N-(3-Phosphonopropyl)-substituted α-amino acids and their phosphine oxide analogs

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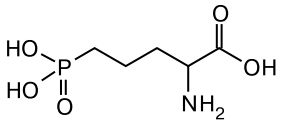
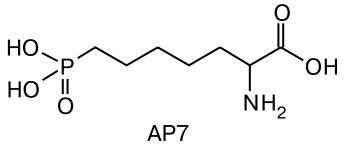
A facile method was developed for the synthesis of *N*-(3-phosphonopropyl)-substituted α-amino acids and their phosphine oxide analogs based on hydrolysis of 2-oxo-1,2-azaphospholanes and 1,2-azaphospholanium salts prepared from readily available reagents. A chelate Cu^{II} *N*-[(3-diphenylphosphoryl)propyl]glycinate was isolated.

Key words: 2-oxo-1,2-azaphospholanes, 1,2-azaphospholanium salts, hydrolysis, *N*-(3-phosphonopropyl)-substituted α-amino acids, *N*-[(3-diphenylphosphoryl)propyl]-substituted α-amino acids, Cu^{II} *N*-[(3-diphenylphosphoryl)propyl]glycinate, IR spectroscopy, NMR spectroscopy, X-ray diffraction study.

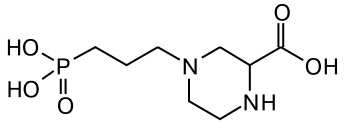
Amino phosphonic acids are structural analogs of amino carboxylic acids and possess a broad spectrum of biological activity.[1] Aminoalkyl phosphonates and aminoalkyl phosphinates were found in natural sources.[2] Phosphonoalkyl-substituted derivatives of α-amino carboxylic acids occupy a special place among synthetic and natural amino phosphonates. They serve as efficient enzyme inhibitors, antibacterial agents, and neuromodulators, show growth regulatory activity, and possess other useful biological and biochemical properties.[3] Phosphorus-containing selective *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as 2-amino-5-phosphonopentanoic acid (AP5), 2-amino-7-phosphonoheptanoic acid (AP7), 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (CPP), *etc.*, have found wide application in neurophysiological studies.[4]



AP5



AP7

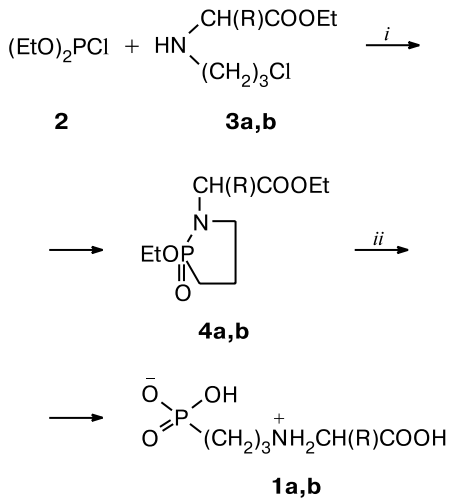


CPP

The phosphonoalkyl group in these compounds is, as a rule, linked with the α-carbon atom of an amino acid. In the present study, we developed a facile and convenient procedure for the synthesis of α-amino carboxylic acid derivatives with 3-phosphonopropyl and 3-(diphenylphosphoryl)propyl groups linked with the nitrogen atom of amino acids.

N-(3-Phosphonopropyl)-substituted α-amino acids **1** (Scheme 1) were synthesized by the reaction of diethyl

Scheme 1



1: R = H (**a**), Me (**b**)

Reagents and conditions: *i*. 1) Et_3N, −5 °C, MeCN, 2) Δ, 2 h. *ii*. 1) 6 *M* HCl, Δ, 2) methyloxirane, 20 °C.

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phosphorochloridite (**2**) with *N*-(3-chloropropyl)glycine ethyl ester or -DL-alanine ethyl ester (**3a,b**) giving rise to 2-oxo-1,2-azaphospholanes **4a,b**, which were subjected to hydrolysis. Compounds **4** have been prepared in individual form.[5] In the present study, their signals were observed in the ^{31}P NMR spectra of the reaction mixtures after the first stage. *N*-(3-Phosphonopropyl)glycine (**1a**) and -DL-alanine (**1b**) (Tables 1—3) were isolated as high-melting crystalline compounds readily soluble in water and insoluble in organic solvents.

The IR spectra of compounds **1a,b** (see Table 3) have absorption bands characteristic of C=O and PO_2^- groups along with broad intense absorption bands at 3500—2000 cm^{-1} corresponding to stretching vibrations of NH_2^+ and OH groups involved in strong hydrogen bonds.[1,6,7] These data suggest that compounds **1a,b** exist as zwitterions containing the deprotonated phosphonic group and the protonated nitrogen atom.

N-(3-Diphenylphosphorylpropyl)-α-amino carboxylic acids were prepared by hydrolysis of 1,2-azaphos-

Table 1. Yields, melting points, and elemental analysis data for compounds **4** and **7—9**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
			C	H	N	P	
4a	68.0	225—230 (decomp.) (EtOH—H_2O)	30.34 30.46	6.09 6.09	6.99 7.10	15.33 15.74	$C_5H_{12}NO_5P$
4b	71.9	230—231.5 (decomp.) (EtOH—H_2O)	34.28 34.12	6.71 6.68	6.44 6.63	14.20 14.67	$C_6H_{14}NO_5P$
7a[a]	76.2	228—230 (decomp.) (EtOH—Et_2O)	57.65 57.71	5.87 5.98	3.91 3.96	8.49 8.75	$C_{17}H_{21}ClNO_3P$
7b[b]	79.4	254—257 (decomp.) (EtOH)	58.75 58.77	6.28 6.30	3.71 3.81	8.21 8.43	$C_{18}H_{23}ClNO_3P$
8a	75.7 (57.7)[c]	237—240 (decomp.) (EtOH—H_2O)	64.19 64.33	6.33 6.35	4.37 4.41	9.63 9.86	$C_{17}H_{20}NO_3P$
8b	70.4 (60.0)[c]	250—252 (decomp.) (EtOH—H_2O)	64.96 65.24	6.60 6.68	4.10 4.22	9.08 9.35	$C_{18}H_{23}NO_3P$
9	48.7	—	55.81 55.77	5.64 5.74	3.81 3.82	8.37 8.47	$C_{34}H_{42}CuN_2O_8P_2$

[a] Found (%): Cl, 10.09. Calculated (%): Cl, 10.03.
[b] Found (%): Cl, 9.76. Calculated (%): Cl, 9.65.
[c] The yield based on consumed Ph_2PCl.

Table 2. Parameters of the ^{31}P—{^1H} and ^1H NMR spectra of compounds **4**, **7**, and **8**

Compound	Solvent	^{31}P-{^1H} NMR δ	^1H NMR, δ ($^3J_{H,H}$/Hz)
4a	D_2O	25.6	1.66—1.74 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 1.88—1.98 (m, 2 H, PCH_2); 3.15 (t, 2 H, NCH_2, J = 7.6); 3.85 (s, 2 H, CH_2CO)
4b	D_2O	25.8	1.47 (d, 3 H, CH_3, J = 7.2); 1.62—1.71 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 1.82—1.92 (m, 2 H, PCH_2); 3.03—3.13 (m, 2 H, NCH_2); 3.87 (q, 1 H, CH, J = 7.2);
7a	CD_3OD	37.8	1.89—2.03 (m, 2H, $CH_2C\underline{H}_2CH_2$); 2.53—2.63 (m, 2 H, PCH_2); 3.19 (t, 2 H, NCH_2, J = 7.6); 3.88 (s, 2 H, CH_2CO); 7.53—7.67, 7.76—7.85 (both m, 10 H, 2 C_6H_5)
7b	CD_3OD	37.9	1.75 (d, 3 H, CH_3, J = 7.2); 2.10—2.23 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.77—2.84 (m, 2 H, PCH_2); 3.39 (t, 2 H, NCH_2, J = 7.6); 4.21 (q, 1 H, CH, J = 7.2); 7.72—7.88, 7.96—8.05 (both m, 10 H, 2 C_6H_5)
8a	D_2O	41.4	1.69—1.84 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.33—2.42 (m, 2 H, PCH_2); 2.96 (t, 2 H, NCH_2, J = 7.6); 3.40 (s, 2 H, CH_2CO); 7.33—7.58 (m, 10 H, 2 C_6H_5)
8b	D_2O	41.2	1.41 (d, 3 H, CH_3, J = 7.2); 1.86—1.99 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.51—2.65 (m, 2 H, PCH_2); 3.07 (t, 2 H, NCH_2, J = 7.6); 3.58 (q, 1 H, CH, J = 7.2); 7.50—7.78 (m, 10 H, 2 C_6H_5)

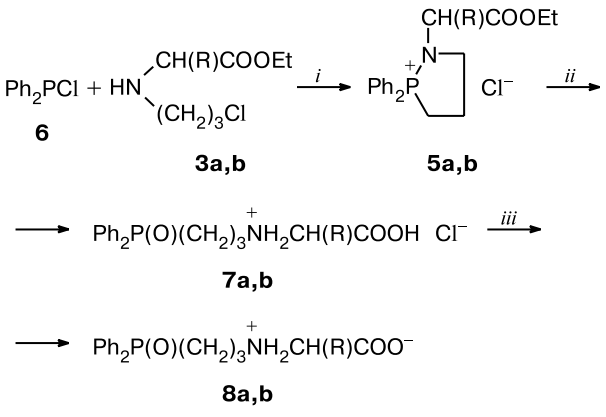
Table 3. Parameters of the IR spectra (KBr) and ^{13}C NMR spectra (D_2O) of compounds **4**, **7**, and **8**

Compound	IR, ν/cm^{-1}	^{13}C NMR, δ, J/Hz
4a	3500—2000 (NH_2^+, OH), 1742 (C=O), 1101, 1059 (PO_2^-)	19.88 (d, $CH_2\underline{C}H_2CH_2$, J = 3.8); 24.39 (d, PCH_2, J = 135.3); 47.71 (s, $N\underline{C}H_2CO$); 47.84 (d, $N\underline{C}H_2CH_2$, J = 18.0); 169.56 (s, CO)
4b	3500—2000 (NH_2^+, OH), 1715 (C=O), 1106, 1060 (PO_2^-)	14.31 (s, CH_3); 20.07 (d, $CH_2\underline{C}H_2CH_2$, J = 2.8); 24.40 (d, PCH_2, J = 135.5); 46.35 (d, NCH_2, J = 17.1); 56.11 (s, CH); 172.92 (s, CO)
7a	3500—2000 (NH_2^+, OH), 1727 (C=O), 1151 (P=O)	18.10 (s, $CH_2\underline{C}H_2CH_2$); 25.05 (d, PCH_2, J = 72.3); 47.39 (s, $N\underline{C}H_2CO$); 47.47 (d, $N\underline{C}H_2CH_2$, J = 16.0); 129.21 (d, *m*-C(Ph), J = 12.4); 129.34 (d, *ipso*-C(Ph), J = 102.4); 130.54 (d, *o*-C(Ph), J = 10.0); 133.05 (s, *p*-C(Ph)); 169.01 (s, CO)
7b*	3500—2000 (NH_2^+, OH), 1719 (C=O), 1147 (P=O)	14.44 (s, CH_3); 19.36 (d, $CH_2\underline{C}H_2CH_2$, J = 3.2); 26.45 (d, PCH_2, J = 72.3); 46.68 (d, $N\underline{C}H_2CH_2$, J = 14.4); 55.82 (s, CH); 129.40 (d, *m*-C(Ph), J = 12.1); 131.10 (d, *o*-C(Ph), J = 9.6); 131.70 (d, *ipso*-C(Ph), J = 101.0); 131.77 (d, *ipso*-C(Ph), J = 101.5); 132.90 (d, *p*-C(Ph), J = 2.4); 171.00 (s, CO)
8a	3150—2000 (NH_2^+), 1619, 1383 (CO_2^-), 1183 (P=O)	16.51 (br.s, $CH_2\underline{C}H_2CH_2$); 23.33 (d, PCH_2, J = 72.3); 45.72 (d, $N\underline{C}H_2CH_2$, J = 17.3); 47.40 (s, $N\underline{C}H_2CO$); 127.53 (d, *m*-C(Ph), J = 12.0); 127.68 (d, *ipso*-C(Ph), J = 102.0); 128.95 (d, *o*-C(Ph), J = 10.0); 131.40 (br.s, *p*-C(Ph)); 169.33 (s, CO)
8b	3150—2000 (NH_2^+), 1585, 1394 (CO_2^-), 1184 (P=O)	14.23 (s, CH_3); 17.72 (br.s, $CH_2\underline{C}H_2CH_2$); 24.36 (d, PCH_2, J = 72.5); 45.41 (d, $N\underline{C}H_2CH_2$, J = 16.7); 57.14 (br.s, CH); 128.50 (d, *m*-C(Ph), J = 12.1); 128.60 (d, *ipso*-C(Ph), J = 101.5); 129.90 (d, *o*-C(Ph), J = 10.1); 132.40 (br.s, *p*-C(Ph)); 173.90 (br.s, CO)

* The ^{13}C NMR spectrum of compound **7b** was recorded in CD_3OD.

pholanium salts **5** (Scheme 2), which were obtained in the reaction of diphenylphosphinous chloride (**6**) with amino acid derivatives **3a,b**. Hydrochlorides **7a,b** are high-melting crystalline products, which are moderately soluble in MeOH and EtOH and readily soluble in water (see Tables 1—3).

Scheme 2



R = H (**a**), Me (**b**)

Reagents and conditions: *i*. 1) Et_3N, −5 °C, $CHCl_3$—C_6H_6, 2) Δ, 1 h. *ii*. 6 *M* HCl, Δ. *iii*. Methyloxirane, 20 °C.

The IR spectra of compounds **7a,b** have absorption bands of P=O and C=O groups along with broad intense absorption bands at 3500—2000 cm^{-1} corresponding to stretching vibrations of NH_2^+ and OH groups involved in strong hydrogen bonds (see Table 3). These data are consistent with the presence of phosphoryl, carboxy, and NH_2^+ groups in hydrochlorides **7a,b**. The structure of hydrochloride **7a** was confirmed by X-ray diffraction. Hydrochloride **7a** crystallizes with two independent cations and anions per asymmetric unit (Fig. 1). The nitrogen atoms in both independent cations are protonated. The bond lengths and bond angles and the all-*trans* conformation of the P(1)—C(5) fragment in two independent cations of **7a** are virtually identical (Table 4). The phosphoryl group is synperiplanar (sp) to the alkyl chain. However, one independent molecule adopts the +sp conformation, whereas another molecule is in the −sp conformation. The O(1)—P(1)—C(1)—C(2) and O(1′)—P(1′)—C(1′)—C(2′) torsion angles are 39.5 and −41.3°, respectively.

In the crystal structure of **7a**, the cations are linked to each other by strong O—H...O hydrogen bonds between the carboxy and phosphoryl groups (O(3)...O(1′) and O(3′)...O(1) are 2.561(2) and 2.530(2) Å, respectively) to form chains along the crystallographic axis *b*. These chains are additionally cross-linked by the Cl^- anions through the N—H...Cl hydrogen bonds (N...Cl, 3.026(2)—3.071(2) Å).

The reactions of hydrochlorides **7a,b** with methyloxirane produced *N*-(3-diphenylphosphorylpropyl)glycine (**8a**) and -DL-alanine (**8b**), respectively. These high-melt-

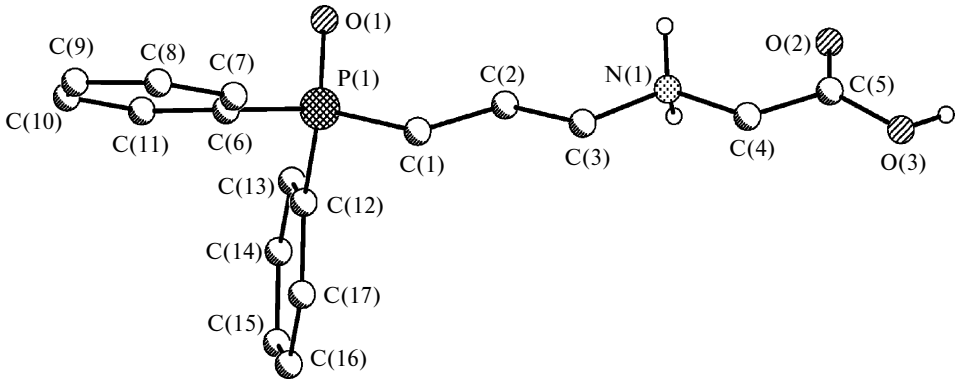


Fig. 1. Overall view of one independent cation in the crystal structure of hydrochloride **7a**.

Table 4. Selected bond lengths (*d*) and bond angles (ω) in two independent cations (**A** and **B**) in the crystal structure of hydrochloride **7a**

Parameter	Value	
	A	**B**
Bond	*d*/Å	
P(1)—O(1)	1.501(1)	1.5034(15)
P(1)—C(1)	1.811(2)	1.803(2)
P(1)—C(6)	1.809(2)	1.802(2)
P(1)—C(12)	1.806(2)	1.808(2)
N(1)—C(4)	1.491(2)	1.484(3)
N(1)—C(3)	1.499(2)	1.497(2)
C(1)—C(2)	1.536(3)	1.540(3)
O(2)—C(5)	1.208(2)	1.214(2)
C(2)—C(3)	1.528(3)	1.523(3)
O(3)—C(5)	1.325(2)	1.318(3)
Angle	ω/deg	
O(1)—P(1)—C(12)	108.81(9)	108.64(9)
O(1)—P(1)—C(6)	111.13(9)	110.25(9)
C(12)—P(1)—C(6)	106.83(9)	108.33(9)
O(1)—P(1)—C(1)	113.57(9)	115.31(9)
C(12)—P(1)—C(1)	109.11(10)	108.95(10)
C(6)—P(1)—C(1)	107.17(9)	105.15(9)
C(4)—N(1)—C(3)	113.29(15)	113.15(15)

ing crystalline compounds are readily soluble in water (see Table 1). The IR spectra (see Table 3) have absorption bands of the P=O group along with intense absorption bands at 1619, 1383 cm^{-1} (**8a**) and 1585, 1394 cm^{-1} (**8b**) characteristic of the carboxylate anion.[8] In addition, the spectra show a continuous series of medium-intensity bands at 3150—2000 cm^{-1} assigned to stretching vibrations of the NH_2^+ group. These data suggest that these compounds exist as zwitterions containing the deprotonated carboxy group and the protonated nitrogen atom. Compounds **8a,b** were also prepared without isolation of intermediate hydrochlorides **7a,b** in 57.7 and 60.0% yields, respectively.

The compositions and structures of compounds **1**, **7**, and **8** were confirmed by elemental analysis, IR spectroscopy, and ^1H, ^{31}P, and ^{13}C NMR spectroscopy (see Tables 1—3).

Compounds **8** are potential complex-forming agents for metals, which are of interest from the point of view of biological activity (Cu, Co, Ni, *etc.*). The reaction of **8a** with $CuCO_3 \cdot Cu(OH)_2$ afforded dihydrate of the Cu^{II} chelate $Cu[Ph_2P(O)(CH_2)_3NHCH_2COO]_2 \cdot 2H_2O$ (**9**) (see Table 1).

The IR spectrum of this compound shows a broad intense absorption band at 1608 cm^{-1} and an intense band at 1375 cm^{-1} characteristic of vibrations of the C=O group in salts of carboxylic acids[8] along with an intense band of the NH group at 3200 cm^{-1} and a broad intense absorption band at 3600—3300 cm^{-1}. The $^{31}P—\{^1H\}$ NMR spectrum in CD_3OD has a broad singlet at δ_P 51.1 shifted downfield with respect to the signal of the starting compound **8a** (δ_P 41.4 in D_2O).

In the crystal structure, complex **9** occupies a crystallographic inversion center, the copper atom lying on this center. The coordination polyhedron of the copper atom is a tetragonal bipyramid with two chelate ligands and two water molecules in the axial positions (Fig. 2, Table 5). The axial Cu(1)—O(1W) bonds with the water molecule are elongated to 2.568(2) Å compared to the equatorial Cu(1)—O(2) bonds (1.928(2) Å). The five-membered metallacycle adopts an envelope conformation with the N(1) atom deviating from the Cu(1)O(2)C(4)C(5) plane by 0.42 Å. The P(1)—C(4) fragment in complex **9**, like that in hydrochloride **7a**, adopts an all-*trans* conformation. The P(1)—C(1)—C(2)—C(3), C(1)—C(2)—C(3)—N(1), and C(2)—C(3)—N(1)—C(4) torsion angles are 169.7, 170.7, and 167.8°, respectively. The phosphoryl group is synperiplanar to the P(1)—C(4) fragment. The O(1)—P(1)—C(1)—C(2) torsion angle is 61.9°.

In the crystal structure, the molecules of salt **9** are linked to each other by N—H...O (N(1)...O(3A), 2.905(3) Å) and O—H...O (O(1W)...O(3), 2.764(2) Å; O(1W)...O(1), 2.900(2) Å) hydrogen bonds to form doubled chains along the crystallographic axis *b*.

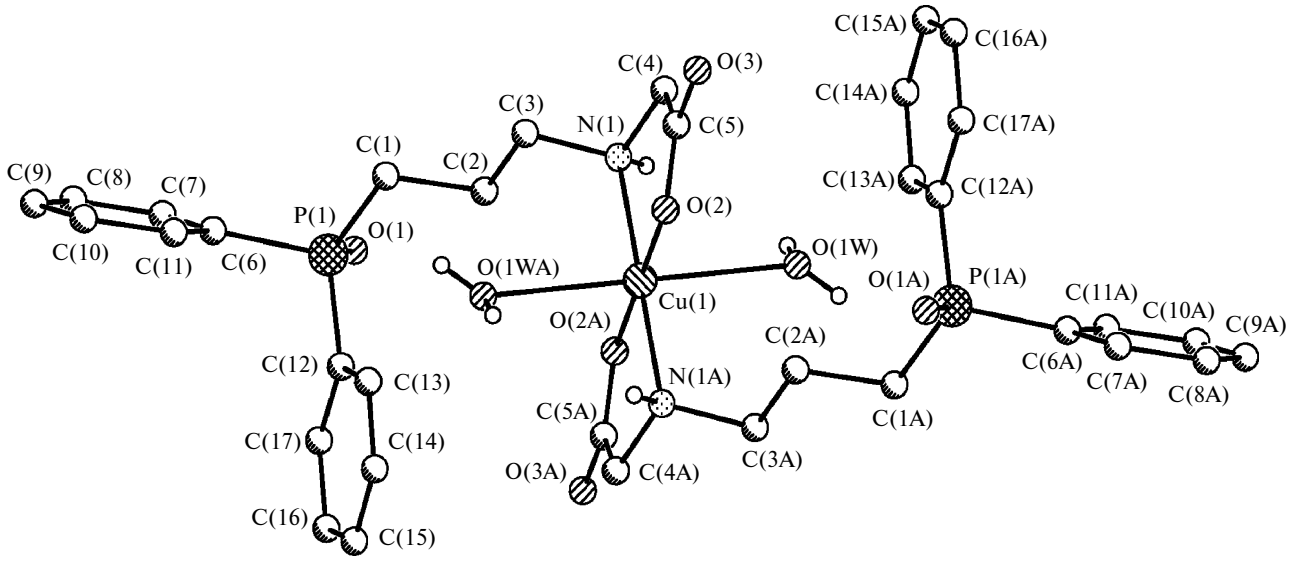


Fig. 2. Overall view of dihydrate of chelate **9** in the crystal structure. The atoms marked with A are related to nonmarked atoms by the symmetry operation ($-x$, $-y$, $-z$).

Table 5. Selected bond lengths (d) and bond angles (ω) in the crystal structure of salt **9**

Bond	d/Å	Angle	ω/deg
Cu(1)—O(2)	1.928(2)	O(2)—Cu(1)—N(1A)	95.43(8)
Cu(1)—N(1)	2.038(2)	O(2)—Cu(1)—N(1)	84.57(8)
Cu(1)—O(1W)	2.658(3)	O(2)—Cu(1)—O(1W)	96.49(9)
P(1)—O(1)	1.487(2)	N(1)—Cu(1)—O(1W)	83.71(9)
P(1)—C(1)	1.795(3)	O(1)—P(1)—C(1)	113.9(1)
P(1)—C(12)	1.799(3)	O(1)—P(1)—C(12)	113.0(1)
P(1)—C(6)	1.811(3)	C(1)—P(1)—C(12)	107.7(1)
O(2)—C(5)	1.270(3)	O(1)—P(1)—C(6)	111.0(1)
O(3)—C(5)	1.238(3)	C(1)—P(1)—C(6)	106.7(1)
N(1)—C(4)	1.478(3)	C(12)—P(1)—C(6)	103.9(1)
N(1)—C(3)	1.486(3)	C(4)—N(1)—C(3)	112.7(2)

Experimental

The NMR spectra were recorded on a Bruker AMX-400 instrument with the use of the signal from the residual protons of $CDCl_3$ as the internal standard (^1H), the signal of $CDCl_3$ as the internal standard (^{13}C), and 85% H_3PO_4 as the external standard (^{31}P). The IR spectra were measured on Magna IR 750 Nicolet and UR-20 instruments in KBr pellets. Commercial reagents $(EtO)_2PCl$ and Ph_2PCl (Aldrich) were used. Compounds **3a,b** were synthesized according to a known procedure.[5]

***N*-(3-Phosphonopropyl)glycine (1a).** A solution of chloride **2** (0.65 g, 4.1 mmol) in MeCN (5 mL) was added dropwise with vigorous stirring to a solution of glycine derivative **3a** (0.90 g, 5 mmol) and Et_3N (0.50 g, 5 mmol) in anhydrous MeCN (10 mL) at −5 °C under argon. The reaction mixture was refluxed for 2 h. The percentage of azaphospholane **4a** in the reaction mixture was 84% (^{31}P NMR spectroscopic data, δ_P 46.8; *cf.* lit. data[5]: δ_P 46.8 in $CDCl_3$). The precipitate was filtered off, MeCN was removed *in vacuo*, benzene (15 mL) was added to the residue, and the mixture was filtered. Benzene was removed *in vacuo*, 6 *M* HCl (50 mL) was added to the residue, and the reaction mixture was refluxed for 16 h. The solution was cooled and washed with CH_2Cl_2 (3×20 mL). The aqueous layer was concentrated to dryness. Water (30 mL) was added to, and distilled from, the residue; this operation was repeated three times. The residue was kept *in vacuo* at 80 °C for 1 h and dissolved in MeOH (30 mL). Methyloxirane (10 mL) was added dropwise with stirring. The reaction mixture was stirred at 20 °C for 4 h and kept in a refrigerator for 16 h. The precipitate that formed was filtered off and dried *in vacuo*. The yield of compound **1a** was 0.55 g (see Tables 1—3).

***N*-(3-Phosphonopropyl)-DL-alanine (1b)** was synthesized analogously from **3b** (1.55 g, 8 mmol), **2** (1.03 g, 6.6 mmol), and Et_3N (1.01 g, 10 mmol) in anhydrous MeCN (30 mL). After refluxing, the percentage of azaphospholane **4b** in the reaction mixture was 83% (^{31}P NMR spectroscopic data, δ_P 46.2 and 47.0 (two diastereomers); *cf.* lit. data[5]: δ_P 46.4 and 47.3 in $CDCl_3$). The reaction mixture was filtered and the solvent was removed. The residue was refluxed with 6 *M* HCl (60 mL) for 16 h and worked up as described above. The residue was dissolved in MeOH (50 mL), and methyloxirane (20 mL) was added dropwise with vigorous stirring. The reaction mixture was stirred for 4 h and kept in a refrigerator for 16 h. The precipitate that formed was filtered off, treated with refluxing MeOH on a filter, and dried *in vacuo*. Compound **1b** was isolated in a yield of 1.00 g (see Tables 1—3).

***N*-(3-Diphenylphosphorylpropyl)glycine hydrochloride (7a)** was synthesized from **3a** (1.33 g, 7.4 mmol) and phosphinous chloride **6** (1.52 g, 6.9 mmol) in the presence of Et_3N (0.86 g, 8.5 mmol) in a 2 : 1 mixture of anhydrous C_6H_6 and $CHCl_3$. The reaction mixture was refluxed for 1 h, after which the percentage of chloride **5a** in the mixture was 88% (^{31}P NMR spectroscopic data, δ_P 55.1; *cf.* lit. data[5]: δ_P 60.0 in $CDCl_3$). The reaction mixture was filtered, the solvent was removed *in vacuo*, and 6 *M* HCl (100 mL) was added to the residue. The reaction mixture was refluxed for 18 h, the solution was cooled and

washed with CH_2Cl_2 (3×40 mL), and the aqueous layer was concentrated to dryness. Water (40 mL) was added to, and distilled from, the residue; this operation was repeated three times. Hydrochloride **7a** was isolated in a yield of 1.86 g (see Tables 1—3).

***N*-(3-Diphenylphosphorylpropyl)-DL-alanine hydrochloride (7b)** was synthesized analogously from **3b** (1.44 g, 7.4 mmol), **6** (1.37 g, 6.2 mmol), and Et_3N (0.76 g, 7.5 mmol) in a 2 : 1 C_6H_6—$CHCl_3$ mixture (20 mL). The reaction mixture was refluxed for 1 h, after which the percentage of salt **5b** in the reaction mixture was 92% (^{31}P NMR spectroscopic data, δ_P 57.5; *cf.* lit. data[5]: δ_P 57.2 in $CDCl_3$). The reaction mixture was filtered, the solvents were removed, and 6 *M* HCl (100 mL) was added to the residue. The reaction mixture was refluxed for 16 h and then worked up as described above for hydrochloride **7a**. After drying *in vacuo*, hydrochloride **7b** was obtained in a yield of 1.81 g (see Tables 1—3).

***N*-(3-Diphenylphosphorylpropyl)glycine (8a).** Hydrochloride **7a** (0.82 g, 2.3 mmol) was dissolved in anhydrous EtOH (25 mL), and methyloxirane (8 mL) was added dropwise with stirring and gentle heating for 5 min. The reaction mixture was stirred for 6 h and then kept in a refrigerator for 4 days. The precipitate that formed was filtered off, washed with ethanol, and dried *in vacuo*. Compound **8a** was obtained in a yield of 0.56 g (see Tables 1—3).

***N*-(3-Diphenylphosphorylpropyl)-DL-alanine (8b)** was synthesized analogously from a solution of hydrochloride **7b** (0.79 g, 2.2 mmol) in anhydrous ethanol (30 mL) and methyloxirane (8 mL). The reaction mixture was stirred for 5 h and kept in a refrigerator for 16 h. The precipitate was filtered off, washed with ethanol, and dried *in vacuo*. Compound **8b** was obtained in a yield of 0.50 g (see Tables 1—3).

Dihydrate of the Cu^{II} chelate of *N*-(3-diphenylphosphorylpropyl)glycine (9). Basic cupric carbonate $CuCO_3 \cdot Cu(OH)_2$ (0.0217 g, 0.11 mmol) was added to a solution of **8a** (0.1245 g, 0.392 mmol) in water (2 mL). The resulting opaque blue solution was filtered, the filtrate was concentrated to dryness, the residue was dissolved in ethanol, diethyl ether was added, and the reaction mixture was kept for 16 h. The lilac crystals that precipitated were filtered off, treated on a filter with hot water to remove unconsumed **8a**, and dried. Salt **9** was obtained in a yield of 0.07 g (see Table 1). IR (KBr), ν/cm^{-1}: 3600—3300 (OH), 3200 (NH), 1608, 1375 (CO_2). ^{31}P—{^1H} NMR (CD_3OD), δ: 51.1 br.s.

X-ray diffraction study of hydrochloride 7a and dihydrate of chelate 9. The structures were solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for nonhydrogen atoms against F^2_{hkl}. The hydrogen atoms were located from difference Fourier maps

Table 6. Principal crystallographic data and parameters of structure refinement for hydrochloride **7a** and chelate **9**

Parameter	**9**	**7a**
Formula	$C_{34}H_{42}CuN_2O_8P_2$	$C_{17}H_{21}ClNO_3P$
T/K	298	120
Diffractometer	Siemens P3	SMART CCD
Radiation	MoKa-α	MoK-α
Scan mode	ω-Scanning technique	ω-Scanning technique
Crystal system	Orthorhombic	Triclinic
Space group	*Pbca*	$P\bar{1}$
a/Å	8.732(2)	9.997(1)
b/Å	11.106(2)	10.551(1)
c/Å	34.851(7)	17.208(2)
α/deg		93.378(3)
β/deg		100.776(3)
γ/deg		90.744(3)
V/Å^3	3379.8(12)	1779.5(4)
Z (Z')	4(0.5)	4(2)
M	732.18	353.77
μ/cm^{-1}	7.95	3.18
F(000)	1532	744
ρ_{calc}/g cm^{-3}	1.439	1.320
$2\theta_{max}$/deg	55	57
Number of measured reflections (R_{int})	3873 (0.0)	13021 (0.0177)
Number of independent reflections	3873	8402
Number of observed reflections with $I > 2\sigma(I)$	2550	6522
Number of parameters	226	439
R_1	0.0428	0.0473
wR_2	0.1035	0.1157
GOOF	1.002	1.072
ρ (max/min)/e Å^{-3}	0.429/−0.685	0.619/−0.462

and refined isotropically. All calculations were carried out using the SHELXTL PLUS program package (Table 6).

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