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The Synthesis and Reactions of Betaines Formed in Reactions of Tertiary Phosphines with Unsaturated Carboxylic Acids and Their Derivatives

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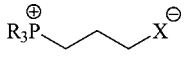
ABSTRACT: *On the basis of our systematic investigations, the main trends concerning synthesis, structure, and reactivity of carboxylate phosphabetaines—phosphorus analogs of organic aminoacids—are considered and analyzed. A wide series of phosphabetaines has been obtained in reactions of tertiary phosphines with unsaturated mono- and dicarboxylic acids, and also with their derivatives—esters and amides. By a plethora of experimental and theoretical methods, it has been shown that the thermodynamic stability of carboxylate phosphabetaines essentially depends on the structure of the initial phosphine and carboxylic acid. In some cases, the reaction between them is equilibrated. On the other hand, for a number of synthesized betaines, it is reliably established that these exist in equilibrium with isomeric phosphoranes. The extremely important condition for stabilization of phosphabetaine structures is the presence of proton-donating reagents, which are included in their crystal lattice. In the series of symmetrically substituted derivatives, the interesting phenomenon of phosphorotropy of the phosphonium group is established. The reactivity of phosphabetaines in reactions with electrophilic reagents (haloid alkyls and acyls, isocyanates, corbodiimides) has been investigated. The majority of key structures have been confirmed by the direct X-ray method.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:557–566, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20276

INTRODUCTION

One of the most interesting classes of organophosphorus compounds, interest in which has sharply increased recently, is the so-called phosphabetaines. In these internal phosphonium salts, cationic phosphoniun and anionic centers, are connected with each other by not only ionic but also by covalent bonds.



X = C, S, O, N

The interest in similar structures stems from the fact that very often they arise as intermediates

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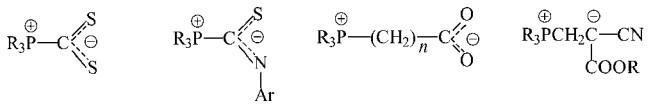
Contract grant sponsor: Scientific-Technical Program "Russian Universities."

in many important organophosphorus reactions, though there is a relatively small number of stable phosphabetaines, some of which are shown below.

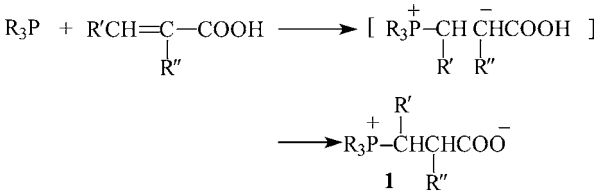


The sharply growing interest in this class of compounds becomes quite understandable when we take into account the fact that phosphabetaines are also the original analogs of organic amino acids, with a wide spectrum of potential chemical and biological properties.

RESULTS AND DISCUSSION

Phosphabetanies on the Basis of Tertiary Phosphines and Unsaturated Monocarboxylic Acids and Their Derivatives

In the past years, our group carried out regular research on the synthesis, structure, and reactivity of phoshabetaines of type **1**, obtained on the basis of tertiary phosphines and unsaturated carboxylic acids [1–14]. The results are presented in this short review.



R′ = H, Ph, *p*-$CH_3OC_6H_4$; R″ = H, CH_3

R = Ph, Bu;

Thus, the essential role of proton-donating reagents and solvents in stabilizing phosphabetainic structures (that is, to stabilize strongly divided charges) has been established [1–4]. For instance in Fig. 1, one can see a molecule of water in the crystal lattice of betaine of type **1** (R = Ph, R′ = R″ = H).

In the reactions of phosphabetaines with aromatic carboxylic acids, it was possible to see the formation of the isomeric phosphorane structure **2** [5,7,12,14]:

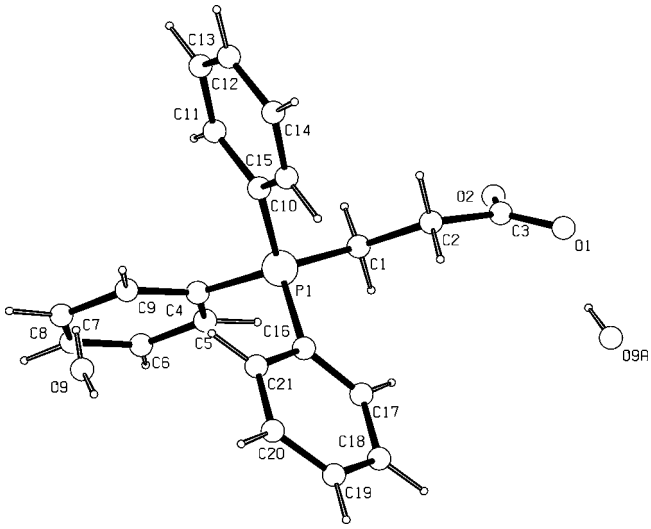
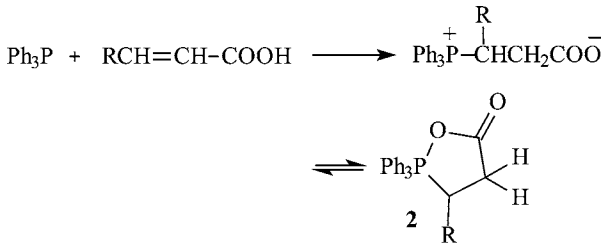
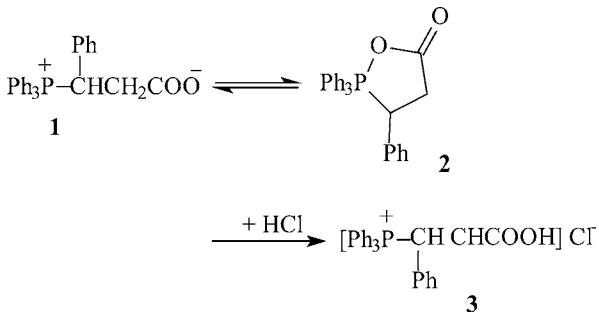


FIGURE 1 Molecular structure of β-triphenylphosphonium ethylcarboxylate **1**.



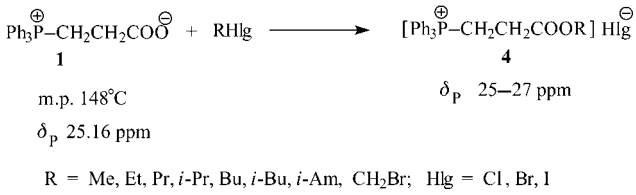
R = Ph, *p*-$CH_3OC_6H_4$

Additional stabilization of phosphoranes in this case is probably promoted by aryl substituents raising the thermodynamic stability of the five-membered phosphorane cycle. Additional proof of phosphorane formation in these reactions is the fact that the addition of HCl to the reaction mixture containing betaine—obtained on the basis of cinnamic acid and isomeric phosphorane—leads to the formation of a cristalline product with melting point 176–181°C, which correspond to the betaine. Addition of a molecule of HCl leads to the formation of phosphonium salt **3**.



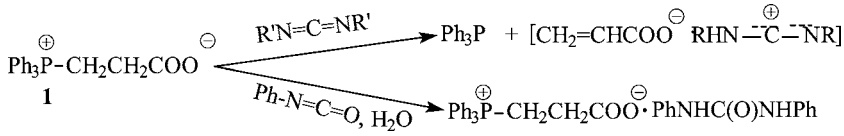
The molecular structure of salt **3** is presented in Fig. 2. An additional molecule of solvent (chloroform) is included in the crystal lattice.

Betaines of type **1** easily react with alkyl halogenides and acyl halogenides to form the corresponding phosphonium salts **4** [1–4,7,12].



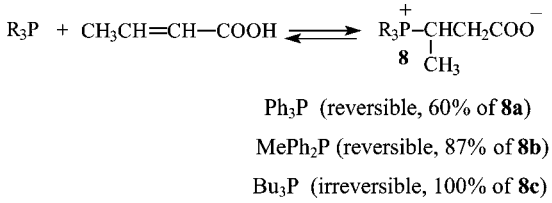
The composition and structure of phosphonium salts **4** have been confirmed by the data of elemental analysis, IR, ^{1}H, and ^{31}P NMR spectroscopy, and for two compounds by the direct method of X-ray analysis (Figs. 3 and 4). It is remarkable that phosphonium salts, distinct from betaine itself, are not so inclined to include a molecule of proton-donating reagents in a crystal lattice.

The reactivity of betaine **1** in reactions with other electrophilic reagents (isocyanates and carbodiimides) has also been studied [1–4,7,12,14].



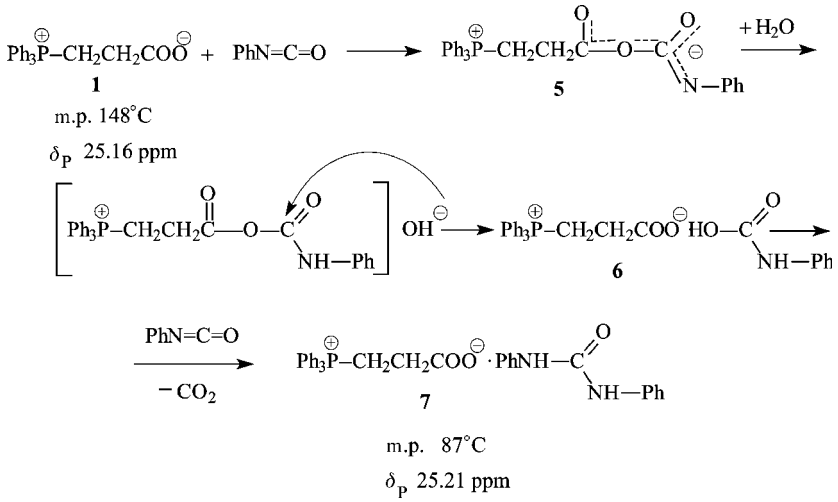
The mechanism of the previous reaction has been studied by kinetics. The product structure has been confirmed by X-ray analysis (Fig. 5).

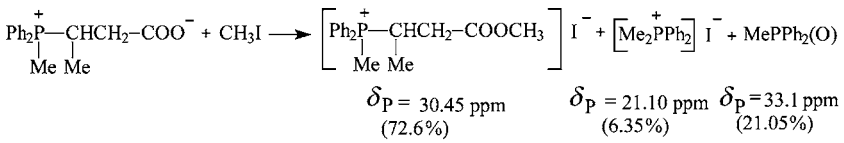
The reaction of triphenylphosphine with crotonic acid in acetronitrile proceeds with the formation of corresponding phosphabetaine **8a**, and according to ^{31}P NMR data is equilibrated. A 60% maximum conversion is achieved.



As expected, the involvement of more basic methyldiphenylphosphine in this reaction results in the displacement of the equilibrium to the product side (**8b**), 87%. Even more basic tributhylphosphine makes this reaction completely irreversible (product **8c**) [14].

It is interesting to note that the alkylation of betaines **8a,b**, obtained in reversible reactions of triphenyl- and methylphenylphosphine with crotonic acid, proceeds with more difficulty. In this case, there is also formation of the corresponding salt **8ba**. However, according to ^{31}P NMR data, there are two additional signals in the reaction mixture, one of which belongs to methyldiphenylphosphonium iodide **8bb** and the second to methyldiphenylphosphine oxide **8bc**.

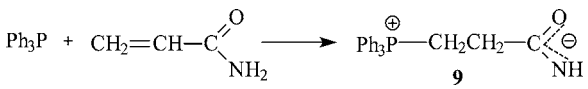




8b **8ba** **8bb** **8bc**

The formation of salt **8bb** is quite normal, if we take into account the equilibrium character of the reaction of formation of betaine **8b** itself, which implies the presence of free methyldiphenylphosphine in the equilibrium mixture. The formation of phosphine oxide **8bc** is also not surprising and proceeds, more probably, through the intermediate formation of the isomeric (in relation to phosphabetaine) unstable phosphorane of type **2** with P—O bond, which then decomposes to phosphine oxide. Similar reactions were repeatedly observed earlier for betaines from triphenylphosphine. During these studies, it was interesting to extend this investigation to other unsaturated carboxylic acids, and also their derivatives—esters and amides. Until now, it was not possible to obtain the products of betainic structure with the last derivatives [11,14].

The reaction with acrylamide proceeds easily enough with the formation of the corresponding betaine **9**, insoluble in most of the organic solvents [11,14]:



However, crystals suitable for X-ray analysis, were obtained only in the presence of fumaric acid, which, obviously, plays the role of co-crystallizing substance and proton-donating reagent (Fig. 6). As mentioned earlier, in a crystal lattice of betaine **9**, there is a molecule of water.

Tertiary Phosphines in Reactions with Unsaturated Dicarboxylic Acids and Their Derivatives

We have also investigated the reactions of phosphines with unsaturated dicarboxylic acids [5,6,8–10,13,14], in which the second carboxylic group would be the internal proton-donating center and thus would promote the increase in stability of the betaines formed.

It has been shown that toxylic acid reacts with triphenylphosphine under mild conditions in diethyl ether medium, forming an insoluble product in organic solvents adduct with a m.p. 67–72°C (with decomposition), which according to

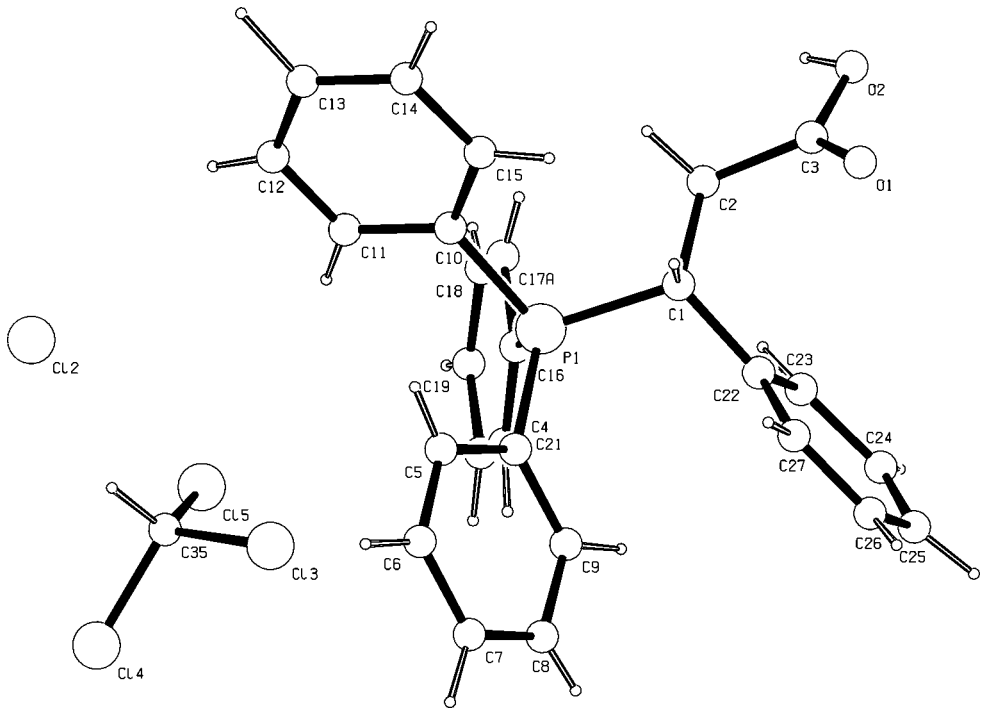


FIGURE 2 Molecular structure of β-carboxyethyl phosphonim chloride **3**.

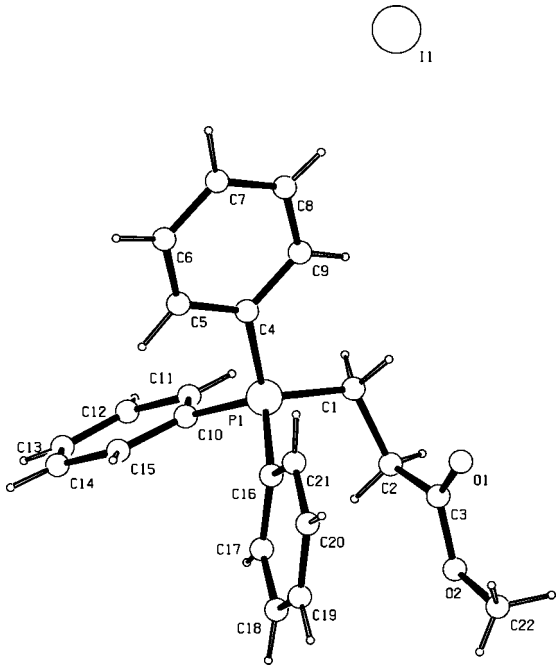
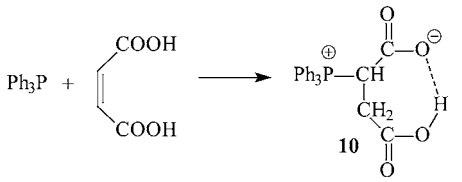
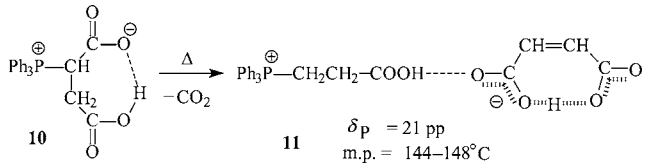


FIGURE 3 Molecular structure of β-carboxymethyl phosphonim iodide.

the IR data is the target dicarboxylate betaine **10**.



However, this betaine is unstable upon heating and sometimes simply on storage, it easily eliminates a molecule of CO_2 with formation of the phosphonium salt **11**, representing the already well-known betaine **1** (R = Ph, R′ = R″ = H), stabilized by a molecule of toxylic acid.



The formation of product **11** accompanying the elimination of CO_2, which was trapped in the experiment on thermal destruction, does not leave any doubt about the structure of the initial betaine **10**.

Because betaine **1** is a weaker acid than toxylic acid, the full transfer of a proton from the last to the first takes place in adduct **11**, which is identified by X-ray analysis (Fig. 7). There is also a strong

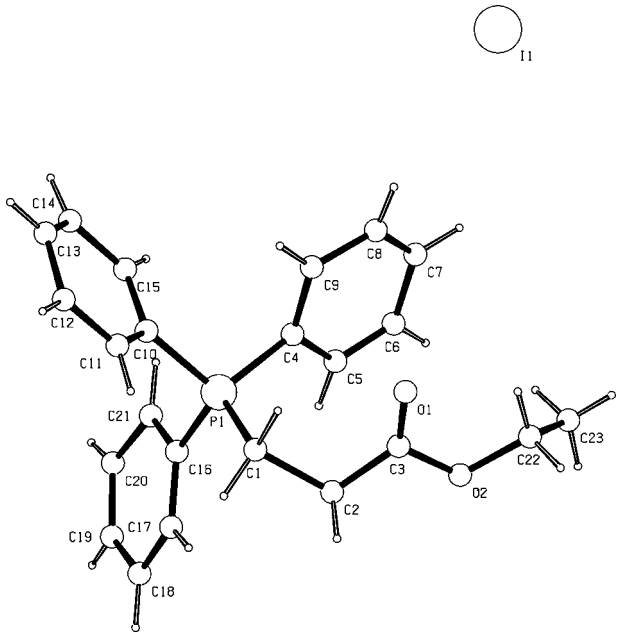


FIGURE 4 Molecular structure of β-carboxyethyl phosphonim iodide.

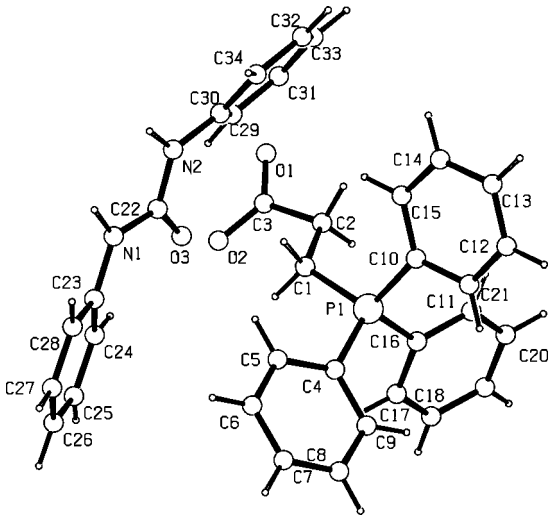


FIGURE 5 Molecular structure of the complex of phosphabetaine with diphenylurea **7**.

hydrogen bond between the protonated betaine and the toxylic anion. Product **11**, unlike betaine **10**, is well soluble in organic solvents. Because of this, its structure was reliably confirmed again by spectral methods (IR and NMR), and then by direct X-ray analysis.

The full proton transfer from toxylic acid to betaine **1** (R = Ph, R′ = R″ = H) in the adduct **11** results in its inertness in previously investigated reactions of alkylation by halogen alkyls.

The reaction of triphenylphosphine with fumaric acid proceeds only at high temperature; hence, it is not possible to identify the intermediate

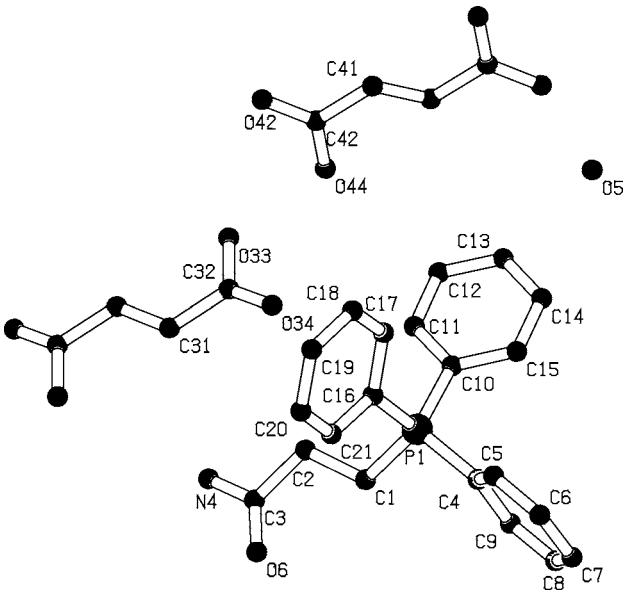
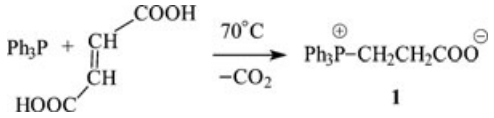
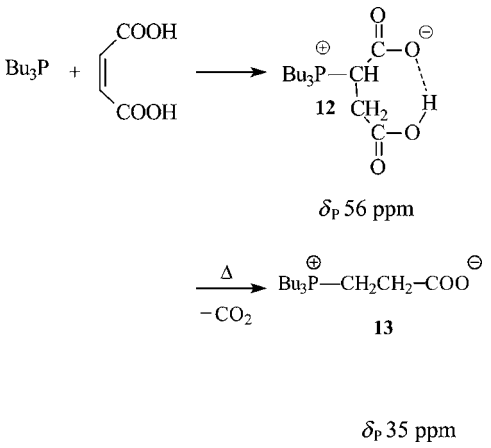


FIGURE 6 Molecular structure of phosphabetaine **9** (without hydrogen atoms).

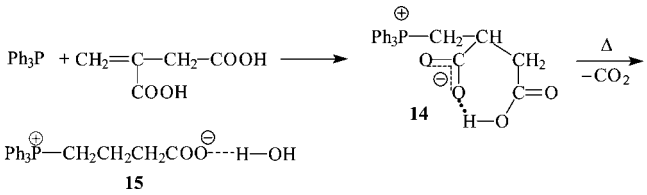
containing an initial dicarboxylic acid. In this reaction, only betaine **1** (R = Ph, R′ = R″ = H) has been obtained, stabilized by one acetonitr molecule. Its structure was confirmed by using IR and NMR spectroscopy methods, and also by X-ray analysis (Fig. 8).



Reaction of tributhylphosphine with toxylic acid proceeds as well as in the case of triphenylphosphine, with the initial formation of dicarboxylate betaine **12**, with δ_p 56 ppm, which in the reaction conditions, is easily decarboxylated to form the tributylphosphonium ethylcarboxylate **13**, with δ_p 35 ppm (Fig. 9).



During our research, we reacted itaconic acid in reaction with triphenylphosphine, in the hope that the product of this reaction, which is distinct from similar products obtained with fumaric and toxylic acids, should be more stable because the nearest carboxylate group in the formed betaine will not be in α- but in β-position in relation to the phosphonium center.



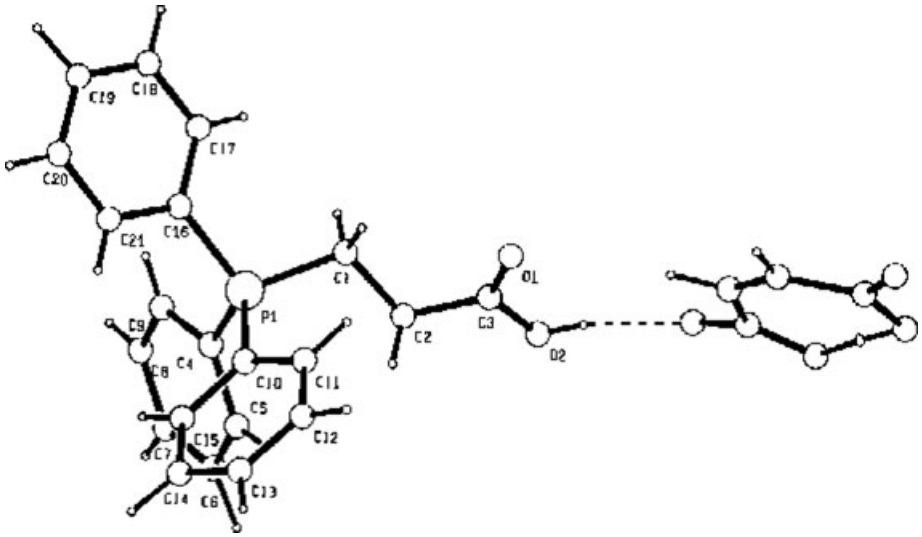


FIGURE 7 Molecular structure of β-carboxyethyl triphenylphosphonim toxylate 11.

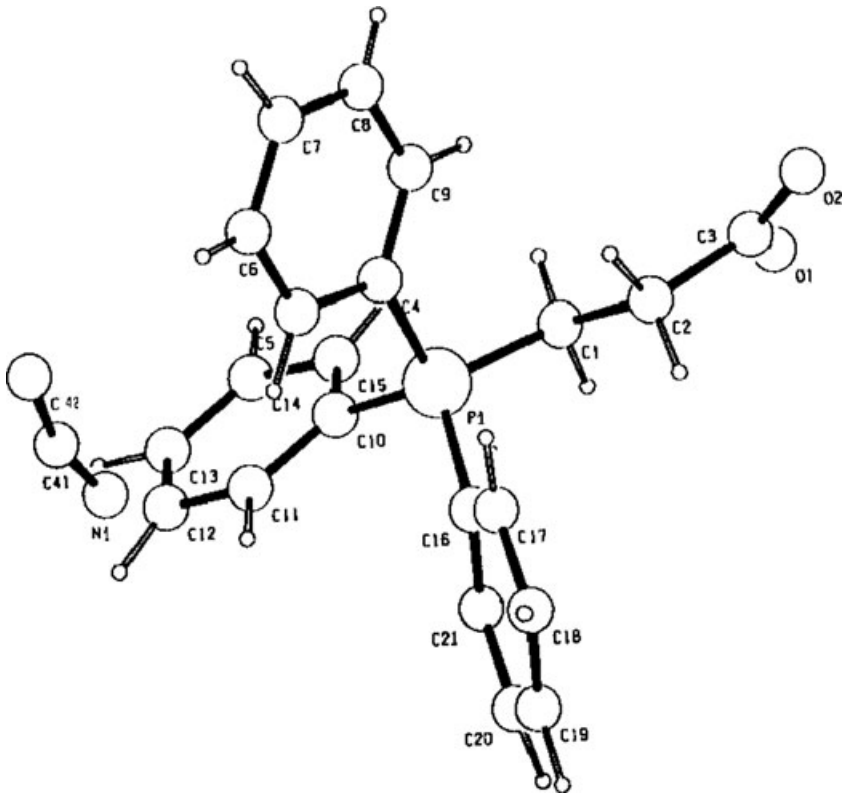


FIGURE 8 Molecular structure of betaine **1**, obtained in the reaction of triphenylphosphine with fumaric acid.

Indeed, this reaction proceeds smoothly with the formation of one crystal product **14** with δ_p 23.9 ppm and m.p. 58–60°C (with decomposition). In the IR spectrum of the product, both the carboxylic centers are precisely visible: a carboxyle COOH group in the field of 1700 cm^{-1} and a carboxylate anion in the characteristic area of 1600 cm^{-1} (Fig. 10).

The NMR spectrum also fully corresponded to the expected phosphabetaine structure. The product obtained was much more stable in comparison with betaines derived from toxylic and fumaric acids and did not differ in high stability. When melting or boiling in the chloroform medium, the clear decomposition with CO_2 elimination are observed. We carried out the preparative reaction of decarboxylation and separated the product phosphabetaine **15** with m.p.

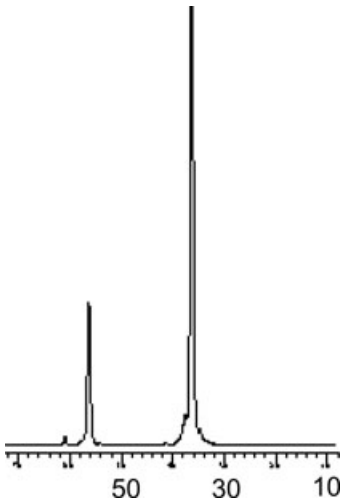


FIGURE 9 ^{31}P NMR spectrum of the reaction mixture in the reaction of tributhylphosphine with toxylic acid.

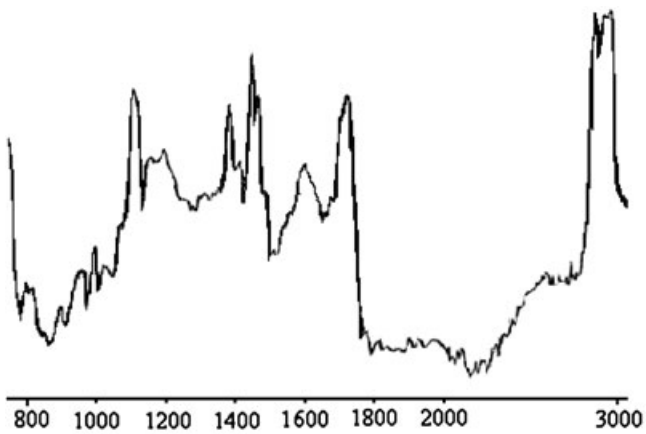


FIGURE 10 IR Spectrum of phosphabetaine **14**.

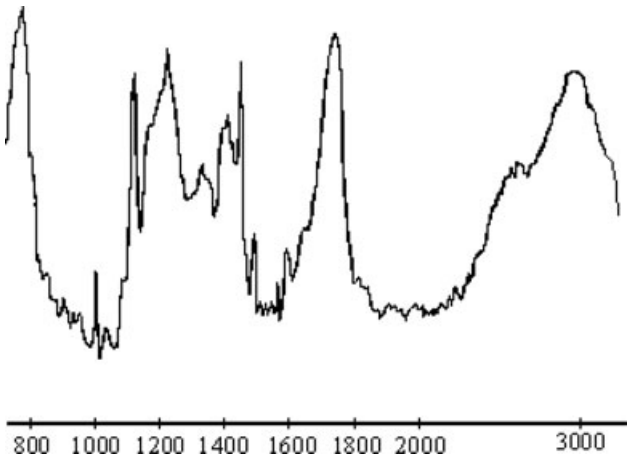


FIGURE 11 IR Spectrum of product **15**.

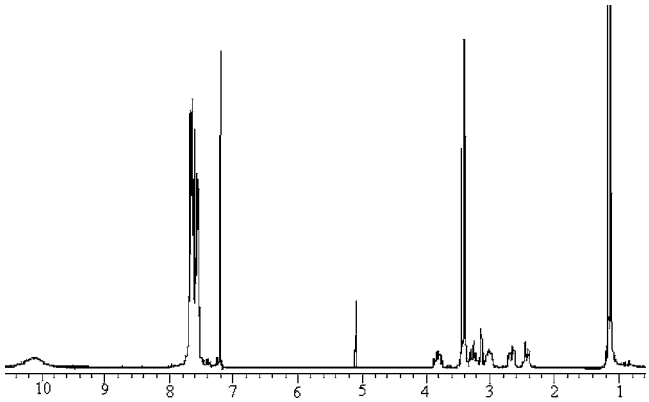
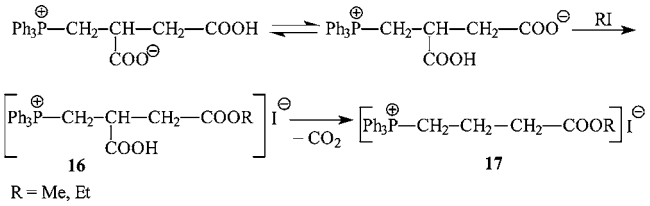


FIGURE 12 ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of phosphonium salt **16** (R = Et).

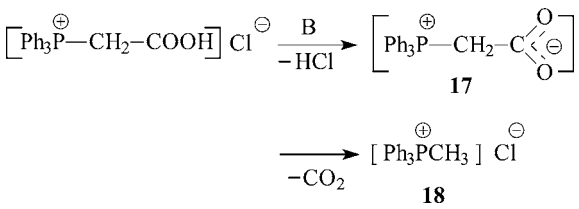
53–57°C and δ_p 22.45 ppm, which undergoes easy hydration by air moisture with formation of the corresponding phosphonium salt. In the IR spectrum of this product, there is no characteristic absorption of carboxylate anion, and there is only a characteristic absorption of one carboxyl group at 1720 cm^{-1} (Fig. 11).

To increase the stability of dicarboxylate phosphabetaine, we carried out its alkylation reactions with methyl and ethyl iodides. Reactions proceeded quantitatively under mild conditions. The alkylation, in our opinion, proceeded on the more distant carboxylic group, which is more basic.



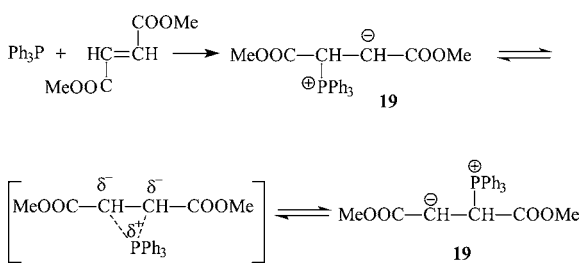
The structure of products obtained was reliably confirmed by IR and NMR spectroscopy. In particular, in an ^{1}H NMR spectrum of product **16** (Fig. 12), the signals of ethyl, methylene, phenyl, and also OH groups protons are clearly visible. The obtained phosphonium salts is also quite stable. Besides, when heated or stored for a long time, they undergo oxidation–reduction decomposition with the elimination of elementary iodine.

Therefore, the investigation shows the essential specificity in behavior of unsaturated carboxylic acids in reactions of betaine formation. It is connected with thermodynamic instability of structures with α-arrangement of phosphonium and carboxylate centers. This supports literature data [15] concerning unsuccessful attempts of obtaining triphenylphosphonium methylcarboxylate **17**. In this case, the process of decarboxylation with elimination of CO_2 and the formation of triphenylphosphonium chloride **18** had also taken place.



The interaction of triphenylphosphine with dimethyl ester or fumaric acid proceeds according to the following scheme [11,14] (Scheme 1).

In chloroform medium, according to NMR and IR spectroscopic data, the reaction proceeds smoothly enough with the formation of one product **19**, with phosphorus nuclear chemical shift of 29.35 ppm. The signal of initial triphenylphosphine disappears almost completely. In the ^{1}H NMR spectrum of the product obtained (Fig. 13), the protons of phenyl substituents at phosphorus, and signals



SCHEME 1

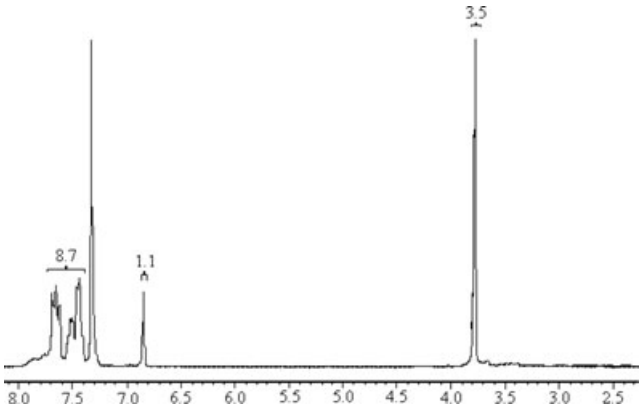
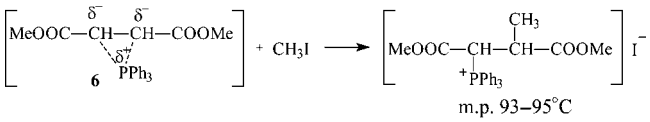


FIGURE 13 ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of phosphabetaine **19**.

corresponding to methyl and methyne protons, are clearly visible.

However, it is surprising that both methyl and methyne protons are shown in ^{1}H NMR spectrum as singlets, displaced in comparison with the protons of the initial dimethyl ester of fumaric acid toward low field by ca 0.2 ppm. The equivalence of methyl and methyne protons in the reaction product unequivocally indicates the presence of fast in NMR time scale migration of the triphenylphosphonium group between the two equivalent carbon centers with the formation of two tautomeric forms completely identical in chemical nature. This phosphonotropy is the first example of its kind, and by its nature is completely similar to the well known phenomena of acylo-, silylo-, and prototropic processes. This does not contradict the chemical theory and does not cause any doubts, because the fact of the formation of only one product in this reaction is clearly demonstrated by spectral methods.

To prove the structure of product **19**, we performed an alkylation reaction with methyl iodide. The reaction proceeded easily at room temperature with the formation of the corresponding salt (with m.p. 93–95°C and δ_P 29.9 ppm) whose structure was proved by a plethora of spectral methods.



Thus, the investigation of reactions of trialkyl- and triaryl-phosphines with unsaturated mono- and dicarboxylic acids and their derivatives in various conditions has shown new interesting results in the field of synthesis, structures, and reactivity of carboxylate phosphabetaines. These new perspectives provide new ways of looking at the formation and the stabilization of major intermediates of organophosphorus reactions.

EXPERIMENTAL

All details concerning synthetic, spectral, X-ray, and other experiments are presented in our previous publications [11–14] and are the bases of this review.

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