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Synthesis of Carboxylate Phosphabetaines from 3-(Diphenylphosphino)propanoic Acid and Unsaturated Monocarboxylic Acids

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Abstract—Stable dicarboxylate phosphabetaines were synthesized by the phosphorylation of a series of unsaturated monocarboxylic acids (acrylic, crotonic, methacrylic, and cinnamic) with 3-(diphenylphosphino)-propanoic acid. The structure of the products was assessed by chemical, physical, and physicochemical methods. Alkylation of 3-(diphenylphosphino)propanoic acid with methyl iodide was studied for the first time to show that the reaction proceeds smoothly and yields the corresponding quaternary phosphonium salt.

Keywords: carboxylate phosphabetaines, unsaturated monocarboxylic acids, phosphonium salts

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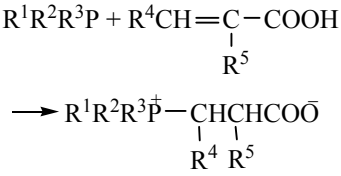
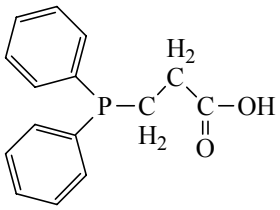
We previously described the syntheses of various phosphabetaines from tertiary phosphines and unsaturated mono- and dicarboxylic acids and the results of their structural assessment and reactivity studies [1–10].



$R^1 = R^2 = R^3$ = Ph, Bu, C_6H_{11}; R^4 = H, CH_3, Ph, COOH; R^5 = H, CH_3.

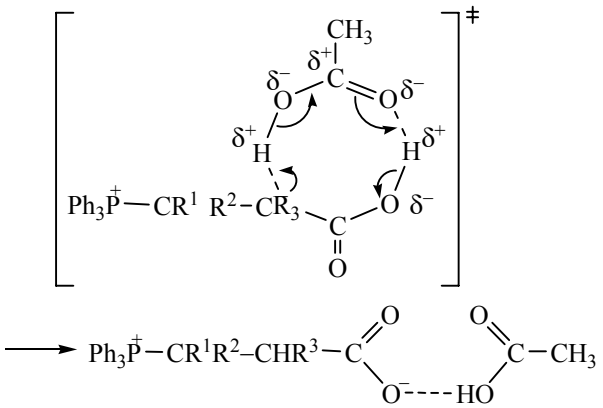
In the present work we set ourselves the task to synthesize new stable dicarboxylate phosphabetaines on the basis of unsaturated monocarboxylic acids. As a tertiary phosphine phosphorylating agent we for the first time used 3-(diphenylphosphino)propanoic acid which is interesting in that it contains not only a tertiary phosphorus atom, but also a carboxylic group (Scheme 1).

Scheme 1.

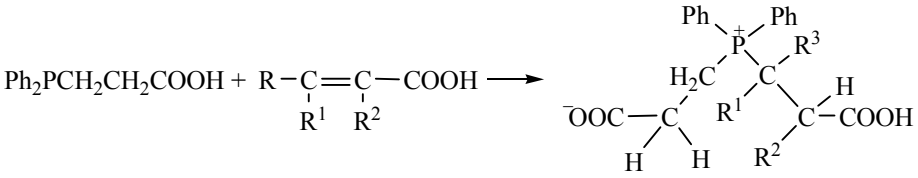


In our previous research on the kinetcs and mechanism of reactions of tertiary phosphines with unsaturated carboxylic acids in various reaction media we found that the phosphorus quaternization process is solvent-dependent and not always requires the third (proton-donor) molecule to be involved [11–14]. It is interesting to note that the carboxylic group of the substrate was not involved in quaternization, and proton was transferred either from the solvent or from the second molecule of the unsaturated carboxylic acid (Scheme 2).

Scheme 2.



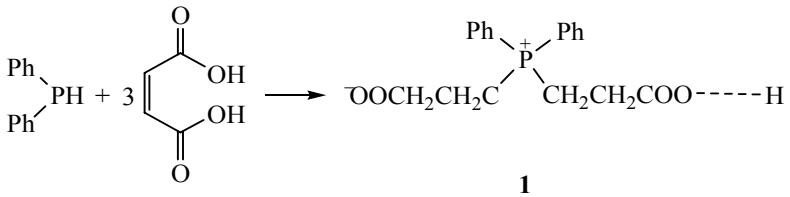
Scheme 3.



1–4

$R^1 = R^2 = R^3 = H$ (**1**); $R^1 = Me$, $R^2 = R^3 = H$ (**2**); $R^1 = R^2 = H$, $R^3 = Me$ (**3**); $R^1 = Ph$, $R^2 = R^3 = H$ (**4**).

Scheme 4.



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Consequently, we suggested that in the present case the carboxyl proton of the phosphorylating agent, namely, 3-(diphenylphosphino)propanoic acid, would act as an additional proton donor.

To check this suggestion, we reacted 3-(diphenylphosphino)propanoic acid with a series of monocarpboxylic acids: acrylic, crotonic, methacrylic, and cinnamic. The reactions all gave stable target products **1**–**4** (Scheme 3). The structure of these compounds was proved by IR and ^1H, ^{31}P, and ^{13}C spectroscopy, as well as differential scanning calorimetry (DSC) and thermo-gravimetry (TG). The composition of the products was confirmed by their elemental analyses.

The reaction of 3-(diphenylphosphino)propanoic acid with acrylic acid smoothly occurs in ethyl acetate (3–5 min) and acetonitrile (1 h).

Apparently, compound **1** has a symmetric structure with respect to the phosphonium center. The IR spectrum shows a single broad band near 1680 cm^{-1}. Consequently, the reaction product does not contain the COOH group per se, which absorbs near 1600 cm^{-1}. Most likely, the negative charge is delocalized over two carboxylic groups and, therefore, the only proton is equally remote from the oxygen atoms of both carboxyls.

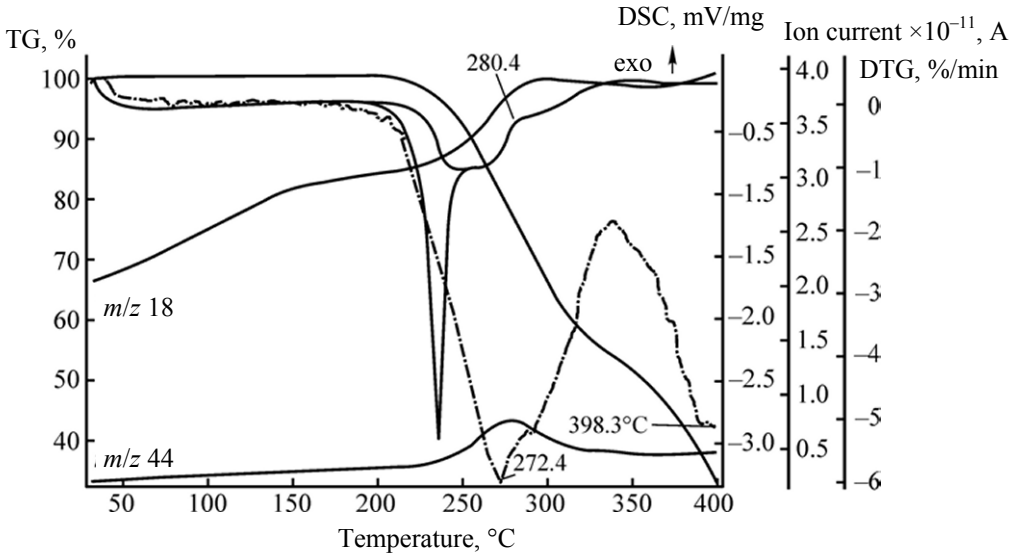
The ^{13}C NMR spectra of compounds **2**–**4** show two doublet signals at 175–180 ppm (J_{CP} 12–17 Hz), which, too, is evidence for the presence of two groups: carboxyl and carboxylate. The spectrum of compound **1** contains only one doublet signal at 175 ppm, which is explained by the symmetry of the molecule with respect to the phosphonium center and magnetic equivalence of the carbon atoms.

It should be noted that dicarboxylate phosphabetaine **1** was earlier prepared by Van Doorn and Wife [15] by the reaction of diphenylphosphine and maleic anhydride. In fact, the reaction involved maleic acid, because the anhydride ring was opened with aqueous alkali. Compound **1** was obtained in a 58% yield in THF under reflux at the starting reagent ratio 1 : 3 (Scheme 4).

Obviously, at the first stage diphenylphosphine adds by the C=C bond of maleic acid, after which decarboxylation and formation of 3-(diphenylphosphino)propanoic acid, the starting tertiary phosphine in our present work, take place. This phosphine then reacts with the second maleic acid molecule also by the C=C bond with analogous decarboxylation of the α-carboxyl group of the intermediate to form dicarboxylate phosphabetaine **1**. The third maleic acid molecule is likely to act as an external proton donor, in keeping with the above-described reaction mechanism.

The spectral characteristics of betaine **1** obtained in the present work are consistent with those in [15].

Thermogravimetry and differential scanning calorimetry revealed a high thermal stability of phosphabetaine **1**. The TG–DSC curve (see figure) shows a well-defined endothermic effect with its maximum at 236°C, which is associated with a weight loss. The decomposition of phosphabetaine **1** involves water and



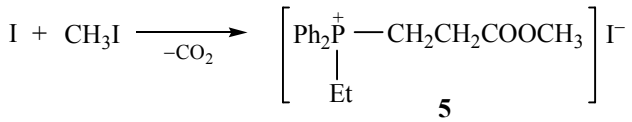
TG–DSC curve of phosphabetaine **1**.

CO_2 release. The absence of weight loss in the range 30–226°C is indicative of a high thermal stability of this compound.

The reactions of 3-(diphenylphosphino)propanoic acid with crotonic, methacrylic, and cinnamic acids in ethylacetate or acetonitrile are complete in 1 day and form the target betaines **2**–**4** as white crystals in 67–76% yields.

Previously we found [3–6] that structurally similar phosphabetaines with various substituents at the phosphorus atom are easily alkylated with alkyl halides. The composition and structure of the resulting phosphonium salts were confirmed by elemental analysis, NMR and IR spectroscopy, and X-ray diffraction analysis. In the present work we performed alkylation of compound **1** with methyl iodide. The latter was also used as a solvent, but because of the limited solubility of the dicarboxylate phosphabetaine in it we had to add a little ethanol to the reaction mixture. The reaction proceeded at room temperature for 2 weeks and was accompanied by decarboxylation, thus providing indirect evidence showing that the starting compound contains two carboxylic groups. The reaction gave ethyl (3-methoxy-3-oxopropyl)diphenylphosphonium iodide (**5**) in 82% yield.

Scheme 5.

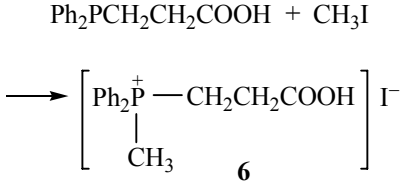


The structure of salt **5** was confirmed by ^{1}H and ^{13}C NMR spectrum. The ^{31}P NMR spectrum shows a quaternary phosphorus signal at 24 ppm (Scheme 5).

Of particular interest was alkylation of the very phosphorylating agent, 3-(diphenylphosphino)propanoic acid, with methyl iodide. This reaction gave the corresponding phosphonium salt (2-carboxyethyl)-(methyl)diphenylphosphonium iodide (**6**) in ≈80% yield. The composition and structure of the product were confirmed by elemental analysis and NMR and IR spectroscopy (Scheme 6).

Thus, the studied alkylation reactions make it possible to attach various substituents to a tertiary phosphorus atom to obtain corresponding phosphonium salts. Previously we showed [16] that the biological activity of phosphonium salts increases with increasing carbon chain length in the alkyl substituents (from 10 to 18 carbon atoms), such reactions provide great scope for the synthesis of new biologically active compounds.

Scheme 6.



EXPERIEMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra ($CDCl_3$) were registered on a Bruker Avance-400 instrument. The IR spectra were obtained on an IR Prestige-21 instrument in the range 400–3700 cm^{-1} in mineral oil or in thin film between KBr plates.

Thermal stability was studied using a Netzsch Jupiter STA 449C mictotermoanalyzer for smultaneous thermogravimetric analysis and differential scanning calorimetry, coupled with a Netzsch QMS 403C Aeolos mass spectrometer; the samples were heated at a rate of 10 deg/min in an argon atmosphere.

3-[(2-Carboxyethyl)diphenylphosphonium]propanoate (1). A solution of 0.08 g (0.0012 mol) of acrylic acid in 3 mL of acetonitrile was added to a solution of 0.3 g (0.0012 mol) of 3-(diphenylphosphino)propanoic acid in 5 mL of acetonitrile at room temperature and continuous stirring. A white precipitate formed and was filtered off, washed many times with diethyl ether, and dried in a vacuum. Yield 0.458 g (80.86%), white powder, mp 236°C. IR spectrum, ν, cm^{-1}: 1680 (COO^-).^1H NMR spectrum (D_2O), δ, ppm: 2.38–2.45 m [4H, $CH_2C(O)$], 3.04–3.11 m (4H, PCH_2), 7.57–7.76 m (10H, Ar). ^{13}C NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 16.73 d (PCH_2, $^1J_{PC}$ 53.0), 27.28 d ($PCH_2\underline{CH_2}$, $^2J_{PC}$ 3.0), 116.51 d (C^{ipso}, $^1J_{PC}$ 85.0), 129.99 d (C^o, $^2J_{PC}$ 13.0), 132.86 d (C^m, $^3J_{PC}$ 10.0), 135.03 d (C^p, $^4J_{PC}$ 3.0), 175.87 d [C(O)O, $^3J_{PC}$ 14.5]. ^{31}P NMR spectrum (D_2O): δ_P 26.5 ppm. Found, %: C 66.27; H 5.50; P 9.09. $C_{18}H_{19}O_4P$. Calculated, %: C 65.45; H 5.85; P 9.39.

3-[(2-Carboxypropyl)diphenylphosphonium]propanoate (2) was prepared in a similar way from 0.5 g (0.0019 mol) of 3-(diphenylphosphino)propanoic acid and 0.17 g (0.0016 mol) of crotonic acid. Yield 0.496 g (74.03%), colorless crystals, mp 176°C. IR spectrum, ν, cm^{-1}: 1630 s (COO^-), 1710 s (COOH). ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 1.09–1.16 d.d (3H, CH_3, $^3J_{PH}$ 18.5, $^3J_{HH}$ 7.0), 1.9–1.99 m (2H, PCH_2), 2.29–2.43 m (1H, PCH), 2.56– 2.68 m (2H, $PCH\underline{CH_2}$), 3.00–3.07 m (2H, $PCH_2\underline{CH_2}$), 7.38–7.76 m (10H, Ar). ^{13}C NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 12.5 d ($CH\underline{CH_3}$, $^2J_{CP}$ 2.0), 15.96 d (PCH_2, $^1J_{CP}$ 52.0), 23.56 d ($P\underline{CH}CH_3$, $^1J_{CP}$ 72.0), 26.30 d ($PCH_2\underline{CH_2}$, $^2J_{CP}$ 3.0), 27.05 d ($PCH\underline{CH_2}$,$^2J_{CP}$ 3.0), 114.26 d (C^{ipso}, $^1J_{CP}$ 84.0), 129.75 d (C^o, $^2J_{CP}$ 12.0), 130.08 d (C^m, $^3J_{CP}$ 11.0), 132.93 d (C^p, $^4J_{CP}$ 3.0), 175.3 d [C(O)O, $^3J_{CP}$ 17.0], 176.42 d [C(O)O, $^3J_{CP}$ 15.0]. ^{31}P NMR spectrum (D_2O): δ_P 33.48 ppm. Found, %: C 65.43; H 5.34; P 8.84. $C_{19}H_{21}O_4P$. Calculated, %: C 65.30; H 5.50; P 8.76.

3-[(1-Carboxypropan-2-yl)diphenylphosphonium]propanoate (3) was prepared in a similar way from 0.5 g (0.0019 mol) of 3-(diphenylphosphino)propanoic acid and 0.17 g (0.0020 mol) of methacrylic acid. Yield 0.453 g (67.16%), white crystals, mp 79°C. IR spectrum, ν, cm^{-1}: 1620 (COO^-), 1680 (COOH). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15 d.d (3H, CH_3, $^4J_{PH}$ 10.0, $^3J_{HH}$ 7.0), 2.37–2.49 m [1H, $\underline{CH}(CH_3)$], 2.54 d.d (2H, $P\underline{CH_2}CH$, $^2J_{PH}$ 15.0, $^3J_{HH}$ 5.5), 2.61 m (2H, $P\underline{CH_2}CH_2$), 3.28 m [2H, $\underline{CH_2}C(O)$], 7.49–7.74 m (10H, Ar), 8.5 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 17.56 d ($P\underline{CH_2}CH_2$, $^1J_{PC}$ 52.0), 19.32 d ($PCH_2\underline{CH}$, $^2J_{PC}$ 9.0), 25.56 d ($P\underline{CH_2}CH$, $^1J_{PC}$ 51.0), 27.21 d ($PCH_2\underline{CH_2}$, $^2J_{PC}$ 3.0), 34.8 (CH_3), 116.51 d (C^{ipso}, $^1J_{PC}$ 85.0), 129.99 d (C^o, $^2J_{PC}$ 13.0), 132.86 d (C^m, $^3J_{PC}$ 10.0), 135.03 d (C^p, $^4J_{PC}$ 3.0), 172.80 d [C(O)O, $^3J_{PC}$ 3.7], 176.16 d [C(O)O, $^3J_{PC}$ 15.3]. ^{31}P NMR spectrum ($CDCl_3$): δ_P 27.1 ppm. Found, %: C 69.48; H 5.19; P 7.76. $C_{19}H_{21}O_4P$. Calculated, %: C 69.70; H 5.13; P 7.89.

3-[(2-Carboxy-2-phenylethyl)diphenylphosphonium]propanoate (4) was prepared in a similar way from 0.3 g (0.0012 mol) of 3-(diphenylphosphino) propanoic acid and 0.17 g (0.0012 mol) of cinnamic acid. Yield 0.512 g (76.12%), white crystals, mp 193–197°C. IR spectrum, ν, cm^{-1}: 1590 (COO^-), 1700 (COOH). ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 2.58 m (2H, $P\underline{CH_2}CH_2$), 3.52 d.d (2H, $PCH\underline{CH_2}$, $^2J_{PH}$ 11.0, $^3J_{HH}$ 7.0), 3.44 m (2H, $P\underline{CH_2}CH_2$), 3.61–3.72 m (1H, PCH), 7.35–7.81 m (15H, Ar). ^{13}C NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 16.75 d ($P\underline{CH_2}CH_2$), 27.03 d ($PCH_2\underline{CH_2}$), 35.27 d ($PCH\underline{CH_2}$, $^2J_{PC}$ 9.0), 65.72 d ($P\underline{CH}CH_2$, $^1J_{PC}$ 61.0), 115.68 d (C^{ipso}, $^1J_{PC}$ 84.0), 124.77 d (C^p, $^5J_{PC}$ 2.0), 127.18 d (C^m, $^4J_{PC}$ 3.0), 128.34 d (C^o, $^3J_{PC}$ 7.0), 129.95 d (C^o, $^2J_{PC}$ 13.0), 132.54 d (C^m, $^3J_{PC}$ 10.0), 134.87 d (C^p, $^4J_{PC}$ 2.0), 135.13 d (C^{ipso}, $^2J_{PC}$ 10), 174.50 d [C(O)O, $^3J_{PC}$ 12.0], 177.16 d [C(O)O, $^3J_{PC}$ 15.0]. ^{31}P NMR spectrum (H_2O): δ_P 30.77 ppm. Found, %: C 70.1; H 5.34; P 7.94. $C_{19}H_{21}O_4P$. Calculated, %: C 70.4; H 5.66; P 7.64.

Ethyl(3-methoxy-3-oxopropyl)diphenylphosphonium iodide (5). Methyl iodide, 0.07 mL (0.0012 mol) was added to a solution of 0.4 g (0.0012 mol) of betaine **1** in 1.5 mL of ethanol. The reaction mixture was leave to stand at room temperature for 2 weeks. The solvent was removed in a vacuum. The residue was an oily substance. ^1H NMR spectrum ($CDCl_3$), δ,

ppm (J, Hz): 1.14 m (3H, $PCH_2\underline{CH_3}$), 2.18 s [3H, OCH_3), 2.71 m (2H, $P\underline{CH_2}CH_2$), 3.55 m (2H, $P\underline{CH_2}CH_3$), 3.97 m [2H, $CH_2C(O)$], 7.65–7.87 m (10H, Ar). ^{13}C NMR spectrum (D_2O), δ_C, ppm (J, Hz): 14.05 d ($PCH_2\underline{CH_3}$, $^2J_{PC}$ 2.0), 18.14 d ($P\underline{CH_2}CH_3$, $^1J_{PC}$ 43.0), 18.39 d ($P\underline{CH_2}CH_2$, $^1J_{PC}$ 53.0), 27.17 d ($PCH_2\underline{CH_2}$, $^2J_{PC}$ 2.7), 61.81 (OCH_3), 116.51 d (C^{ipso}, $^1J_{PC}$ 84.0), 130.58 d (C^o, $^2J_{PC}$ 20.0), 133.41 d (C^m, $^3J_{PC}$ 9.0), 135.29 d (C^n, $^4J_{PC}$ 2.0), 170.62 d [C(O)O, $^3J_{PC}$ 8.0]. ^{31}P NMR spectrum (H_2O): δ_P 27.37 ppm

(2-Carboxyethyl)(methyl)diphenylphosphonium iodide (6). Methyl iodide, 0.17 mL (0.0019 mol), was added to a solution of 0.5 g (0.0019 mol) of 3-(diphenylphosphino)propanoic acid in 1.5 mL of acetonitrile. The reaction mixture was leave to stand at room temperature for 1 week. The solvent was removed in a vacuum, and the residue was washed with diethyl ether and dried in a vacuum. Yield 0.605 g (79.6%), mp 138°C. ^1H NMR spectrum (D_2O), δ, ppm (J, Hz): 2.42 d (3H, PCH_3, $^1J_{PH}$ 13.9), 2.54–2.61 m (2H, PCH_2), 3.06–3.13 m [2H, $CH_2C(O)$], 7.55–7.73 m (10H, Ar). ^{13}C NMR spectrum (D_2O), δ_C, ppm (J, Hz): 6.00 d (PCH_3, $^1J_{PC}$ 56.3), 18.00 d (PCH_2, $^1J_{PC}$ 55.5), 26.40 d [$CH_2C(O)$, $^2J_{PC}$ 1.4], 118.40 d (Ph, $^1J_{PC}$ 88.4), 129.92 d (Ph, $^2J_{PC}$ 12.6), 132.19 d (Ph, $^3J_{PC}$ 10.5), 134.86 d (Ph, $^4J_{PC}$ 3.0), 174.63 d [C(O)OH, $^3J_{PC}$ 14.0]. ^{31}P NMR spectrum (H_2O): δ_P 23.49 ppm.

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