In the case of the FP-LMTO calculations, we made use of valence band s, p, and d basis functions for both Al and In. For In pseudocore 4d states were included in the basis as well; that is, the resulting basis always formed a single, fully hybridizing basis set. The exchange–correlation potential was parametrized according to Hedin and Lundqvist.[5d] For sampling the irreducible wedge of the BZ we used the special k points with a Gaussian smearing of width 20 mRy.

To ensure convergency several standard tests were performed for both methods, such as increasing the number of k points used in the summation over the BZ. The calculated energy differences ($E_{c/a} - E_{fcc}$) and band structures were found to be virtually identical for the two full-potential techniques. The presented energy differences and density of states were obtained from FP-LMTO calculations, the presented band structures from FLAPW calculations.

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Design and Development of the First Peptide-Chelating Bisphosphane Bioconjugate from a Novel Functionalized Phosphorus(III) Hydride Synthon**

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Dedicated to Professor S. S. Krishnamurthy on the occasion of his 60th birthday

The incorporation of metal-chelating units into peptide backbones (and related biomolecules) has become an area of intense interest because of the potential applications to catalysis[1] and biomedicine.[2] Among various ligands available, phosphanes are unique because they display versatile coordination chemistry with transition metals.[3] The secondary and tertiary structures of peptides to which they are attached may subsequently help in controlling the reactivity of phosphane-coordinated transition metals. Specifically, the chirality and related important stereospecific characteristics associated with biomolecules (e.g. peptides or proteins) may be transferred to the transition metals if peptides are immobilized with chelating units that are capable of coordinating with transition metals.[4] This approach of conjugating catalytically active transition metals to chiral biomolecules provides a straightforward route to chiral compounds with potential applications in enantioselective catalysis.[4] The incorporation of phosphanes into peptides (and proteins) will also help to engineer metal binding sites, which may eventually provide conformational integrity, biospecificity, and enhanced enzymatic activities.[5]

Bioconjugation of cytotoxic transition metals to receptor-active peptides may eventually provide effective vehicles for delivering cytotoxic moieties to specific tumors through receptor-mediated agonist or antagonist interactions.[6] In this context, peptides (or receptor-binding biomolecules) containing phosphane substituents are important in the design and development of tumor-specific radiopharmaceuticals.[7, 8] Despite significant catalytic and biomedical applications offered by such peptides (and proteins), synthetic strategies for producing such bioconjugates are still in their infancy. The elegant work by Gilbertson and co-workers on the incorporation of aryl- and cyclohexylphosphanes into specific peptides has provided impetus to this potentially burgeoning field of chemical and biomedical sciences.[9]

As part of our ongoing research on the development of functionalized phosphanes for biomedical and catalytic ap-

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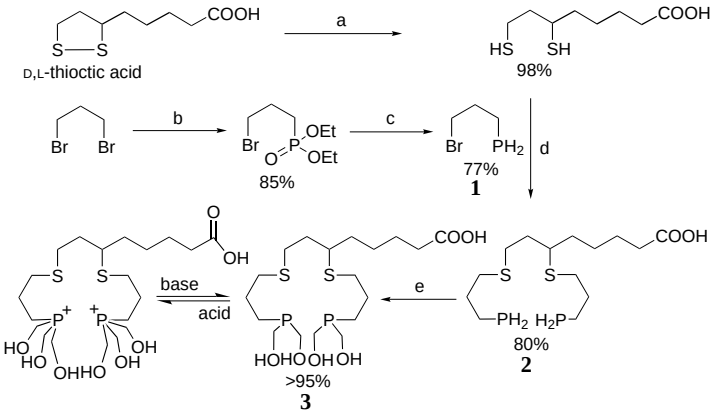
plications,[10] we have recently developed a novel strategy which allows bisphosphanes with heteroatoms and chelating functionalities to be directly incorporated into peptide backbones, under mild conditions, to produce the first example of a biomolecule functionalized with hydrophilic phosphane chelating units. We discuss here the synthetic utility of 3-bromopropylphosphane (**1**) in the development of a functionalized, water-soluble phosphane based on the dithio-bisphosphane (P_2S_2) framework of 6,8-bis[(3-phosphanylpropyl)thio]octanoic acid (**2**). We also demonstrate that the COOH group in **2** can be efficiently conjugated to peptides while retaining the phosphane moieties.

Our approach to the synthesis of ligand framework **2** is shown in Scheme 1. It involves the use of **1** as a key synthon which was recently obtained in our laboratory by the reduction of diethyl 3-bromopropylphosphonate with dichloroaluminum hydride.[11] Reaction of **1** with the dianion of 6,8-dithiooctanoic acid produced the COOH-functionalized P_2S_2 framework **2**. The proton-coupled ^{31}P NMR of **2** showed two merged triplets ($^1J_{P,H} = 193.2$ Hz), which confirmed the presence of two different phosphanyl groups. The thermally stable P^{III} hydride **2** was then formylated with 37% formaldehyde in ethanol to produce the corresponding water-soluble phosphane framework **3** in greater than 95% yields (Scheme 1). Both **2** and **3** were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, and HR-FAB mass spectrometry.



Scheme 1. a) $NaBH_4$ (3.0 equiv), H_2O, EtOH, 25 °C, 5 h; b) $P(OEt)_3$ (0.2 equiv), △, 1 h; c) $LiAlH_4$ (1.5 equiv), $AlCl_3$ (4.6 equiv), tetraglyme, 0 → 25 °C, 12 h; d) NaH (4.1 equiv), THF, △, 12 h; e) HCHO (4.0 equiv), EtOH, 25 °C, 15 min.

The co-existence of phosphanyl and carboxyl groups within the same molecule is difficult to achieve because the reaction conditions that are used to reduce a $P(O)(OEt)_2$ group to a PH_2 group can also reduce COOH groups. Thus, **1** can be used as a versatile synthon to produce compounds in which a chemical functionality that is susceptible to reduction (e.g. a carboxyl or amide group) and a highly reduced phosphanyl group coexist.

In general, primary phosphanes tend to be unstable towards oxidation. For example, PH_3 and RPH_2 (R = Me, Et) are oxidized instantaneously upon contact with atmospheric oxygen and water or during reactions in various organic solvents. In contrast, the new primary phosphane **2** exhibited a much improved stability profile under an even wider range of chemical conditions. Furthermore, the reactivity of the PH_2 groups in these compounds toward molecules containing a wide spectrum of functional groups (including carboxylic acids, amines, thiols, and proteins) was remarkably low or nonmeasurable. To our knowledge, this is the first report of compounds containing phosphanyl groups which exhibit such a degree of oxidative stability and lack of reactivity toward solvents and chemical functionalities. Preliminary AM1 calculations carried out with the MOPAC program[12a] on **2** and related molecules suggest there are atomic orbital contributions from the heteroatom (e.g. S in **2**) to the frontier molecular orbitals. It is conceivable, therefore, that there is negative hyperconjugation involving specific orbitals of S and the P^{III} centers in **2**. This electronic effect may explain the unusual stability towards oxidation of **2** and related molecules with heteroatoms on their backbone.[12b] More detailed calculations are underway. This electronic effect appears to operate even in the hydroxymethylated phosphanes **3**. For example, **3** is stable towards oxidation in aqueous media over several days (Figure 1). Such stability of alkyl-substituted phosphanes is remarkable.

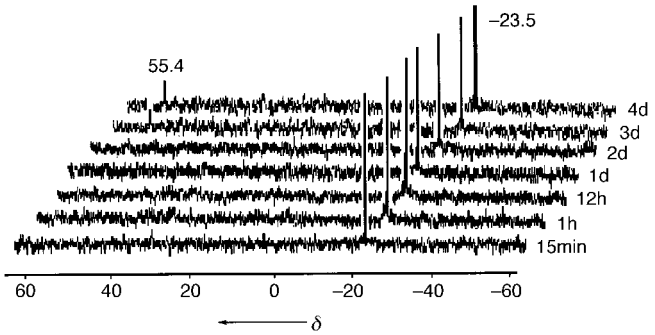
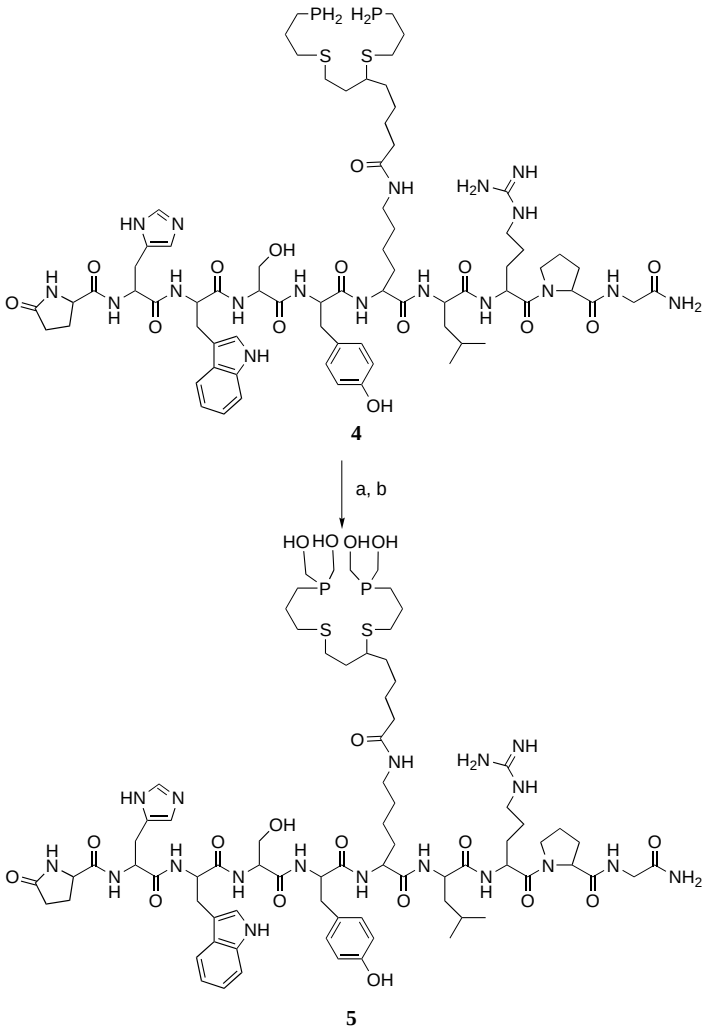


Figure 1. ^{31}P NMR spectra of **3** (aqueous sodium bicarbonate solution, pH 8.5) at various timepoints. Peaks at $\delta = -23.5$ and 55.4 refer to **3** and the corresponding phosphane oxide, respectively.

To determine the feasibility of linking compounds containing PH_2 groups to biomolecules, a P_2S_2-D-Lys conjugate was prepared and then used to synthesize a P_2S_2 conjugate of a luteinizing hormone releasing hormone peptide, the D-Lys^6–LHRH conjugate **4**, by automated solid-phase peptide synthesis (SPPS; Scheme 2). This method involved repeated use of a variety of chemicals in high concentrations (including trifluoroacetate (TFA) for cleavage of the peptide from the resin. Peptide **4** was purified by HPLC and analyzed by ^{31}P NMR spectroscopy and mass spectrometry (Figure 2). These data demonstrate that the peptide conjugate **4** was formed in high yields with no modification of the PH_2 groups. These results also confirm that the PH_2 groups of **2** are resistant to oxidation and are unreactive towards other functional groups in the LHRH peptide and the reagents used in SPPS. The synthesis of such biomolecules which contain PH_2 groups allows their conversion into hydrophilic alkylphosphanes. Thus, formaldehyde reacted rapidly with the PH_2 groups of **4** to produce the peptide-functionalized phosphane **5** (Scheme 2) now containing additional P–C bonds. Either PH_2 groups or their disubstituted analogues PR_2 may be used as a part of the chelator framework of biomolecules to form well-defined metalated conjugates by complexation with transition metals.



Scheme 2. a) 37% aq. HCHO, 0.1N HCl, 25°C, 5 min; b) 1M aq. $NaHCO_3$, 25°C, 5 min.

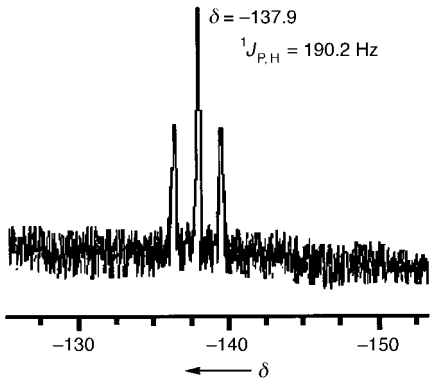


Figure 2. Proton-coupled ^{31}P NMR spectrum of peptide–phosphane conjugate **4**.

The chemistry described herein demonstrates for the first time that primary phosphanes containing thioether groups possess high oxidative and thermal stabilities. Furthermore, the COOH group of such primary phosphanes provides an elegant opportunity for their incorporation into peptide backbones. Metalated analogues of **5** and related biomolecules may open up new avenues in the design of chiral transition metal compounds for catalytic applications. Moreover, the metalation of functionalized peptides with cytotoxic metals, for example Pt^{II}, will also enable the design and development of site-specific drugs for delivery of cytotoxic agents to specific cancer sites through receptor-mediated agonist–antagonist interactions. Therefore, the new bioconjugate chemistry reported herein has implications in both catalysis and biomedicine fields.

Experimental Section

Diethyl 3-bromopropylphosphonate was synthesized by the Arbuzov reaction.[13] Typically, triethyl phosphite in a tenfold excess of 1,3-dibromopropane was heated at reflux for 1 h to yield diethyl 3-bromopropylphosphonate in 95% yield after distillation under reduced pressure (85°C, 2 mm Hg). D,L-6,8-dithiooctanoic acid was synthesized according to the literature procedure.[14]

1: To a well-stirred cold (0°C) suspension of $LiAlH_4$ powder (5 g, 135 mmol) in tetraglyme (100 mL) was added anhydrous $AlCl_3$ powder (55 g, 412 mmol) over 15 min. After the reaction mixture was stirred for 30 min at 0°C, diethyl 3-bromopropylphosphonate (23 g, 89 mmol) was added dropwise over 20 min. Stirring was continued at 25°C for 12 h, and then the reaction mixture was distilled under reduced pressure (50°C, 2.5 mm of Hg) to afford **1** (12 g, 77%), which was collected in a cooled receiver at −77°C. ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 1.99$ (br m, 2H), 2.32 (br m, 2H), 2.98 (br m, 2H), 3.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.59$ (d, $J_{P,C} = 9.2$ Hz), 33.72 (s), 35.81 (s); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = -138.37$ (s).

2: D,L-6,8-dithiooctanoic acid (7.8 g, 37.8 mmol) in dry tetrahydrofuran (25 mL) was added dropwise to a well-stirred suspension of 60% NaH (6.2 g, 155 mmol) in dry tetrahydrofuran (200 mL) at 0°C. After the reaction mixture was stirred for 20 min at 0°C, a solution of **1** (11.8 g, 76.1 mmol) in dry tetrahydrofuran (25 mL) was added. The reaction mixture was then heated at reflux under nitrogen for 12 h. Excess NaH was quenched with a minimum of 10% HCl, the mixture was filtered through silica gel, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (3:2) to give pure **2** (10.8 g, 80%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.44-1.61$ (m, 6H), 1.69–1.78 (m, 6H), 2.29–2.34 (m, 2H), 2.46–2.66 (m, 12H), 2.93–2.99 (m, 4H), 11.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.46$ (t, $J_{P,C} = 13.8$ Hz), 24.9 (s), 26.62 (s), 29.72 (s), 31.23 (d, $^2J_{P,C} = 8.8$ Hz), 33.05 (m), 33.38 (d, $^3J_{P,C} = 3$ Hz), 34.34 (s), 35.02 (s), 35.08 (s), 44.1 (s), 180.34 (s); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = -136.38$ (s), -136.34 (s); ^{31}P NMR (121 MHz, proton coupled, $CDCl_3$): $\delta = -136.29$ (t, $J_{P,H} = 193.2$ Hz), -136.24 (t, $J_{P,H} = 193.2$ Hz); IR (NaCl): $\tilde{\nu} = 2294$ (P–H), 1723 (C=O) cm^{-1}; HR-MS (FAB): m/z calcd for $[M^+ + H]$: 357.1240; found: 357.1237.

3: To a solution of **2** (1 g, 2.8 mmol) in degassed ethanol (5 mL) at room temperature (25°C) was added 37% aqueous formaldehyde solution (0.92 mL, 11.3 mmol), and the reaction mixture was stirred for 1 h under nitrogen. Removal of the solvent under reduced pressure afforded **3** (1.3 g, 97%) as a colorless viscous oil. ^{31}P NMR (121 MHz, D_2O): $\delta = -25.16$ (s), -25.03 (s). For characterization and all other studies **3** was converted into its bisphosphonium chloride salt by the addition of 5N hydrochloric acid (0.5 mL) and 37% aqueous formaldehyde (0.5 mL, 5.6 mmol) to a solution of **3** (1.3 g, 2.7 mmol) in degassed ethanol (5 mL) at room temperature (25°C). After removal of solvent under reduced pressure the crude product was purified by chromatography on a C-18 Sep-Pak reverse phase column with water/methanol (3:2) to afford a pure bisphosphonium chloride (1.6 g, 94%) as a colorless viscous oil. ^1H NMR (300 MHz, D_2O): $\delta = 1.18-1.23$ (m, 2H) 1.31–1.36 (m, 4H), 1.50–1.63 (m, 2H), 1.65–1.80 (m, 4H), 2.10–2.31 (m, 6H), 2.42–2.46 (m, 6H), 2.55–2.60 (m, 1H), 4.32 (br s, 12H); ^{13}C NMR (75 MHz, D_2O): $\delta = 12.0$ (d, $J_{P,C} = 10.56$ Hz), 12.54 (d, $J_{P,C} = 10.5$ Hz), 20.52 (s), 20.98 (s), 23.62 (s), 25.2 (s), 27.91 (s), 29.76 (d, $^1J_{P,C} = 15.7$ Hz), 31.32 (d, $^3J_{P,C} = 15.8$ Hz), 33.36 (s), 43.66 (s), 49.64 (d, $^1J_{P,C} = 54.4$ Hz), 178.27 (s); ^{31}P NMR (121 MHz, D_2O): $\delta = 28.98$ (s), 28.99(s); HR-MS (FAB): m/z calcd for $[M^+ - Cl]$: 573.1641; found: 573.1649.

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4: Conjugate **4** was synthesized on a solid-phase peptide synthesizer. Standard fmoc-protected amino acids (fmoc = 9-fluorenylmethoxycarbonyl) were used for the synthesis. Conjugate **4** was purified by HPLC and analyzed with ^{31}P NMR spectroscopy and mass spectrometry (Figure 1). ^{31}P NMR (121 MHz, D_2O): $\delta = -137.91$ (s). ^{31}P NMR (121 MHz, proton coupled, D_2O) $\delta = -137.90$ (t, $J_{P,H} = 190.2$ Hz). LR-MS (FAB) m/z calcd for $[M^+ + H]$: 1591.9; found: 1592.0.

5: To a solution of **4** (0.5 mg) in ethanol (400 μL) and DMF (100 μL) were added 0.1N HCl (25 μL) and 37% aqueous formaldehyde (25 μL), and the reaction mixture was stirred at room temperature (25 °C) for 5 min. The formation of P_2S_2-D-Lys^6-LHRH hydroxymethylphosphonium chloride was confirmed by the ^{31}P NMR signal at $\delta = 31.39$(s). The P_2S_2-D-Lys^6-LHRH hydroxymethylphosphonium chloride was converted into **5** by the addition of 1M aqueous sodium bicarbonate (30 μL) in near quantitative yields as demonstrated by the ^{31}P NMR chemical shift at $\delta = -24.23$.

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Modeling a Nitrogenase Key Reaction: The N_2-Dependent HD Formation by D_2/H^+ Exchange**

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Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Biological N_2 fixation is one of the fundamental natural synthetic processes and is catalyzed by FeMo, FeV, or FeFe nitrogenases.[1] X-ray structure analyses have revealed the molecular structure of FeMo nitrogenase and its active centers, in particular the structure of the FeMo cofactors (FeMoco).[2] However, the intimate molecular mechanism of biological N_2 reduction and the concomitant "obligatory dihydrogen evolution" (OHE) has remained a mystery. The OHE is an integral part of enzymatic N_2 reduction and cannot

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