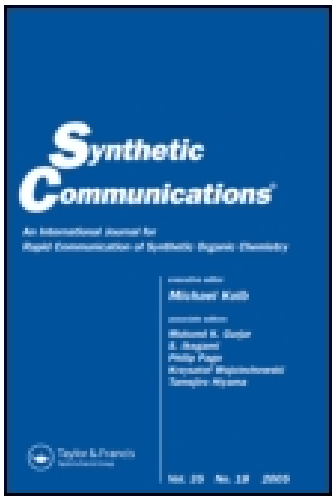

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SYNTHESIS OF PHOSPHINIC ACID ANALOGUES OF GLYCYL-GLYCINE AND CRYSTAL STRUCTURE OF N-GLYCYL-AMINOMETHYL-(PHENYLPHOSPHINIC) ACID

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SYNTHESIS OF PHOSPHINIC ACID ANALOGUES OF GLYCYL–GLYCINE AND CRYSTAL STRUCTURE OF *N*-GLYCYL-AMINOMETHYL-(PHENYLPHOSPHINIC) ACID

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ABSTRACT

Phosphinic acid analogues of Gly-Gly, $NH_2CH_2CONHCH_2$-$P(R)O_2H$ (R=Me, Ph, *t*-Bu), were synthesised by the active ester method from free aminomethylphosphinic acids purified on cation exchange resins. The crystal and molecular structure was determined for Gly–Gly(P^{Ph})·H_2O (R=Ph). The results point to similar bond parameters as were found for Gly–Gly and its phosphonic analogue Gly–Gly(P).

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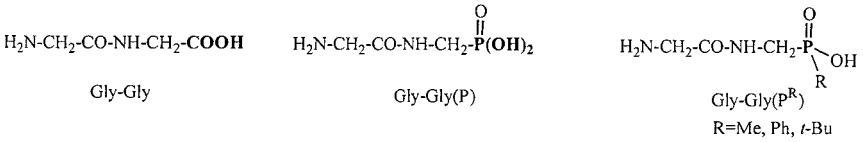
Phosphonic ($-PO(OH)_2$) and phosphinic ($-PO(R)OH$, R=H, alkyl, aryl) acid analogues of amino acids and their oligopeptides are a well-known class of enzyme inhibitors.[1] Phosphinic acid derivatives strongly inhibit enzymes such as matrix metalloproteinases and astacin,[2] angiotensin I converting enzyme,[3] thrombin,[4] endothelin converting enzyme[5] and alter functions of receptors, e.g. GABA receptors.[6] Aminoalkylphosphinic acid peptides have been proposed as compounds of interest for new drug design, e.g. analgetics,[7] antibiotics[8] or agents against protozoa infections.[9] Numerous complex oligopeptides containing aminoalkylphosphinic acids has been synthesised; however, surprisingly no attention has been paid to synthesis of the simplest dipeptides like analogues of Gly–Gly.

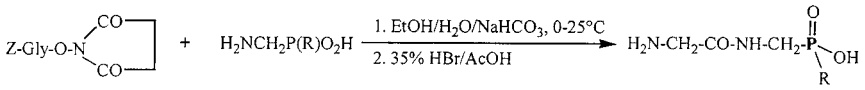
To continue our investigations on complexing properties of the metal cations with dipeptides containing aminoalkylphosphonic acids[10] and with simple aminoalkylphosphinic acids,[11] we envisaged to obtain a series of simple phosphinodipeptides (Scheme 1). They contain phosphinic acid group with a substituent exhibiting different electronic effects (methyl, phenyl and *t*-butyl) to investigate a change in the complexing ability, similarly to our previous studies.[11] The results on the synthesis are presented in this paper.



Scheme 1.

SYNTHESIS

We used a route utilising easily available aminoalkylphosphinic acids and *N*-hydroxysuccinimidyl esters of benzyloxycarbonyl-protected amino acids patented[12] some time ago. In the patents, dipeptides containing alkyl/aryl chains were obtained in high yields and in pure state due to precipitation of benzyloxycarbonyl-protected dipeptides. In contrast to the patents, we used simplest amino acids (Scheme 2), glycine, aminomethyl-(methylphosphinic) acid (Gly(P^{Me}), aminomethyl(phenylphosphinic) acid (Gly(P^{Ph}) and aminomethyl(*tert*-butylphosphinic) acids Gly($P^{t\text{-}Bu}$). Two of the acids were prepared by a known method[11] from dichlorophosphines $RPCl_2$ (R=Ph, *t*-Bu). As $MePCl_2$ is an expensive and very air-sensitive compound, Gly(P^{Me}) was synthesised using a new route based on the



Scheme 2.

reaction of *N*-tritylmethanimine $TrN{=}CH_2$ with MeP(O)(H)(OEt) under conditions for synthesis of aminoalkylphosphonic acid esters.[13] The starting ethyl methylphosphinate acid was synthesized[14] from hypophosphorous acid, hexamethyldisilazane and methyl iodide[15] followed by esterification of the methylphosphinic acid obtained with ethyl chloroformate.

The peptide bond formation proceeded with reasonable yields (NMR check), however, separation of the dipeptides from the reaction mixtures was difficult. The protected glycine dipeptides did not precipitate from reaction mixtures as was described[12] for derivatives containing other amino acids with more hydrophobic side chains. Therefore, purification of crude products was a crucial point of the syntheses. For aminomethyl(methylphosphinic) dipeptide, the pure protected dipeptide was obtained by a extraction (removing nonpolar by-products and Z-Gly) and chromatography on the sulfonic acid cation exchange resin to remove free aminomethyl(methylphosphinic) acid which was trapped on the resin. Deprotection with HBr/AcOH gave pure phosphinodipeptide in 80% yield.

Unfortunately, the same strategy could not be used for the other two phosphinic acid dipeptides as the protected dipeptides are insoluble in water at acid pH and their extraction properties are similar to those of the starting materials and by-products. Therefore, the partly purified crude reaction mixture was used in following deprotection steps. Removing of benzyloxycarbonyl group with HBr/AcOH gave a mixture of glycine, aminophosphinic acid and their dipeptide. The mixture was subsequently purified by a combination of chromatography on sulfonic and carboxylic acid cation exchange resins. Aminomethylphosphinic acids were removed from sulfonated resins by gradient elution with water and dilute ammonia solutions (0.1–2%) with a mixture of glycine and the dipeptide being eluted first. Water elution of carboxylic resin afforded the pure phosphinic dipeptides and glycine was trapped on the resin. We found that extractions (see Experimental) removed a major part of impurities but reduced yields of the pure dipeptides. Thus, mixtures of common amino acids, aminoalkylphosphinic acids, and even aminophosphonic aicds,[14] and their dipeptides could be separated in a multigram scale using chromatography on sulfonic and/or carboxylic acid ion-exchange resins.

CRYSTAL STRUCTURE OF GLY–GLY(P^{PH})·H_2O[16]

Molecular structure of *N*-glycyl-aminomethyl(phenylphosphinic) acid is depicted in Figure and selected bond distances are presented in Table. The peptide in the solid state is present in the zwitterionic form. Parameters of the peptide moiety are the same as those for Gly–Gly[17] as well as for Gly–Gly(P).[18] The presence of the phosphinic acid moiety does not alter the bond arrangement.

An interesting feature of the structure is its crystal packing. The structure consists of hydrophilic and hydrophobic layers. The hydrophilic part is filled with water molecules linked by hydrogen bonds (2.77–2.86 Å) to the dipeptide molecules and themselves. A water molecule interacts with two closest molecules of Gly–Gly(P^{Ph}) in the same elementary cell: with phosphinic acid group of one molecule and carbonyl oxygen of the other. Non-bonding interactions between benzene rings stabilise the hydrophobic layer. The layered arrangement in the structure differs from three-dimensional structures of the other two dipeptides stabilised by hydrogen bonds.

Table. Bond Lengths (Å) and Angles (°) in Molecule of Gly–Gly(P^{Ph})

Bond Lengths		Angles	
P–O1 1.485(2)	C1–N1 1.455(3)	O1–P–O2 117.6(1)	P–C1–N1 110.8(1)
P–O2 1.517(1)	N1–C2 1.330(2)	O1–P–C1 108.7(1)	C1–N1–C2 122.6(2)
P–C1 1.836(2)	C2–C3 1.514(3)	O1–P–C11 108.3(1)	N1–C2–C3 114.2(2)
P–C11 1.804(2)	C2–O3 1.233(2)	O2–P–C1 107.6(1)	N1–C2–O3 124.6(2)
	C3–N2 1.470(3)	O2–P–C11 109.1(1)	C3–C2–O3 121.3(2)
		C1–P–C11 104.7(1)	N2–C3–C2 111.3(2)

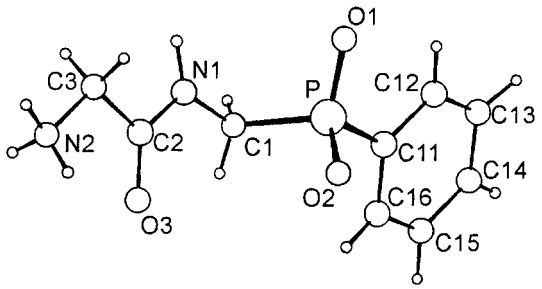


Figure. Molecular structure of Gly–Gly(P^{Ph}) with atom numbering scheme.

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We synthesised three new phosphinic acid dipeptides which can be used for investigation of the phosphorus peptides interaction with metal cations. Unprotected amino acids and phosphinic acid dipeptides can be separated on cation exchange resins probably due to small differences in pK_A's of the compounds and the separation suggests general utilization. The same conditions with the cation exchange resins were also successfully used for purification of phosphorus acid derivatives of tetraazamacrocycles.[14] Molecular structure of phenylphosphinic acid dipeptide reveals no differences in bonds and angles between phosphinic and phosphonic dipeptides and common glycyl–glycine.

EXPERIMENTAL

Reactions with trivalent phosphorus compounds were done in a standard Schlenk apparatus. Solvents were purified using established procedures.[19] *N*-(benzyloxycarbonyl)glycine,[20] succinimidyl *N*-(benzyloxycarbonyl)glycinate,[21] Gly(P^{Ph}),[11] Gly($P^{t\text{-}Bu}$),[11] *N*-tritylmethanimine[13a] were synthetized by the methods published. Other chemicals were obtained from commercial sources. Cation exchange resins used were Dowex 50 W × 4 (50–100 mesh, sulfonic acid resin) (Fluka) and Amberlite CG50/N1 (100–200 mesh, carboxylic acid resin) (Rohm & Haas) in the H^+ form.

NMR spectra were recorded on a Varian Unity Plus at 400 MHz (^1H, internal reference TMS ($CDCl_3$) or *t*-BuOH (D_2O)), 161.9 MHz ($^{31}P\{^1H\}$, external reference 85% H_3PO_4) and 100.6 MHz (^{13}C, internal reference *t*-BuOH (D_2O)). TLC silica plates ("Silufol", Kavalier, Czech Republic) were developed in the following mixtures: *i*-PrOH:25% aq. NH_3:H_2O = 10:1:1 (A); BuOH:AcOH:H_2O = 4:2:3 (B); *i*-PrOH:25% aq. NH_3:H_2O = 15:3:3 (C), $CHCl_3$:acetone = 1:3 (D). Detection with ninhydrin (0.3% in EtOH) or with Bromocresol Green (0.5% in EtOH with several drops of aqueous Na_2HPO_4 solution to give a persistent blue colour). Melting points were determined on a Kofler hot-plate apparatus and were uncorrected. Elemental analyses were performed in the Institute of Macromolecular Chemistry of the Academy of Sciences of the Czech Republic.

X-ray structure analysis: CAD 4 (Enraf Nonius) at 293(1) K with MoK_α ($\lambda = 0.71073$ Å); scan $\omega - 2\vartheta$; lattice parameters determined from 25 reflections (ϑ; 13–14°); Lorenzian-polarization correction were applied using program JANA 98;[24] no absorption correction were applied; the structure solved by the combination of direct methods and Fourier method; refined by full-matrix least-squares techniques (SHELXS86,[25] SHELXK97[26]); the positions of hydrogen atoms found on the difference maps and refined isotropically. Crystallographic data for the structure

reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-138778. Copies of the data can be obtained free of charge on application to CCDC; e-mail: deposit@ccdc.cam.ac.uk.

Aminomethyl(methylphosphinic) Acid Gly(P^{Me})

Ethyl methylphosphinate (4.20 g, 0.039 mol) was dissolved in 4 mL of dry toluene, the solution was heated to 100°C and a hot solution of $TrN{=}CH_2$ (10.60 g, 0.039 mol) in 20 mL of dry toluene was quickly added. The mixture was kept at 100°C for 4 h, cooled and left in a refrigerator overnight. The crystalline product $TrNHCH_2P(O)(Me)(OEt)$[22] was filtered off and hydrolysed in a refluxing mixture of 20 mL of EtOH and 20 mL of conc. HCl for 12 h. Solvents were removed using vacuum evaporator and the semi-solid was dissolved/suspended in 20 mL of water. Insoluble Tr-Cl and other non-polar impurities were extracted with 3×20 mL of chloroform. The aqueous solution was purified on Dowex 50 (H^+-form, 2×15 cm) by elution with water (200 mL) followed by 5% aq. ammonia. The fractions containing the product were evaporated and three times co-distilled with water to remove excess of ammonia. The residue was dissolved in 10 mL of water and acetone was added to cloudiness and the mixture left overnight. The product was filtered off, washed with acetone and dried in air. 3.30 g (77%). M.p. 290–295°C (dec.), $R_f = 0.7$ (A). ^{1}H NMR (KOD/D_2O): 1.20 (d, 3H, $^2J_{PH}$ 13.1 Hz, $PC\mathbf{H}_3$); 2.63 (d, 2H; $^2J_{PH}$ 9.6 Hz, $NC\mathbf{H}_2P$). ^{31}P NMR (KOD/D_2O): 42.5.

N-Glycyl-aminomethyl(methylphosphinic) Acid Gly–Gly(P^{Me})

Aminomethyl(methylphosphinic) acid (1.00 g, 9.17 mmol) and $NaHCO_3$ (1.54 g, 18.34 mmol) was dissolved in a mixture of 50 mL of EtOH and 25 mL of water and filtered through a small plug of cotton wool. The filtrate was cooled to 0–5°C in an ice-water bath. Succinimidyl *N*-(benzyloxycarbonyl) glycinate (2.81 g, 9.17 mmol) was dissolved in 35 mL of hot EtOH and dropped over 15 min to the phosphinic acid solution. The resulting solution was stirred in an ice-water bath for 2 h and at room temperature for 20 h. Solvents were evaporated in vacuum, the residue was dissolved in 80 mL of water and the solution was extracted with 3×15 mL of EtOAc. The water phase was acidified with 10 mL of 2 M HCl and again extracted with the same amount of EtOAc. The water phase was evaporated to the dryness and redissolved in 10 mL of water containing some ammonia.

The solution was transferred onto the top of a cation exchange resin (H^+-form, Dowex 50, 2×15 cm) column, eluted with water (500 mL) and the fractions containing protected dipeptide[23] were evaporated. Excess of HCl was removed by co-distillation with water (2×10 mL) and the residue was dried by co-distillation with anhydrous EtOH (3×10 mL). 35 mL of HBr/AcOH (35%) was added to the oily residue at 0°C. The mixture was stirred for 1.5 h at the temperature then evaporated to dryness. The resulting hydrobromide of the product was converted to the free acid on a Dowex 50 (H^+-form, 2×15 cm) column by elution with water (200 mL) followed by 8% aq. ammonia. Peptide fractions were evaporated to give an oily residue, which was dissolved with heating in 30 mL of MeOH and 3 mL of water and evaporated. The residue was redissolved with heating in 30 mL of MeOH and 0.5 mL of water. Anhydrous EtOH was carefully added up to persistent cloudiness which was redissolved with one drop of MeOH. After standing overnight at room temperature, the product was filtered off, washed with anhydrous MeOH and left to dry in air. Yield 1.20 g (80%).

Elemental analysis (calc): C 29.03% (28.92%), H 6.40% (6.67%), N 16.63% (16.86%). M.p. 233–235°C (dec.), $R_f = 0.7$ (B). ^{1}H NMR (D_2O): 1.14 (d, 3H, $^2J_{PH}$ 13.6 Hz, PC**H**$_3$); 3.31 (d, 2H, $^2J_{PH}$ 10.0 Hz, NC**H**$_2$P); 3.74 (d, 2H, $^5J_{PH}$ 1.2 Hz, C**H**$_2$C(O)NHCH$_2$P). ^{31}P NMR (D_2O): 15.84. ^{13}C NMR (D_2O): 17.35 (d, $^1J_{PC}$ 93.4 Hz, P**C**H$_3$); 43.40 (d, $^1J_{PC}$ 99.6 Hz, NCH$_2$P); 43.51 (s, CH$_2$C(O)N); 169.49 (d, $^3J_{PC}$ 4.3 Hz, **C**(O)NHCH$_2$**P**).

N-Glycyl-aminomethyl(phenylphosphinic) Acid Gly–Gly(P^{Ph}) and *N*-Glycyl-aminomethyl(*tert*-butylphosphinic) Acid Gly–Gly($P^{t\text{-}Bu}$)

AMP(P^{Ph}) or AMP($P^{t\text{-}Bu}$) (6.6 mmol) and $NaHCO_3$ (1.10 g, 13.2 mmol) were dissolved in a mixture of 30 mL of water and 15 mL of EtOH and the solution was cooled in an ice-water bath. Z-Gly-OSuc (2.02 g, 6.6 mmol) dissolved in 20 mL of hot EtOH was dropped into the solution during 15 min. The mixture was stirred in the bath for 2 h and at room temperature for 20 h. The cloudy solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water (50 mL) and the solution was alkalinized with 5 M NaOH to pH ≈12. The alkaline solution was extracted with 4×15 mL of EtOAc. The water phase was acidified to Ph ≈1with conc. HCl, diluted to 100 mL with water and extracted again with 4×15 mL of EtOAc. The organic phase was evaporated to dryness and dissolved in EtOH. Residual water was removed by co-distillation with anhydrous EtOH (3×15 mL) and peptide was deprotected with 10 mL of HBr/AcOH (35%, room temperature, 1.5 h). The mixture was evaporated to dryness, co-distilled with anhydrous EtOH (3×15 mL) and

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dissolved in 10 mL of water. The resulting hydrobromide of the product was purified by chromatography on a Dowex 50 (H^+-form, 2×15 cm) column by elution with water (200 mL) followed by 0.1% aq. ammonia. Peptide fractions were evaporated to dryness. A residual amount of glycine was removed using a carboxylic acid exchange resin (Amberlite CG50/N1) column by elution with water. The pure peptide fractions were evaporated, redissolved in a minimum amount of water and decolorized with charcoal. The peptide was obtained after addition of THF to cloudiness, standing of the solution for several days, filtration and drying at room temperature.

Gly–Gly(P^{Ph})·H_2O, Yield 65%. Elemental analysis (calc.): C 43.91% (44.21%), H 6.14% (6.31%), N 11.37% (11.38%). M.p. 259–261°C (dec.), $R_f = 0.75$ (A); 0.4 (B). ^{1}H NMR (D_2O): 3.47; 3.56 (s, 2H, C**H**$_2$C(O)N); 7.3–7.7 (m, 5H, Ph). ^{31}P NMR (D_2O): 26.96. ^{13}C NMR (D_2O): 43.91 (s, **C**H$_2$C(O)N; 43.92 (d, $^1J_{PC}$ 104.1 Hz, N**C**H$_2$P); 131.06 (d, $^2J_{PC}$ 12.3 Hz, **C2**–P); 134.10 (d, $^3J_{PC}$ 9.5 Hz, **C3**–P); 134.63 (d, $^4J_{PC}$ 2.6 Hz, **C4**–P); 169.28 (d, $^3J_{PC}$ 4.2 Hz, **C**(O)NHCH$_2$P).

Single crystals of Gly–Gly(P^{Ph})·H_2O suitable for X-ray studies were grown from water solution by slow evaporation (3 weeks).

Gly–Gly($P^{t\text{-}Bu}$): Yield 55%. Elemental analysis (calc.): C 38.21% (40.38%); H 8.13% (8.23%); N 12.03% (13.46%). M.p. 280–285°C (dec.), $R_f = 0.5$ (B). ^{1}H (D_2O): 0.95 (d, 9H, $^3J_{PH}$ 14.7 Hz, PC$_4$**H**$_9$); 3.40 (d, 2H, $^2J_{PH}$ 7.7 Hz, NC**H**$_2$P); 3.70 (s, 2H, C**H**$_2$C(O)N). ^{31}P (D_2O): 45.10. ^{13}C (D_2O): 26.02 (s, PC(**C**H$_3$)$_3$); 33.80 (d, $^1J_{PC}$ 95.5 Hz; P-**C**(CH$_3$)$_3$); 37.80 (d, $^1J_{PC}$ 88.5 Hz; **C**H$_2$P); 42.59 (s, **C**H$_2$C(O)N); 168.5 (d, $^3J_{PC}$ 4.6 Hz; **C**(O)NHCH$_2$P).

ACKNOWLEDGMENT

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16. Formula: $C_9H_{15}N_2O_4P$; mol. weight: 246.20; space group $Pca2_1$ (no. 29); monoclinic; $a = 11.6921(8)$ Å, $b = 13.532(1)$ Å, $c = 7.3996(8)$ Å, $V = 1170.8(2)$ Å^3; $Z = 4$; ϑ range: $2\vartheta \leq 28^\circ$; $R = \Sigma||F_O| - |F_C||/\Sigma|\Delta F_O| = 0.025$;
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22. ***Tr-NHCH$_2$P(Me)(O)(OEt)***: ^{1}H NMR ($CDCl_3$): 1.28 (t, 3H, $^3J_{HH}$ 6.8 Hz, $OCH_2C\mathbf{H}_3$); 1.65 (d, 3H, $^2J_{PH}$ 14.0 Hz, $PC\mathbf{H}_3$); 1.9 (bs, 1H, N**H**); 2.4–2.6 (m, 2H, $NC\mathbf{H}_2P$); 7.1–7.3 (m, 15H, Ph); ^{31}P NMR ($CDCl_3$): 51.2.
23. ***Z-NHCH$_2$C(O)NHCH$_2$P(O)(Me)OH***: m.p. 140–144°C (dec.) (hot water); ^{1}H NMR ($LiOD/D_2O$): 1.32 (d, 3H, $^2J_{PH}$ 14.0 Hz, $PC\mathbf{H}_3$); 3.49 (d, 2H, $^2J_{PH}$ 8.0 Hz, $NC\mathbf{H}_2P$); 3.79 (d, 2H, $^5J_{PH}$ 0.8 Hz, $CH_2C(O)NHCH_2P$); 4.79 (s, 2H, $C\mathbf{H}_2Ph$); 7.31–7.36 (m, 5H, Ph); ^{31}P NMR ($CDCl_3$): 44.9.
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