o| - |F_c|)^2/\sum|F_o|^2]$, where $w = 1/[\sigma^2|F_o| + 0.0008(F_o)^2]$.

The structures were solved by Patterson and Fourier methods and refined by full matrix least squares methods, which minimized $\sum\Sigma(F_o - |F_c|)^2$ where $\omega^{-1} = (\sigma^2(\text{counting}) + (0.008(F_o^2)^2/4F_o^2$. Atomic scattering factors, which included anomalous scattering contributions, were from ref 11. All the hydrogen atoms were introduced in the last step of the refinement procedure in calculated positions. The final agreement factor (R) for **8** was 0.043 and the highest peak in the final difference Fourier map was 0.530 e Å^{-3}. Atomic positional parameters are listed in Table 2 for **8**. Selected bond distances and angles for compound **8** are summarized in Table 4. The programs used for crystallographic computations are reported in ref 12. Listings of full experimental details, coordinates, temperature factors, and anisotropic temperature factors are deposited as supplementary material.

Results and Discussion

Different functional groups (e.g., –NCS, –COOH, etc.) attached to inorganic frameworks have been widely and effectively used as active sites for the covalent coupling of bifunctional chelates (BFCs) and bifunctional chelating agents (BFCAs) to biomolecules.[13] Therefore, we reasoned that selective introduction of one carboxylate unit on the BHPS (**1**) ligand leaves the phosphorus chalcogenide and the hydrazide sites for ligating interactions with the metal while providing the –COOH active site for coupling with biomolecules. However, the Schiff base coupling reactions of specific aldehydes with BHPS (**1**) as shown in Scheme 1 generally produced mixtures of the mono and bis adducts. The slow addition of the reactants at low temperatures (–70 °C) resulted in improved yields (70–75%) of the unsymmetrical Schiff base adducts. The final separations of the mono from the bis adducts were achieved by column chromatographic procedures. All the new ligands have been fully characterized by C, H, and N analysis and ^{31}P, ^{1}H, and ^{13}C NMR and IR spectroscopy (details in Table 3 and in the Experimental Section).

The symmetrically disubstituted Schiff base adducts may not be useful for radiotherapeutic applications because the multiple –COOH groups could produce cross linking of the proteins which, in turn, may destroy the protein specificity. However, bis(carboxylic acid) derivatives **3** and **5** might be used as versatile

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Table 2. Positional Parameters and their Estimated Standard Deviations

	x	*y*	*z*	B_{iso}[a] (Å^2)
Pd	0.52673(8)	0.38647(3)	0.11215(4)	3.32(3)
Cl1	0.4610(3)	0.48699(11)	0.15385(17)	4.85(11)
Cl2	0.3375(3)	0.34186(13)	0.19116(19)	5.92(13)
S	0.5910(3)	0.28895(10)	0.06720(15)	3.83(10)
P	0.6992(3)	0.31934(10)	–0.04059(15)	3.13(9)
N1	0.8082(8)	0.3823(3)	0.0032(5)	3.3(3)
N2	0.7071(9)	0.4250(3)	0.0466(6)	3.6(3)
C1	0.9359(11)	0.4137(4)	–0.0413(7)	4.3(4)
N3	0.5471(8)	0.3318(3)	–0.1475(5)	3.7(3)
C3	0.3616(12)	0.3299(6)	–0.1641(7)	6.0(6)
N4	0.6281(8)	0.3524(3)	–0.2199(5)	3.7(3)
C4	0.5375(12)	0.3681(4)	–0.3071(7)	4.5(4)
C5	0.6246(12)	0.3866(4)	–0.3859(6)	4.1(4)
C6	0.8015(14)	0.3821(5)	–0.3687(7)	5.4(5)
C7	0.8807(15)	0.4001(5)	–0.4441(10)	6.6(7)
C8	0.7806(22)	0.4245(5)	–0.5349(8)	7.1(8)
C9	0.6053(21)	0.4286(6)	–0.5496(8)	7.9(7)
C10	0.5291(15)	0.4097(5)	–0.4771(7)	6.5(6)
C11	0.8505(21)	0.4485(6)	–0.6314(13)	10.4(9)
C12	0.9955(19)	0.4509(6)	–0.6125(11)	8.5(8)
C13	1.0555(21)	0.4693(5)	–0.7197(11)	6.3(7)
O1	1.2260(11)	0.4674(4)	–0.6894(5)	6.9(4)
O2	0.9771(10)	0.4806(4)	–0.8026(7)	7.4(5)
C14	0.8588(10)	0.2686(3)	–0.0673(6)	3.3(4)
C15	1.0130(11)	0.2616(4)	0.0052(6)	4.0(4)
C16	1.1419(11)	0.2250(4)	–0.0152(8)	5.0(5)
C17	1.1142(15)	0.1955(4)	–0.1090(9)	5.5(5)
C18	0.9595(15)	0.2005(4)	–0.1789(8)	5.3(5)
C19	0.8300(12)	0.2364(4)	–0.1585(7)	4.5(5)
ENLA	0.658(11)	0.455(4)	0.005(7)	4.7
EN1B	0.767(10)	0.450(4)	0.116(7)	4.7
HLA	0.865	0.442	–0.103	5.3
H1B	1.013	0.442	0.019	5.3
H1C	1.011	0.379	–0.069	5.3
H3A	0.337	0.315	–0.094	6.8
H3B	0.307	0.299	–0.227	6.8
H3C	0.313	0.376	–0.183	6.8
H4	0.398	0.368	–0.324	5.2
H6	0.878	0.365	–0.297	6.4
H7	1.020	0.397	–0.431	8.0
H9	0.528	0.446	–0.621	8.9
H10	0.390	0.413	–0.490	7.3
H11	0.755	0.457	–0.701	10.1
H12	1.087	0.445	–0.541	8.7
H15	1.032	0.285	0.077	4.8
H16	1.263	0.218	0.041	5.8
H17	1.216	0.168	–0.127	6.8
H18	0.939	0.176	–0.250	6.1
H19	0.706	0.240	–0.212	5.2

[a] B_{iso} is the mean of the principal axes of the thermal ellipsoid.

Table 3. ^{1}H,[a] ^{31}P,[b] NMR and IR[c] Spectroscopic Data

compd	^{1}H NMR [$\delta(^1H)$, ($^3J_{P-H}$ in Hz)] P–N–CH_3 region	^{31}P NMR [$\delta(^{31}P)$]	IR (cm^{-1}) $\nu(NH_2)$	IR (cm^{-1}) $\nu(P{=}S)$[d]
2	2.9 (12.1); 2.41 (14.1)	82.34	3216	603
3	3.21 (12.3)	80.04		605
4	2.82 (11.2); 3.4 (12.2)	81.37	3179	608
6	2.43 (11.8); 3.24 (12.4)	84.38	3245	553
7	3.25 (11.3); 3.61 (10.8)	82.79		555
8	2.86 (11.0); 3.64 (12.1)	83.62	3193	557

[a] Spectra recorded in $CDCl_3$ or DMSO; ppm vs $SiMe_4$. [b] ppm vs. 85% H_3PO_4. Values quoted are those determined at normal probe temperatures. [c] Spectra recorded using Nujol mulls. [d] Spectra recorded in KBr cells.

carboxylate-based monomers for the development of a new class of specialty polymers via condensation reactions with diamines.[14]

The bifunctional ligands **2** and **4** are stable in aqueous media for over 24 h and therefore meet the primary criteria for radiopharmaceutical applications as complexing agents for metallic radioisotopes which require aqueous workup procedures.

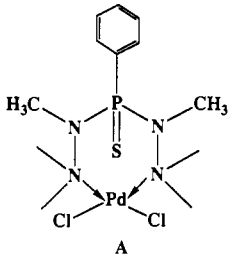
(14) Katti, K. V.; Singh, P. R. Unpublished results.

Table 4. Selected Bond Lengths (Å) and Bond Angles (deg) for $PhP(S)(NMeNH_2)(NMeNC_6H_4CH{=}CHCOOH)\cdot PdCl_2$, **8**

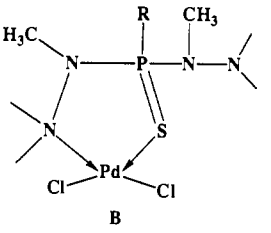
Bond Lengths (Å)			
Pd–Cl1	2.3338(24)	P–C14	1.785(8)
Pd–Cl2	2.2757(23)	N1–N2	1.444(9)
Pd–S	2.2844(24)	N1–C1	1.474(10)
Pd–N2	2.050(6)	N3–C3	1.441(11)
S–P	1.993(3)	N3–N4	1.382(9)
P–N1	1.643(6)	N4–C4	1.275(11)
P–N3	1.671(16)		
Bond Angles (deg)			
Cl1–Pd–Cl2	93.52(9)	N1–P–C14	103.9(3)
Cl1–Pd–S	178.50(8)	N3–P–C14	108.7(4)
Cl1–Pd–N2	84.70(20)	P–N1–N2	112.1(5)
Cl2–Pd–S	87.58(9)	P–N1–C1	125.9(5)
Cl2–Pd–N2	177.14(22)	N2–N1–C1	113.0(6)
S–Pd–N2	91.55(20)	Pd–N2–N1	116.4(5)
Pd–S–P	93.60(10)	P–N3–C3	128.8(5)
S–P–N1	106.89(23)	P–N3–N4	108.0(5)
S–P–N3	110.08(25)	C3–N3–N4	122.8(6)
S–P–C14	114.3(3)	N3–N4–C4	119.7(7)
N1–P–N3	112.9(3)	N4–C4–C5	119.5(8)

Reactions of Carboxylate Functionalized Phosphorus Hydrazides with a Pd(II) Precursor. The interaction of the new phosphorus hydrazides **2–4** with $PdCl_2(PhCN)_2$ in dichloromethane produced the Pd(II) complexes **6–8** (Scheme 2) respectively in high yields. The chemical constitution of **6–8** as established by C, H, N, and Cl analytical data showed that these complexes have one ligand unit per metal center. The Pd(II) compounds **6–8** are air stable and dissolve readily in mixtures of ethanol and water.

The interaction of Pd(II) with the phosphorus hydrazide can occur in two possible ways as shown below: (i) one that involves the coordination of the two hydrazenic nitrogens (structure **A**) and (ii) one that uses one hydrazenic nitrogen and the phosphorus chalcogenide P(S) center to give a five-membered ring (structure **B**).



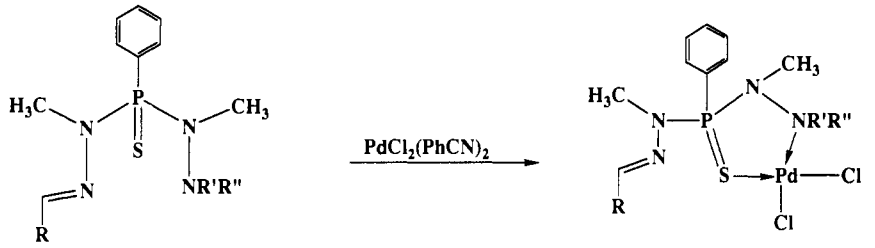
A



B

The ^{1}H and ^{13}C chemical shifts of the metallacyclic compounds **6–8** appear to be diagnostic of the interaction of Pd(II) with only one of the imine nitrogens as outlined in Scheme 2. For example, the imine hydrogen (in ^{1}H NMR) and the carbon (in ^{13}C NMR) in **3** resonate at 7.67 and 139.39 ppm, respectively. However, in the metal complex **7**, there is a deshielding of the ^{1}H and ^{13}C chemical shifts of the coordinated imine group (e.g., $\delta(^1H)$ = 8.81 and $\delta(^{13}C)$ = 144.7). The ^{1}H and ^{13}C chemical shifts of the uncoordinated imine group in **7** remained unchanged as compared to the free ligands **3**. The comparison of the ^{1}H and ^{13}C spectroscopic pattern of **7** with **6** and **8** revealed that the Pd(II) center in **6** and **8** is not bonded to the imine group. The ^{1}H and ^{13}C chemical shifts of the imine groups in **2** ($\delta(^1H)$ = 7.57; $\delta(^{13}C)$ = 143.1), **4** ($\delta(^1H)$ = 7.34, $\delta(^{13}C)$ = 146.37), **6** ($\delta(^1H)$ = 7.61, $\delta(^{13}C)$ = 143.9) and **8** ($\delta(^1H)$ = 7.43, $\delta(^{13}C)$ = 147.0) are very similar. These observations support the five-membered metallacyclic formulations for **6–8** as shown in Scheme 2. The substitution across one of the hydrazine arms in **2** and **4** resulted in the $-NCH_3$ signals being inequivalent. The ^{1}H NMR spectra of **6** and **8** consisted of two pairs of doublets (due to the coupling of NCH_3 groups with the P(V) center) centered at δ 2.43 and 3.24 and δ 2.86 and 3.64, respectively. The high field doublets

Scheme 2



R = C_6H_4COOH, R' = R" = H, 2
R = C_6H_4COOH, R'R" = CHC_6H_4COOH, 3
R = $C_6H_4CH{=}CHCOOH$, R' = $HCC_6H_4CH{=}CHCOOH$, 4

R = C_6H_4COOH, R' = R" = H, 6
R = C_6H_4COOH, R'R" = CHC_6H_4COOH, 7
R = $C_6H_4CH{=}CHCOOH$, R' = $HCC_6H_4CH{=}CHCOOH$, 8

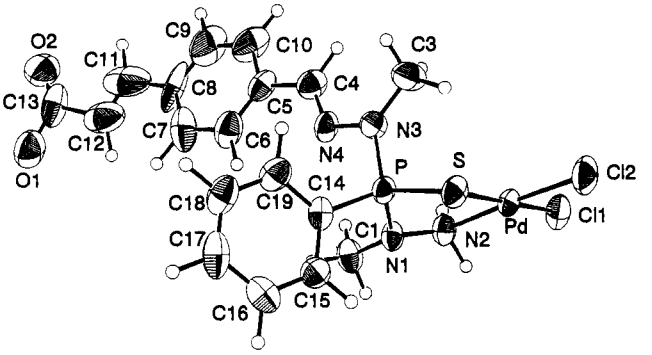
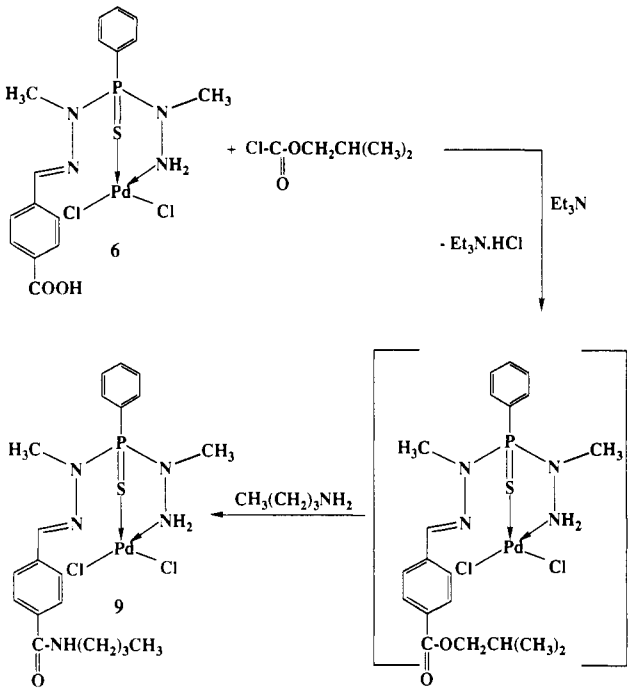


Figure 1. ORTEP drawing of the molecular structure of compound **8** with 50% thermal ellipsoids.

Scheme 3



at δ 2.43 and 2.86 in **6** and **8**, respectively, have remained virtually unchanged as compared to the free ligands. However, the doublets at δ 3.24 and 3.64 observed in **6** and **8**, respectively, have shifted to low fields compared to the corresponding signals in the free ligands **2** and **4**, respectively. A similar spectroscopic pattern for **7** indicates the formation of a five-membered ring as shown in Scheme 2. Comparison of the ν(P=S) stretching frequency of the ligands **2–4** with those of the corresponding Pd(II) complexes proved to be diagnostic of the metal coordination with the P=S unit. The ν(P=S) in **2–4** consisted of an intense band in the 600–615-cm^{-1} region, and this band moved to lower wavenumbers by $\sim$50 cm^{-1} in the metal complexes **6–8**. The νC=O due to the –COOH in **6–8**, which was observed at 1700 cm^{-1}, remained unchanged compared to that in the ligands **2–4**, suggesting that there was no bonding interaction of the carboxylate group(s) with the Pd(II) center.

The ^{31}P NMR spectrum of the free ligands **2–4** and their metal complexes **6–8** consisted of a single sharp resonance indicating the presence of a single chemical species (Table 3).

To obtain a conclusive proof for the structures proposed in Scheme 2, X-ray structural analysis of a representative Pd(II) complex **8** was carried out. The ORTEP plot is shown in Figure 1, and the selected bonding parameters are described in Table 4. The structure shown in Figure 1 comprises the five-membered metallacyclic unit involving coordination of the P=S unit and the terminal hydrazido nitrogen with the Pd(II) center. The structure of **8** is further characterized by the square planar geometry around the Pd(II) center with a *cis* disposition of the P=S and the terminal hydrazido groups. The Pd–S (2.284 Å) and the Pd–N (2.050 Å) bond lengths observed in **8** are in the normal range.[9,15] The presence of the coordinated free hydrazine (–MeN–NH_2) and the uncoordinated Schiff base-hydrazine adduct (–MeN—N=CHR) within the same molecule **8** has allowed us to make some internally consistent comparisons of bonding features. For example, the P–N (1.643 Å) and the N–N (1.44 Å) bonds in the five-membered metallacyclic unit are modestly shorter compared to the P–N (1.671 Å) and the N–N (1.382 Å) distances in the uncoordinated part of the molecule. However, there is some bond lengthening observed in the P=S bond (1.993 Å) in **8** compared to the P=S distance (1.947 Å) observed in the free unsubstituted phosphorus hydrazide precursor $(H_2NNMe)_2P(S)C_6H_5$.[16] This elongation of the P=S bond length is consistent with the coordination of the phosphorus chalcogenide unit with the Pd(II) metal center.[9] In fact, the interaction of Cu(I) with the P=S unit of a similar phosphorus hydrazide also results in the lengthening of the P=S bond.[17] The narrow Pd–S–P angle (93.6°) observed in **8** and several other related metal complexes[9,17,18] of phosphorus hydrazides appears to be a common feature associated with these cyclometallaphosphohydrazides.

Reaction of Carboxylate Functionalized Pd(II) Complex 6 with *n*-Butylamine: Model Reactions to Protein/Peptide Conjugation. The facile reactivity of carboxylate functionalized ligating systems or their metal complexes with primary amines is considered to be a good model to extend such reactions with –NH_2 functionalities

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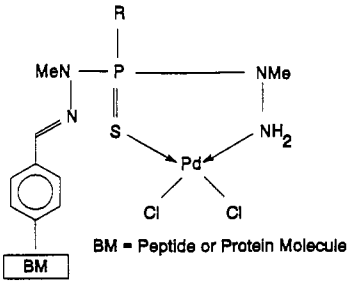
of protein/peptide units to produce the protein/peptide conjugates of the metal complexes. Compound **6** was chosen to investigate the conjugation reaction of the –COOH group with butylamine as a representative example of a primary amine. The conjugation was carried out by first activating the –COOH group in **6** to an activated ester intermediate via reaction with isobutyl chloroformate in the presence of triethylamine (Scheme 3).[13a] The activated ester intermediate upon treatment with butylamine at 25 °C *in situ* produced the amine conjugate **9** in ~70% yield. The chemical constitution of **9** was ascertained by ^{1}H NMR and IR spectroscopy.

Conclusions

Synthesis of new phosphorus hydrazides and the fine tuning of their functionalities to introduce active sites (e.g., –COOH) for attachment to primary amines as models to biomolecules have been demonstrated in the present study. The development of the fundamental coordination chemistry of this new class of ligating system with Pd(II), as shown in the present study, opens up the possibility of using radioactive ^{109}Pd. Such type of ^{109}Pd bound metal chelates can be used to prepare a new generation of therapeutic drugs for targeting cancerous sites through attachment to specific peptides or proteins:



Studies to fully evaluate this potential application are being undertaken.

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Supplementary Material Available: Tables giving an extended listing of bond lengths and angles, full crystallographic and experimental data, anisotropic thermal parameters, and hydrogen atom coordinates (4 pages). Ordering information is given on any current masthead page.