Preparation and Properties of ω-Phosphino-phosphonocarboxylic Acids and their Betaines

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ω-Phosphino-phosphonocarboxylic Acids, Phosphobetaines, Organophosphorus Compounds, Organophosphorus Ligands

In an attempt to provide phosphorus analogues of amino-carboxylic acids and their betaines, ω-ω-bis(diphenylphosphino)alkanes (dpdm, dppe, dppp, dppb) were converted into ω-phosphino-phosphonocarboxylates and diphasphonium-bis-carcboxylates. While the reactions with haloacetic acids or haloacetates only lead to methylphosphonium derivatives owing to decarboxylation of the intermediates, β-chloropropionic acids converts Ph2P(CH2)nPPn+((CH2)mCOOH)2Cl~ (1) and CH3[PPh2(CH2)mCOOH]2Cl~ (2), for n = 1. For n = 2, 3 and 4, only the analogues of 2 could be prepared (3–5). Treatment of 1 and 2 with sodium bicarbonate afforded the corresponding betaines Ph2P(CH2)mPPh2+(CH2)nCOO− (isolated as a dihydrate 6) and CH3[PPh2+CH2 CH2 COO−]2 (isolated as the tetrahydrate 7).

Introduction

Carboxylic acids with a cationic phosphonium function integrated in the organic group (A) are well documented [1–4]. Some of these compounds have been converted into their zwitterionic betaines (B) [2], and cationic esters of the acids and other derivatives have also been prepared (C) [3]. Interest in representatives of these families of compounds stems from their potential biological activity as suggested by their relation with amino acids, which are known to exist in cationic, zwitterionic, or anionic form. With free carboxylic functions they can act as ligands to many metals in biological systems. Apart from these bioinorganic aspects, phosphonium-functionalyzed carboxylic acids and their salts can also be envisaged as components in laboratory or industrial metal extraction processes.

\[
\begin{align*}
R_3P^+&+\text{(CH}_2\text{)}_n\text{COOH} \quad \text{A} \\
R_3P^+&+\text{(CH}_2\text{)}_n\text{COO}^- \quad \text{B} \\
R_3P^+&+\text{(CH}_2\text{)}_n\text{COOR}^- \quad \text{C}
\end{align*}
\]

Compounds of types A–C are available through the reactions of ω-halofunctional carboxylic acids (or esters) with tertiary phosphines [2, 3]. This procedure is not always trivial, however, since side reactions, mainly decarboxylation or other β-elimination processes, can lead to unexpected products. This is particularly true for haloacetic acids XCH2COOH, which are known to afford only methylphosphonium salts owing to rapid loss of CO2 in the course of the anion salt formation:

\[
R_3P+\text{CICH}_2\text{COOH} \rightarrow R_3\text{PCH}_3^+\text{Cl}^-+\text{CO}_2
\]

In an attempt to introduce an additional phosphine donor site at a terminal position of compounds of type A, we have now studied the reaction of ω-halo carboxylic acids with di-tertiary phosphines. Depending on the stoichiometry of the reactions, products of the types D and E were expected. The former would provide phosphine and carboxylate functions for coordination to metals, while the latter could act as chelating neutral (double-zwitterionic) dicarboxylates:

\[
\begin{align*}
R_3P(\text{CH}_2)_nPR_2^+&\text{(CH}_2\text{)}_m\text{COO}^- \quad \text{D} \\
\text{OOC}(\text{CH}_2)_nPR_2^+&\text{(CH}_2\text{)}_m\text{PR}_2^+\text{(CH}_2\text{)}_m\text{COO}^- \quad \text{E}
\end{align*}
\]

This study is part of a current research program on metal complexes of amino acids and related ligands of biological relevance [5].

Results

As perhaps expected from previous findings [2], the reaction of equimolar quantities of
bis(diphenylphosphino)methane dppm with chloroacetic acid in toluene as a solvent at ambient temperature does not afford a phosphino-phosphoniocarboxylate. With loss of carbon dioxide diphenylphosphinomethyl-diphenylmethylphosphonium chloride is formed instead. Phosphinomethyl-phosphonium salts have been fully characterized in earlier work [6].

\[
\text{Ph}_2 \text{PCH}_2 \text{PPh}_2 + \text{ClICH}_2 \text{COOH} \rightarrow \text{Ph}_2 \text{PCH}_2 \text{PPh}_2 \text{CH}_3^+ \text{Cl}^- + \text{CO}_2
\]

Similar reactions occur with 1,2-bis(diphenylphosphino)ethane dppe, but the products proved more difficult to purify and have therefore been identified only on the basis of their NMR spectra. No reaction was observed with 1,3- and 1,4-bis(diphenylphosphino)propane and -butane, respectively, under comparable conditions.

The elimination of CO\(_2\) in the above reactions is a consequence of the excellent leaving group properties of ylidic functions: The stabilization of \(R_2\text{PCH}_2\text{(R}_2\text{)}^+\text{CH}_2^-\) groups [7] leads to rapid heterolytic cleavage of the \(\text{C}^-\text{C}\) bond in \(\text{P}^+-\text{CH}_2^-\text{CO}_2^-\). The ylide is finally reprotonated by the acid present in the reaction mixtures.

Such an elimination mechanism should not be operative in the corresponding phosphonio-phosphonates or -butyrate, however, and in fact no CO\(_2\) elimination is observed with \(\beta\)-chloropropionic acid or \(\gamma\)-chlorobutyric acid.

dppm reacts with Cl\(\text{CH}_2\text{CH}_2\text{COOH}\) in 1:1 or 1:2 stoichiometry to give theonium-carboxylic acids 1 and 2 in good yields:

\[
\text{dppm + ClICH}_2\text{CH}_2\text{COOH} \rightarrow \text{Ph}_2\text{PCH}_2\text{PPh}_2^+\text{(CH}_2\text{)}_2\text{COOH Cl}^- \quad 1
\]
\[
\text{dppm + 2ClICH}_2\text{CH}_2\text{COOH} \rightarrow \text{CH}_2[\text{Ph}_2\text{P}^+\text{(CH}_2\text{)}_2\text{COOH}]_2^2 2\text{Cl}^- \quad 2
\]

With dppe, 1,3-bis(diphenylphosphino)propane dppp or 1,4-bis(diphenylphosphino)butane dppb and \(\beta\)-chloropropionic acid, only the symmetrical bis(onium)-bis(carboxylic acids) (3–5) could be obtained:

\[
\text{Ph}_2\text{P(}\text{CH}_2\text{)}_n\text{PPh}_2 + 2\text{ClICH}_2\text{CH}_2\text{COOH} \rightarrow \text{Ph}_2\text{P(}\text{CH}_2\text{)}_n^+\text{PPh}_2 \quad 2\text{Cl}^- \\
\text{HOOC(}\text{CH}_2\text{)}_n \quad (\text{CH}_2\text{)}_2\text{COOH}
\]

3: \(n = 2\); 4: \(n = 3\); 5: \(n = 4\).

Compounds 1–3 and 5 can be crystallized from chloroform/diethyl ether or ethanol/diethyl ether. Compound 4 could not be isolated in a pure form, but has been identified through its IR and NMR spectra.

In weakly basic medium compounds 1 and 2 can be converted into the corresponding betains. To this end, aqueous solutions of the carboxylic acids are treated with sodium bicarbonate in aqueous solution at ambient temperature. A dihydrate 6 and a tetrahydrate 7 are obtained, respectively. The products are soluble in water, alcohol, and chloroform, and 7 is noticeably hygroscopic in air.

\[
\begin{align*}
1 + \text{NaHCO}_3 & \rightarrow \text{NaCl+CO}_2+\text{Ph}_2\text{PCH}_2\text{PPh}_2^+\text{CH}_2\text{CH}_2\text{COO}^- \quad 2\text{H}_2\text{O} \quad 6 \\
2 + 2\text{NaHCO}_3 & \rightarrow 2\text{NaCl}+2\text{CO}_2+\text{CH}_2[\text{Ph}_2\text{P}^+\text{CH}_2\text{CH}_2\text{COO}^-]_2^2 \quad 4\text{H}_2\text{O} \quad 7
\end{align*}
\]

The IR and NMR spectra of the pairs of compounds 1/6 and 2/7 show small, but significant differences, which prove the presence of protonated and free carboxylate groups, respectively. The P(III)CH\(_2\)P(V) groups produce doublets in the \(\text{^31P} NMR\) spectra with characteristic shift and coupling values. All other compounds have singlet phosphorus resonances (Exp. Part).

**Experimental Part**

**General:** The experiments were carried out under purified dry nitrogen. The starting materials were commercially available and of analytical grade. Microanalyses were performed in the Analytical Laboratory of this Institute. Standard analytical and spectroscopic equipment was used.

**Diphenylphosphinomethyl-diphenyl(methyl)phosphonium chloride from dppm and ClICH\(_2\)COOH**

dppm (0.768 g, 2.00 mmole) and chloroacetic acid (0.188 g, 2.00 mmole) are mixed in toluene (30 ml) and the mixture kept at 20 °C for 3 days. Upon evaporation of the solvent to half the original volume a white precipitate appears, which is filtered and recrystallized from ethanol/diethyl ether [1:1]. The product (0.67 g, 77% yield) is soluble in polar solvents. For spectroscopic data see ref. [6].

C\(_{26}\)H\(_{25}\)ClP\(_2\) (434,88)

**Calcd** C 71.81 H 5.79 Cl 8.15.

**Found** C 70.92 H 5.62 Cl 8.74.
3,3-Diphenyl-5-diphenylphosphino-3-phosphoniapentanoic acid chloride (1)

Dppm (0.768 g, 2.00 mmole) is mixed with 2-chloropropionic acid (0.216 g, 4.00 mmole) and heated to 140 °C for two hours. A glassy product is obtained on cooling to room temperature, which is dissolved in chloroform and precipitated with diethyl ether. The product (0.77 g, 81% yield) is soluble in water (pH = 2.35), alcohol, and chloroform; m.p. 188 °C.

C_{28}H_{28}Cl_{2}O_{4}P_{2} (492,92)
Calcd C 68.23 H 5.52 Cl 7.19,
Found C 67.40 H 5.47 Cl 7.27.

IR (KBr): 1728 cm⁻¹, ν(CO₂).

1H NMR (CDCl₃): δ = 4.2 ppm, d, 2H, J(CH₂P) = 14.2 Hz, PCH₃, 2.7-3.4, m, 4H, CH₂CH₂; 7.6, m, 20H, Ph.

31P NMR (CDCl₃): δ = 26.9 and -28.5, d, /J(PP) = 60 Hz.

4,4,6,6-Tetraphenyl-4,6-diphosphonia-nonadioic acid dichloride (2)

As described for 1, product 2 is obtained (0.805 g, 67% yield) when two equivalents of ClCH₂CH₂COOH are used; m.p. 205 °C. The compound is soluble in water (pH = 2.49).

C_{31}H_{32}Cl₂O₄P₂ (601,45)
Calcd C 61.91 H 5.36 Cl 11.78,
Found C 60.22 H 5.69 Cl 10.71.

IR (KBr): 1729 cm⁻¹, ν(CO₂).

1H NMR (CDCl₃): δ = 5.01, t, 2H, J(CH₂P) = 15.0 Hz; 2.6-3.5, m, 8H, PCH₂CH₂; 7.4, m, 20H, Ph.

31P NMR (CD₂OD): δ = 24.7, s.

3-[Diphenylphosphinomethyl-diphenylphosphonio]propionate dihydrate (6)

Compound 1 (3.39 g, 6.89 mmole) is dissolved in ethanol (25 ml) and treated with a solution of NaHCO₃ (0.578 g, 6.89 mmole) in water (10 ml). After ceasure of the CO₂ evolution the solvents are removed in vacuo. The residue is extracted with ethanol, filtered and treated with diethyl ether. The colourless precipitate is collected, washed with diethyl ether and dried in vacuo. Hygroscopic solid, m.p. 70 °C. Aqueous solutions have p_H = 5.74.

C_{31}H_{28}O₄P₂ (492,50)
Calcd C 68.29 H 6.13,
Found C 68.39 H 6.19.

IR (KBr): 3430 cm⁻¹, ν(OH₂); 1595 ν(CO₂).

1H NMR (CDCl₃): δ = 4.2, d, 2H, J(PCH₂P) = 14.0 Hz; 2.60 and 3.50, m, 4H, CH₂CH₂; 7.50, m, 20H, Ph.

31P NMR (CDCl₃): δ = 26.5 and -27.6, dd, J(PCP) = 65 Hz.

4,4,7,7-Tetraphenyldiphenyldiphenylphosphonio-1,10-decaadioic acid dichloride (3)

A mixture of dppe (0.796 g, 2.00 mmole) and 3-chloropropionic acid (0.216 g, 4.00 mmole) are heated to 140 °C for 2 h. The glassy product is washed with diethyl ether and dried in vacuo; m.p. 200 °C. Aqueous solutions have p_H = 3.00.

C_{32}H_{34}Cl₂O₄P₂ (615,47)
Calcd C 62.44 H 5.56 Cl 11.52,
Found C 60.47 H 5.65 Cl 11.10.

IR (KBr): 1715 cm⁻¹, ν(CO₂).

1H NMR (CDCl₃): δ = 2.40, m, 8H, PCH₂CH₂; 2.70, m, 4H, PCH₂CH₂P; 7.52, m, 20H, Ph.

31P NMR (CD₂OD): δ = 30.9.

1,2-Ethanediyl-bis(diphenylphosphonio-3-propionate) tetrahydrate (7)

A solution of compound 3 (1.081 g, 1.75 mmole) in 20 ml ethanol is treated with a solution of sodium bicarbonate (0.300 g, 3.57 mmole) in 5 ml water. After 1 h, the solvents are removed in vacuo and the residue dried over P₂Os. Redissolved in ethanol, the product is precipitated with diethyl ether after filtration, m.p. 130 °C. Aqueous solutions have p_H = 5.20.

C_{32}H_{40}O₈P₂ (614,64)
Calcd C 62.44 H 6.71,
Found C 61.47 H 6.45.

IR (KBr): 3416 cm⁻¹, ν(H₂O); 1588 ν(CO₂).

1H NMR (D₂O): δ = 2.40, m, 8H, PCH₂CH₂; 3.11, m, 4H, PCH₂CH₂P; 7.62, m, 20H, Ph.

31P NMR (D₂O): δ = 30.3.

4,4,9,9-Tetraphenyldiphenyldiphenylphosphonio-dodecaadioic acid dichloride (5)

Dpbb (0.852 g, 2.00 mmole) and 3-chloropropionic acid (0.216 g, 2.00 mmole) are mixed and heated to 140 °C for 2 h. Work-up as described for 3 above affords a colourless, solid product, m.p. 135 °C. Aqueous solutions show p_H = 2.90.

C_{34}H_{38}Cl₂O₄P₂ (643,53)
Calcd C 63.46 H 5.95 Cl 11.01,
Found C 63.54 H 6.17 Cl 10.40.
IR (KBr): 1722 cm\(^{-1}\), \(\nu\)(CO).  \(^1\)H NMR (D\(_2\)O): \(\delta\) = 1.40, m, 4H, C(CH\(_2\))C; 2.75, m, 16H, PCH\(_2\); 4.60, br, COOH/OHD; 7.45–7.60, m, 20H, Ph.  

\(^31\)P NMR (CDCl\(_3\)): \(\delta\) = 27.1.

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