Solvation and Catalysis in Displacement at Phosphorus. Reaction of Imidazole and Benzoate Ion with *p*-Nitrophenyl and 2,4-Dinitrophenyl Diphenylphosphinates[1,2]

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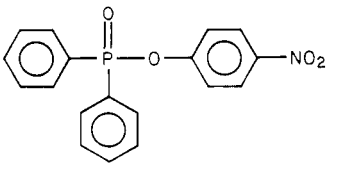
The reactions of two phosphorus esters, *p*-nitrophenyl diphenylphosphinate (I) and 2,4-dinitrophenyl diphenylphosphinate (II), have been investigated in acetonitrile containing variable amounts of water. The effectiveness of imidazole and benzoate ion as catalysts has been investigated. Whereas the reaction of imidazole with II is quite rapid, the reaction with I is very slow. However, I reacts predominantly by the rate term $k[C_6H_5CO_2^-]$ and shows no $k[C_6H_5CO_2^-]$[imidazole] term. Nucleophilic catalysis and the existence of an anhydride intermediate have been confirmed with I by observation of the carbonyl region in the infrared: a C=O peak appropriate for an anhydride appears with $C_6H_5CO_2^-$ and then disappears if imidazole is added. This correlates with kinetic evidence for an equilibrium with benzoate ion alone but complete reaction if benzoate and imidazole are both present. The reaction of II has been shown to proceed by reversible formation of 1-(diphenylphosphinyl)imidazole as an intermediate.

The study of reactivity of substrates in dipolar aprotic solvents enables additional insight into mechanisms of catalysis from studies in water for several reasons.[3,4] In water, the solvation properties, both basic and acidic, may stabilize the transition state as a reaction proceeds; because water, as the solvent, is in great excess, these functions of water are difficult to detect; therefore, there may be many catalytically important phenomena which cannot be elucidated by studies in aqueous solvents. Also, catalysts, electrophiles and nucleophiles, and acids and bases, are solvated strongly in water, and this will alter their catalytic effectiveness: a basic catalyst, for example, an alcohol, could be potentiated by acting as a hydrogen bond donor, but it would be inhibited by acting as a hydrogen bond acceptor by the energy required both to break the hydrogen bond and to move through the solvation layer in order to reach its catalytic focus. Rate terms obtained in water, therefore, may be less important without the catalytic effects of water, and new rate terms may appear in dipolar aprotic solvents. Some of these expectations have been realized in our studies of displacements at acyl carbon.[2d,5]

The proteinoid nature of enzymes is a boundary condition on their effective solvent properties.[6,7] Crystallography has confirmed the expected tight fit between enzyme and substrate so that there is little space for water molecules.[8-10]

We have chosen acetonitrile as our solvent partly because it has a dielectric constant which appears to be similar to that of active sites of enzymes.[6,7] Acetonitrile has a high dipole moment (approximately 4 D), so dipole interactions with solutes may be expected to mimic the dipolar interaction between the highly dipolar amide bonds in a protein and substrates. In addition, acetonitrile has the important advantage of being a poor acid and base so that solutes can be investigated for their catalytic function without being overwhelmed by solvent as is the problem in water.

Displacement at phosphorus is an important biological process both in regard to the phosphorylation reactions which underlie energy transfer[2a] and in regard to the metabolism of nucleic acids.[2b] Our discovery of important rate terms involving both imidazole and benzoate ion led us to this study of the effects of these reagents on displacement at phosphorus in the *p*-nitrophenyl and 2,4-dinitrophenyl esters of diphenylphosphinic acid (I and II, respectively).



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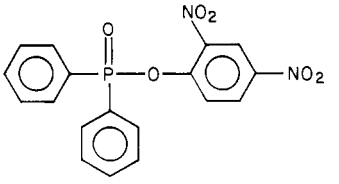

II

Experimental Section

Methods. Reactions were followed spectrophotometrically by measurement of the increase in absorption of *p*-nitrophenol and 2,4-dinitrophenol. *p*-Nitrophenol was followed at 320 nm, *p*-nitrophenolate ion at 410 nm, and 2,4-dinitrophenolate ion at 370 nm. A Hitachi Perkin-Elmer Model 139 UV-vis spectrophotometer and a Cary 16 spectrophotometer were used to follow the

(1) Research supported by Grant AM-12743 from the National Institute of Arthritis and Metabolic Diseases.

(2) Previous publications which contain references to other papers in the indicated areas are as follows. (a) On metaphosphate mechanisms: P. Haake and G. W. Allen, *J. Am. Chem. Soc.*, **98**, 4990 (1976). (b) On guanidinium catalysis of displacement at phosphorus: B. Springs and P. Haake, *Tetrahedron Lett.*, 3223 (1977). (c) On phosphinate ester chemistry: J. Rahil, R. D. Cook, and P. Haake, *J. Am. Chem. Soc.*, **101**, 1322 (1979). (d) On reactions at acyl carbon in media similar to those used in this paper: P. Haake, J. Boger, and G. Wallerberg, manuscript in preparation.

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(4) J. F. Coetzee and C. D. Ritchie, "Solute-Solvent Interactions", Marcel Dekker, New York, 1969.

(5) G. Wallerberg, J. Boger, and P. Haake, *J. Am. Chem. Soc.*, **93**, 4938 (1971); a number of studies are now in progress.

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(7) D. C. Turner and L. Brand, *Biochemistry*, **7**, 3381 (1968).

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reactions. The spectrophotometers were equipped with thermostated cell compartments constant to ±0.2 °C. Reactions were carried out in cuvettes of 1.0-cm path length. Reaction mixtures were prepared from solutions and solvent that were temperature equilibrated before being mixed. Absorbance readings (A_t) were followed to about 90% completion, and infinity points (A_∞) were obtained after 10 half-lives. Pseudo-first-order rate constants (k_{obsd}) were obtained by plotting ln ($A_\infty - A_t$) vs. time.

Hydrolysis of (diphenylphosphinyl)imidazole was followed on a Cary 16 at 273 nm. The substrate concentration was 1×10^{-2} M in acetonitrile and 1.0 M in water. The hydrolysis, which was very slow, was followed to about 10% reaction; the infinity point was calculated by measuring the extinction coefficient of a solution of the hydrolysis product, diphenylphosphinate.

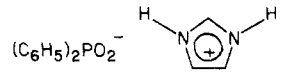
The experimental errors in some runs were large either because of the slowness of the reactions as mentioned above or because of approach to equilibrium (see the Results and Discussion).

Infrared Studies. Infrared spectra were run on a Perkin-Elmer Model 621 instrument. The solvent used was acetonitrile, the temperature in the cell compartment was 37 °C, and the cell path length was 0.5 mm.

2,4-Dinitrophenyl Diphenylphosphinate (II). $(C_6H_5)_2PCl$ was dissolved in dry benzene and oxidized for 5 h by oxygen to diphenylphosphinyl chloride. After treatment with oxygen the reaction mixture was degassed by nitrogen and distilled under reduced pressure [150 °C (0.05 mmHg)]. A solution of 2,4-dinitrophenol (8 g, 4.22×10^{-2} mol) in pyridine (4.22×10^{-2} mol) was added to neat diphenylphosphinyl chloride (10 g, 4.22×10^{-2} mol). This addition was carried out at 0 °C while the solution was stirred by means of a magnetic stirrer. A precipitate of pyridine hydrochloride formed immediately after the addition of pyridine and 2,4-dinitrophenol, benzene was added, and the pyridine hydrochloride was filtered off. The benzene solution was evaporated to dryness, and the residue was recrystallized from benzene–cyclohexane to yield small, light yellow crystals: mp 120 °C; yield 60%. The structure of the ester was confirmed by ^1H NMR spectroscopy, IR spectroscopy, and elemental analysis.

Anal. Calcd for $C_{18}H_{13}N_2O_6P$: C, 56.26; H, 3.41. Found: C, 56.12; H, 3.66.

1-(Diphenylphosphinyl)imidazole (III). A solution of imidazole (1.36 g, 0.02 mol) in dry ether at 0 °C was added to a stirred solution of $(C_6H_5)_2P(O)Cl$ (0.01 mol) in dry ether at 0 °C. A precipitate of imidazolium hydrochloride formed immediately and was filtered off. The ether solution was evaporated to a white residue which was very hygroscopic and could not be recrystallized. Repeated attempts at recrystallization yielded white crystals (mp 132 °C) with an NMR spectrum appropriate for the imidazolium salt A in $CDCl_3$: singlet at τ 2.6 (2 H), multiplet at τ 1.9 (11 H),



A

singlet at τ −6.1 (2 H). But, immediately after evaporation of the ether used as solvent in the preparation, the residue appeared to be the desired product; the NMR gave no evidence for the N–H peaks found at low field in the spectrum of the salt, and the aromatic region had the expected complexity; the aromatic region could not be resolved with shift reagents.

The synthesis of *p*-nitrophenyl diphenylphosphinate was described previously.[11]

1-Deuterioimidazole. Imidazole was dissolved in excess D_2O and evaporated to dryness. Analysis by ^1H NMR indicated >95% 1-deuteration.

Determination of Solvent Isotope Effect. The experiments were run under the same conditions as with H_2O except that 1-deuterioimidazole and D_2O were used. Since $Me_4NOH \cdot 5H_2O$ was used to prepare $C_6H_5CO_2^-$ from $C_6H_5CO_2H$ and imidazole was added as 1-deuterioimidazole, the calculated percentages of D in the solutions were as follows: at 0.05 M D_2O, 70% D; at 0.2 M D_2O, 82% D; at 0.5 M D_2O, 90% D; at 1.0 M D_2O, 94% D.

^{31}P NMR spectra were obtained in acetonitrile on a Varian XL-100 spectrometer using proton decoupling. The chemical shifts were taken relative to diphenylphosphinyl chloride but are reported relative to phosphoric acid by correction.

Table I. Rate Constants from Initial Slopes for the Reaction of 2,4-Dinitrophenyl Diphenylphosphinate (5×10^{-5} M) in Acetonitrile[a]

[IM],[b] M	[H_2O], M	$10^4 k_{obsd}$ s^{-1}
0.0005	1.0	0.32
0.0015	1.0	0.39
0.002	1.0	0.59
0.0025	1.0	0.58
0.003	1.0	0.94, 1.07, 0.84
0.005	1.0	1.05, 0.85, 1.09
0.01	1.0	2.18, 2.64
0.0025	0.5	0.67
0.0025	c	0.55

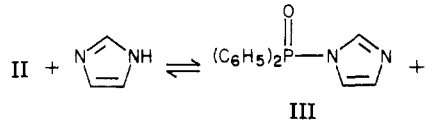
[a] At 30.1 °C and a constant salt concentration maintained at 0.01 M by addition of n-$Bu_4N^+ClO_4^-$. [b] IM = imidazole. [c] No water added.

Results and Discussion

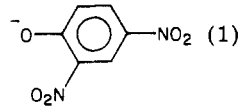
Rates of reaction of *p*-nitrophenyl diphenylphosphinate (I) and 2,4-dinitrophenyl diphenylphosphinate (II) with imidazole were measured in acetonitrile by following the rate of appearance of the phenols. Initial experiments with I and imidazole indicated very slow rates, so II was synthesized and studied in comparison with I and *p*-nitrophenyl acetate which had been studied previously.[2d,5] Rates in acetonitrile with variable amounts of water and no benzoate ion or imidazole are immeasurably slow for both esters at room temperature. When we have investigated benzoate ion, it was added in equimolar amounts with benzoic acid in order to buffer the medium because of the strong basicity of benzoate ion in acetonitrile.[12]

Rates of Reaction of the 2,4-Dinitrophenyl Ester II. The rate of reaction of II with imidazole in CH_3CN (with 1.0 M H_2O) was fast but measurable by conventional spectrophotometric techniques. The usual first-order plot of log ($A_\infty - A_t$) vs. time showed an initial fast rate slowing gradually. A straight line was obtained for the initial rates over about 1 half-life, and the first-order rate constants so obtained are in Table I. In all cases, observed infinity points (A_∞) were used, and these were shown to be approximately equal to the absorbance expected for complete reaction. A plot of k_{obsd} from these initial rates vs. [imidazole] shows that the rate law is $v = k_1$ [II][imidazole] and $k_1 = 0.28$ M^{-1} s^{-1}. There was some scatter in this plot due to the usual problems in evaluating initial rates from the slope of a curved line.

These kinetic results with imidazole suggest that an equilibrium is established (eq 1) followed by slower completion of the reaction due to eq 2. The presence of III



III



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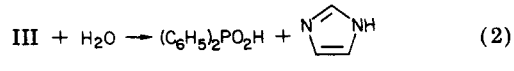

(2)

from the initial reaction was supported by its synthesis and rate of reaction in this medium. The hydrolysis of IV in

(11) P. Haake and G. H. Hurst, *J. Am. Chem. Soc.*, 88, 2544 (1966).

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Table II. ^{31}P Nuclear Magnetic Resonance Spectral Data[a]

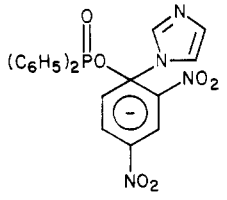
compd	state	chemical shift, ppm from H_3PO_4
2,4-dinitrophenyl diphenylphosphinate (II)	identified compound	−34.7
	mixture[b]	−34.9
1-(diphenylphosphinyl)-imidazole (III)	identified compound	−23.6
	mixture[c]	−23.6
	mixture[d]	−23.3
diphenylphosphinic acid ($(C_6H_5)_2PO_2H$)	mixture[e]	−28.1
		−28.8
		−28.5
diphenylphosphinyl chloride ($(C_6H_5)_2P(O)Cl$)		−42.9
	mixture[c]	−43.1

[a] Chemical shifts from H_3PO_4. The solvent was CH_3CN. [b] Mixture of II and imidazole. [c] Mixture of diphenylphosphinyl chloride and imidazole. [d] Mixture of III and imidazole.

the presence of 1.0 M H_2O in acetonitrile was slow; $k_{obsd} = 8 \times 10^{-6}$ s^{-1} at 30.1 °C.

If the scheme in eq 1 and 2 is correct, 2,4-dinitrophenolate ion, which is released in the first step, should react with III to regenerate II. This was confirmed by experiments in which we followed the decreasing absorbance of 2,4-dinitrophenol after it was added to a solution of III. Rates of reaction of II were measured in the presence of initially added 10^{-4} M 2,4-dinitrophenol; the rate of reaction decreased, and the plot straightened as predicted by eq 1. However, some curvature in the rate plots was still observed, and it was impossible to add high concentrations of 2,4-dinitrophenol because spectral changes were then obscured.

We spent considerable effort on the question of whether the reaction of II with imidazole proceeds through III or through the Meisenheimer intermediate (IV) formed by



IV

attack of imidazole at aryl carbon. Spectrophotometry from 245 to 445 nm indicated that the calculated amount of 2,4-dinitrophenol was released: II plus imidazole, II plus NaOH, and 2,4-dinitrophenol plus NaOH all gave similar spectra. The question of III or IV as intermediate was also investigated by the following infrared spectra. The reaction of II in acetonitrile with imidazole resulted in a new band at 1307 cm^{-1} which increased with time as expected on the basis of the kinetics. This band is in the correct region for a P=O band, but it could also be a (CN) stretch from the imidazole ring of III.[13] As the reaction proceeded a doublet band appeared at 950 cm^{-1} which is the region of P–N stretching.[14] There was good agreement between the reaction product and synthesized III in the parts of the infrared spectrum transparent in CH_3CN, including the fingerprint region. The results gave strong support to III as the reaction product of imidazole and II. We carried

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(14) R. A. Chittenden and L. C. Thomas, *Spectrochim. Acta*, **22**, 1449 (1966).

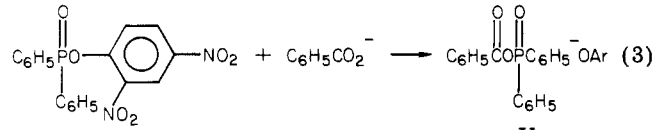
Table III. Reaction of 2,4-Dinitrophenyl Diphenylphosphinate (5×10^{-5} M) in Acetonitrile[a,b]

$10^5[RCO_2^-]$, M	10^3k_{obsd},[c] M^{-1} s^{-1}	$10^5[RCO_2^-]$, M	10^3k_{obsd},[c] M^{-1} s^{-1}
0.5	0.20	2.0	0.60
0.75	0.21	3.0	0.78
1.0	0.47	4.0	1.4

[a] The concentration of water was 1 M and that of imidazole was 0.0005 M in every case. [b] At 30.1 °C and a total salt concentration maintained at 0.01 M by addition of n-$Bu_4N^+ClO_4^-$. [c] The value of 10^3k_{obsd} with 0.0005 M water and no RCO_2^- was 0.032 M^{-1} s^{-1}.

out another investigation of this problem using ^{31}P NMR spectra (Table II). The results in the first and second sections of Table II support reaction of II with imidazole to give III. Therefore, we conclude that the Meisenheimer complex, IV, is not involved and that the reaction proceeds as shown in eq 1 and 2.

On addition of a 1:1 mixture of benzoic acid and benzoate ion to II, the rate of reaction of II increased so much that the spectrophotometric change could be followed only at concentrations of imidazole and benzoate ion comparable to [II]. Crude results (Table III) indicate that there is a $k_2[II][C_6H_5CO_2^-]$ term in the rate law, and $k_2 = 3$ M^{-1} s^{-1}. Therefore, II appears to react rather rapidly with benzoate ion alone to produce an anhydride intermediate (V, eq 3). We have not ruled out a $k[II][imidazole][C_6H_5CO_2^-]$ term, but by analogy with I (see below), this seems unlikely to be the source of the rate increase shown in Table III.



II V

The formation of V is supported by examination of infrared spectra. Because V is a mixed anhydride, it will have only one band in the carbonyl region. When II and benzoate ion are mixed in CH_3CN, the benzoate band at 1711 cm^{-1} disappears, and a new band appears at 1741 cm^{-1}, a reasonable position for the carbonyl stretching vibration of V. Additional evidence comes from the reaction of the p-nitrophenyl ester I with $C_6H_5CO_2^-$; the same anhydride, V, should also be formed from this ester, and the same band at 1741 cm^{-1} is observed.

We also noted acid-catalyzed hydrolysis of II in the presence of methanesulfonic acid (0.01–0.03 M). However, the infinity points were not reproducible, and the extent of acid-catalysis was not accurately determined. The investigation of water dependence in the catalyzed hydrolysis of II showed that there is little dependence on concentration of water.

Reaction of I. Kinetic and spectral studies on the reaction of p-nitrophenyl diphenylphosphinate (I) with imidazole and benzoate ion give different results from studies on II. As in the kinetic studies with II, rates of reaction were evaluated by spectrophotometric observation of the phenolic product at a constant salt concentration maintained at 0.01 M by addition of n-$Bu_4N^+ClO_4^-$. Imidazole alone had no catalytic effect, but addition of benzoate ion caused p-nitrophenol to be released at a measurable rate (Table IV). When the data in Table IV are plotted against $[C_6H_5CO_2^-]$, a straight line results with no significant deviations in slope or intercept due to different imidazole concentrations. Therefore, the rate increase due

Table IV. Rate Constants for the Reaction of *p*-Nitrophenyl Diphenylphosphinate (6×10^{-5} M) in Acetonitrile[a]

[IM], M	$[RCO_2^-]$, M	$10^4 k_{obsd}$ s^{-1}
0.25	0.004	0.677
0.25	0.006	0.91
0.25	0.008	1.04
0.30	0.004	0.95
0.30	0.006	0.64
0.30	0.008	0.77
0.30	0.01	1.04
0.10	0.002	0.43
0.10	0.003	0.54
0.10	0.004	0.62
0.2	0.006	0.64
0.2	0.008	0.95
0.2	0.01	1.21
0.2	0.01	1.42
0.2	0.01	1.28
0.3	0.01	1.28
0.2	0.01	1.46
0.15	0.01	1.46
0.10	0.01	1.46

[a] At 30.1 °C; $[H_2O]$ = 1.0 M; total salt concentration = 0.1 M by addition of n-$Bu_4N^+ClO_4^-$; IM = imidazole.

Table V. Rate Constants for the Water-Dependent Reaction of *p*-Nitrophenyl Diphenylphosphinate (6×10^{-5} M) in Acetonitrile[a]

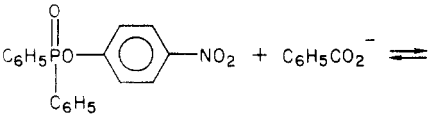
$[H_2O]$, M	$10^4 k_{obsd}$, s^{-1}	k_H/k_D
none	4.35	
0.05	4.4, 3.0[b]	1.5
0.20	3.8, 2.35[b]	1.6
0.5	1.96, 1.55[b]	1.3
1.0	1.22, 0.85[b]	1.4
2.0	0.62	
0.1	2.0[b]	

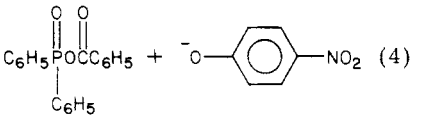
[a] At 30.1 °C. The concentration of imidazole was 0.2 M and that of RCO^- was 0.01 M in every case. [b] In D_2O instead of H_2O.

to $C_6H_5CO_2^-$ must be due to a $k[I][C_6H_5CO_2^-]$ term, and k = 0.011 M^{-1} s^{-1}.

Unlike the dependence of $[H_2O]$ on the reaction of II plus imidazole, the reaction of I with $C_6H_5CO_2^-$ shows a large rate inhibition when the concentration of water is increased (Table V). This suggests that the water molecules, by protic solvation, interfere with the reactivity of benzoate ion. There is also a significant deuterium isotope effect on reaction of I with $C_6H_5CO_2^-$ at 0.5 M H_2O or D_2O (k_H/k_D = 1.26). Solvation of acetonitrile with its strong dipole of about 4 D, solvation of benzoate ion, and solvation of the substrate I could all be important and could contribute to the ground-state-energy difference between H_2O and D_2O. The transition state in this reaction probably involves loss of *p*-nitrophenoxide from the tetrahedral intermediate because of the greater basicity of this leaving group than of benzoate ion. Therefore, the deuterium isotope effect may be associated with proton transfer to the leaving group in the rate-determining step.

Although imidazole does not cause the release of *p*-nitrophenol from I, reaction of I with $C_6H_5CO_2^-$ shows an initial burst and then slows. With both imidazole and $C_6H_5CO_2^-$ present there is good first-order rate behavior over 3 half-lives and no evidence for an equilibrium. The infinity point corresponds to complete release of *p*-nitrophenol. Therefore, the reaction pathway appears to be that shown in eq 4 and 5.





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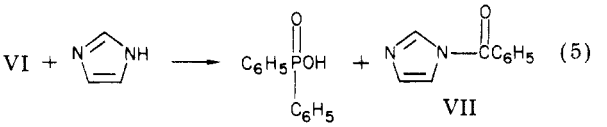

(5)

VII

Infrared studies are in agreement with this scheme. When I and $C_6H_5CO_2^-$ are mixed in CH_3CN, the appearance of a C=O band at 1741 cm^{-1} was concurrent with a decrease in intensity of the C=O band initially present at 1711 cm^{-1} (benzoate ion). After equilibrium was reached, imidazole was added, the bands at 1741 and 1711 cm^{-1} gradually disappeared, and a new band at 1701 cm^{-1} appeared as one would expect from eq 4 and 5.[2d] The latter band is in a reasonable position for VII.

The reversible equilibria in eq 2 and 4 are undoubtedly partially due to the high basicity and nucleophilicity of oxyanions in acetonitrile. The results demonstrate that different reaction pathways and phenomena can be found in low protic media from those normally found in water.

Registry No. I, 10259-20-8; II, 75599-76-7; III, 71638-08-9; diphenylphosphinous chloride, 1079-66-9; 2,4-dinitrophenol, 51-28-5; diphenylphosphinyl chloride, 1499-21-4; imidazole, 288-32-4; diphenylphosphinic acid imidazole salt, 75599-77-8; 1-deuterioimidazole, 2519-73-5; diphenylphosphinic acid, 1707-03-5.