2-Cyanoethyl and *p*-Nitrophenethyl α-Hydroxyimino- and α-Methoxyimino-phosphonates: Potential Precursors of Metaphosphate Anion

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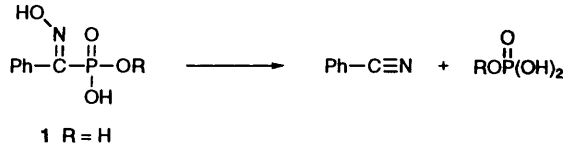
Methyl benzoylphosphonochloridate **3** reacted with 2-cyanoethanol or *p*-nitrophenethyl alcohol to yield methyl 2-cyanoethyl benzoylphosphonate **4a** or methyl *p*-nitrophenethyl benzoylphosphonate **4b**. Ketones **4a** and **4b** were converted into the corresponding oximes, **5a** and **5b** as a mixture of *E* and *Z* isomers, by hydroxylamine. Oximes **5a** and **5b** were demethylated by treatment with sodium iodide or lithium bromide to give the corresponding monester monosalts **6a** and **6b**. Reaction of lithium 2-cyanoethyl or *p*-nitrophenethyl benzoylphosphonate with methoxylamine afforded the respective oxime methyl ether salts **8a** and **8b** as predominantly *E* isomers. Base treatment of **6a** and **6b** caused their dealkylation to the anion of α-hydroxyiminobenzylphosphonic acid **9** which did not decompose further. In contrast, **8a** and **8b** in aqueous base gave the dianion of α-methoxyaminobenzylphosphonic acid **10**, which slowly fragmented to benzonitrile and phosporic acid. The fragmentation is interpreted in terms of a dissociative mechanism involving the formation of metaphosphate anion.

It was reported from our laboratory that α-hydroxyimino-benzylphosphonic acid **1** undergoes fragmentation to metaphosphate, and thus may serve as a phosphorylating agent.[1-4] Compound **1** is unstable and spontaneously fragments to benzonitrile and phosphoric acid (Scheme 1) under a wide



1 R = H

Scheme 1

range of pHs. Consequently, we are interested in stable precursors, from which compound **1** and its analogues can be liberated under mild conditions.

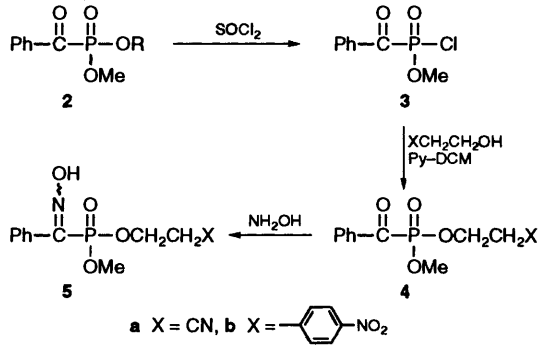
We recently reported the synthesis of other metaphosphate precursors based on hydroxyiminophosphonate esters. These include benzyl esters, from which **1** can be liberated by ultraviolet irradiation,[5] and 2,2,2-trihalogenoethyl esters from which **1** can potentially be liberated by treatment with Zn.[6]

2-Cyanoethyl and *p*-nitrophenethyl esters have been developed as protecting groups of phosphates in nucleotide chemistry.[7,8] A characteristic of these groups is that they can be cleaved by base through β-elimination with the respective formation of acrylonitrile or *p*-nitrostyrene as by-products.

In this paper we describe our studies concerning the synthesis of α-hydroxyiminobenzylphosphonic 2-cyanoethyl and *p*-nitrophenethyl esters and their evaluation as potential metaphosphate precursors under alkaline conditions.

Results and Discussion

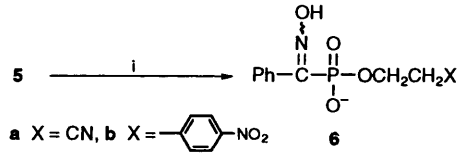
Synthesis of 2-*Cyanoethyl and* p-*Nitrophenethyl* α-*Hydroxyiminobenzylphosponate Salts.*—Methyl hydrogen benzoylphosphonate[9] **2** was converted into methyl benzoylphosphonochloridate **3** by reaction with thionyl chloride.[6] Compound **3** was allowed to react with 2-cyanoethanol, or with *p*-nitrophenethyl alcohol, in dichloromethane in the presence of pyridine to yield methyl 2-cyanoethyl benzoylphosphonate **4a** or methyl *p*-nitrophenethyl benzoylphosphonate **4b**, respectively. The reactions of ketones **4** with hydroxylamine yielded the desired oximes **5** (Scheme 2). The two steps can be carried out conveniently in a one-pot procedure.



a X = CN, **b** X =

Scheme 2

Oximes **5**, obtained as mixtures of *E*- and *Z*-isomers,[10] could be smoothly demethylated to the corresponding monoester salts **6** by treatment with sodium iodide in dry acetone at room temperature or by lithium bromide in boiling acetonitrile (Scheme 3). In all reactions, selective removal of the methyl

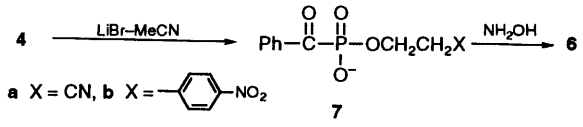


a X = CN, **b** X =

Scheme 3 *Reagents:* i, NaI–acetone or LiBr–MeCN

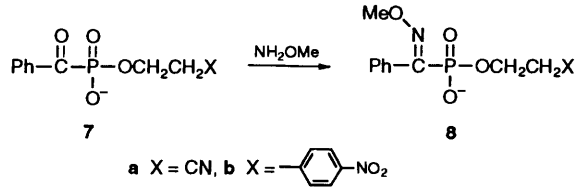
group was seen. The distribution of the geometrical isomers was preserved during the dealkylation reactions. Thus, by this sequence of reactions lithium β-cyanoethyl α-hydroxyiminobenzylphosphonate **6a** and *p*-nitrophenethyl α-hydroxyiminobenzylphosphonate **6b**, could be obtained, as mixtures of *E*- and *Z*-isomers.

Alternatively, oxime salts **6** could be prepared by first monodealkylating the mixed benzoylphosphonate esters **4** to the respective salts **7** and treating a suspension of these in methanol with hydroxylamine free base (Scheme 4). This synthetic route leads predominantly to *E*-isomers in excellent yields.



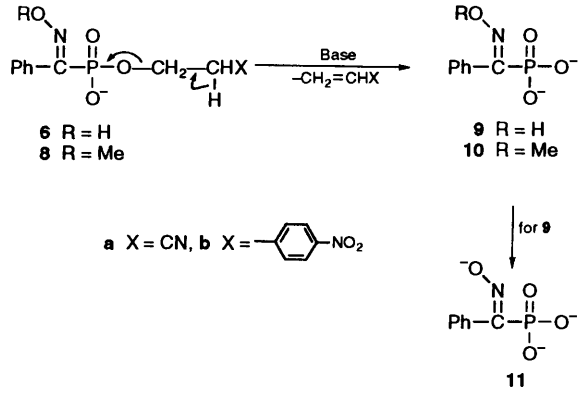
Scheme 4

The latter approach was found to be also applicable for the preparation of lithium 2-cyanoethyl methoxyiminobenzylphosphonate **8a** and lithium *p*-nitrophenethyl methoxyiminobenzylphosphonate **8b**. Benzoylphosphonate anions **7** were treated with methoxylamine free base in methanol, to yield the respective salts **8**, as predominantly *E*-isomers (Scheme 5).

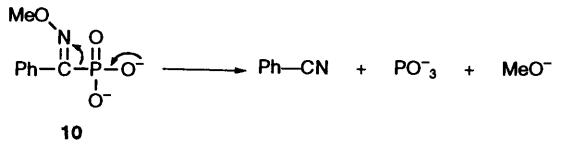


Scheme 5

Fragmentation Experiments.—α-Hydroxyiminobenzylphosphonate **6** and α-methoxyiminobenzylphosphonate **8** salts were dissolved in various alkaline solutions and monitored by ^{31}P NMR spectroscopy. By this methodology it was possible to monitor the progress of conversion of esters into the dealkylated oxyiminobenzylphosphonate anions, and fragmentation of the latter to phosphoric acid. It was found that **6a** or **6b**, and **8a** or **8b** were completely converted into anions of α-hydroxyiminobenzylphosphonic acid **9** or α-methoxyimonobenzylphosphonic acid **10** (Scheme 6), respectively at room temperature within 2 h in 0.1 mol dm^{-3} NaOH in water–dioxane. The conversion was slower in MeOH. Complete conversion of **6a** or **6b** into **9** required 10 h, using 0.1 mol dm^{-3} NaOH in MeOH, while it took 6 h for **8a** and **8b** to be converted into **10**. Compound **9** was stable indefinitely in the reaction media mentioned above. In contrast, dianion **10** decomposed slowly ($t_{1/2}$ = 7 days) in aqueous NaOH solution with the formation of orthophosphoric acid, as established by ^{31}P NMR spectroscopy (Scheme 7). In other solvents (methanol, ethanol, acetonitrile and dioxane) dianion **10** was stable indefinitely. These results are in accordance with our previous observation regarding the pH profile of compound **9**'s fragmentation. The stability of **9** in strongly alkaline conditions was rationalized in terms of formation of trianion **11**, which cannot undergo fragmentation since the ionized oxime oxygen cannot function as a leaving group. In compound **10** such ionization is blocked, therefore, in water slow fragmentation is observed. Acidification of the strongly alkaline water–dioxane reaction media containing **9** or **10**, gave immediate fragmentation to phosphoric acid, thus confirming the identity of the ionized species. α-Hydroxyiminophosphonic acids undergo rapid fragmentation with acid catalysis.[3]



Scheme 6



Scheme 7

Compounds **6** and **8** were examined in the presence of 5 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry acetonitrile. Removal of the 2-cyanoethyl and *p*-nitrophenethyl groups was slow in both cases at room temperature. (*e.g.* 50% reaction for **8b** in 20 h). The dianions **9** and **10** formed in acetonitrile were stable at room temperature for at least one week. Boiling a solution of **8b** in the presence of DBU in MeCN caused complete conversion into **9** in a few minutes. Examining the solution by ^{31}P NMR showed the evolution of a new peak at δ −9 (16 and 26%, after 4 and 20 h, respectively). This chemical shift is consistent with a pyrophosphate type structure. Formation of pyrophosphate type compounds in fragmentation of hydroxyiminophosphonates in aprotic solvents was noted previously,[5] and it is consistent with a dissociative type mechanism involving the formation of metaphosphates in the first step, and its subsequent dimerization in the absence of reactive compounds. Similar behaviour was seen in the fragmentation of other types of metaphosphate precursors.[11–13]

The lack of fragmentation of **10** in less polar media is attributed to a solvent effect. It is assumed that the water facilitates the fragmentation, relative to less polar media, by hydrogen bonding to the leaving methoxy group. A separate comparative kinetic study of the fragmentation of α-hydroxyiminobenzylphosphonic acid and α-methoxyiminobenzylphosphonic acid revealed that the latter fragments markedly slower in the pH range of 7–13, than the former.[14] This is attributed to the inferior leaving group properties of the methoxy group relative to those of the hydroxy group.

In conclusion, it appears that 2-cyanoethyl and *p*-nitrophenethyl α-oxyiminophosphonates can function as precursors of metaphosphates. These can be generated from such esters at high temperature in aprotic conditions or in aqueous solution by lowering of the pH after the dealkylation is complete, since both **9** and **10** undergo fragmentation at lower pH.[1,14] We are currently studying hydroxyiminophosphonate derivatives with improved leaving groups on the oxime function as potential metaphosphate precursors.

Experimental

Elemental analyses were performed by the Analytical Laboratory of the Hebrew University, Givat-Ram, Jerusalem. IR spectra were determined on an Analect FTIR spectrometer. NMR spectra were recorded on a Varian VXR-300S instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)tetradeuteriopropionate (TSP) as internal standards in ^{1}H spectra and from 85% H_3PO_4 as external standard in ^{31}P spectra. Positive chemical shifts are at low field with respect to the standard. Peak multiplicities are given in parentheses. *J* Values are given in Hz.

Methyl 2-Cyanoethyl Benzoylphosphonate **4a**.—To a solution of methyl benzoylphosphonochloridate **3** (21.8 g, 0.1 mol) in dry dichloromethane (70 cm^3), stirred under nitrogen at 0 °C, was added dropwise a solution of pyridine (8 cm^3, 0.1 mol) and 2-

cyanoethanol (7.1 g, 0.1 mol) in dry dichloromethane (70 cm^3) over a period of 30 min. After the reaction mixture had been stirred for 2 h at ambient temperature, the solvent was removed at reduced pressure and the residue was taken up in anhydrous diethyl ether. Pyridinium chloride was removed by filtration, and evaporation of the diethyl ether yielded crude **4a** (22 g, 87%) as an oil, ν(neat)/cm^{-1} 1656, 1260 and 1031 cm^{-3}; δ_P −0.8 (sextet). This product was used immediately without further purification for the synthesis of **7a**.

Methyl p-*nitrophenethyl benzoylphosphonate* **4b**. The procedure used to prepare ketone **4a** was followed to give crude **4b** (29 g, 83%). $\delta_P(CDCl_3)$ −1.2 (sextet). This product was used immediately without further purification for the synthesis of **7b**.

Synthesis of Benzoylphosphonate Monosalts **7**.—A solution of ketone **4** (0.1 mol) in dry acetonitrile (100 cm^3), was added to a solution of lithium bromide (9.5 g, 0.11 mol) in dry acetonitrile (30 cm^3). The reaction mixture was refluxed for 5 h. The precipitated salt was filtered off, washed with dry acetone and then dried in air.

Lithium 2-*cyanoethyl benzoylphosphonate* **7a**. Yield 22 g (90%), ν(KBr)/cm^{-1} 1650, 1240 and 1090; $\delta_P(D_2O)$ −2.2 (t); $\delta_H(D_2O)$ 7.4 (5 H, m), 3.8 (2 H, quintet) and 2.7 (2 H, t, *J* 6.7) (Found: C, 48.7; H, 3.7; N, 5.5. Calc. for $C_{10}H_9LiNO_4P$: C, 48.99; H, 3.67; N, 5.46%).

Lithium p-*nitrophenethyl benzoylphosphonate* **7b**. Yield 30 g (88%), ν(KBr)/cm^{-1} 1654, 1600, 1235 and 1090; $\delta_P(D_2O)$ −3.2 (t); $\delta_H(D_2O)$ 7.9 (2 H, m), 7.3 (5 H, m), 7.1 (2 H, m), 4.2 (2 H, quintet) and 2.9 (2 H, t, *J* 6).

Methyl p-*nitrophenethyl α-Hydroxyiminobenzylphosphonate* **5b**. *One-pot Procedure*.—To a solution of methyl benzoylphosphonochloridate **3** (21.8 g, 0.1 mol) in dry dichloromethane (70 cm^3), stirred at 0 °C, was added dropwise a solution of dry pyridine (8 cm^3, 0.1 mol) and *p*-nitrophenethyl alcohol (16.7 g, 0.1 mol) in dry dichloromethane (70 cm^3) over 30 min. After the reaction mixture had been stirred for 2 h at room temperature, dry pyridine (10.4 cm^3, 0.13 mol) and hydroxylamine hydrochloride (9 g, 0.13 mol) were added. The reaction mixture was stirred for 3 h, the solvent was removed at reduced pressure, and then the residue was mixed with HCl (1 mol dm^{-3}; 50 cm^3). The aqueous mixture was extracted with chloroform (4 × 70 cm^3). The combined extracts were dried over anhydrous magnesium sulfate, filtered, evaporated and then the product was purified by recrystallization from ethyl acetate to give the title compound **5b** (16 g, 46%), m.p. 129 °C; ν(KBr)/cm^{-1} 1640, 1260 and 1030; $\delta_P(CDCl_3)$ 8.2 (sextet, *E*-**5b**) and 3.7 (sextet, *Z*-**5b**); $\delta_H(CDCl_3)$ 7.95 (2 H, m), 7.3 (5 H, m), 7.1 (2 H), 4.3 (2 H, quintet), 3.6 (3 H, d, *J* 11) and 2.9 (2 H, t, *J* 6).

Synthesis of α-Hydroxyiminobenzylphosphonate Salts **6**.—(*A*) *Monodealkylation of oxime* **5** *by lithium bromide*. A solution of oxime **5** (0.1 mol) in dry acetonitrile (100 cm^3), was added to a solution of lithium bromide (9.5 g, 0.11 mol) in dry acetonitrile (100 cm^3). The reaction mixture was refluxed overnight. Product **6** precipitated and was filtered off, washed with dry acetone and dried in air.

(*B*) *Reaction of lithium benzoylphosphonate* **7** *with hydroxylamine*. Hydroxylamine free base was prepared by neutralizing hydroxylamine hydrochloride (8.34 g, 0.12 mol) in methanol (100 cm^3) with sodium methoxide (6.48 g, 0.12 mol). The precipitated sodium chloride was filtered off and lithium benzoylphosphonate **7** (0.1 mol) was added to the filtrate. The reaction mixture was stirred at room temperature for 3 h, the solvent evaporated and the solid residue was washed with diethyl ether and dried.

Lithium 2-*cyanoethyl α-hydroxyiminobenzylphosphonate* **6a**. Yield 22.5 g (87%), ν(KBr)/cm^{-1} 3160, 1640, 1220 and 1090; $\delta_P(D_2O)$ 5.3 (t, *E*-**6a**) and 0.93 (t, *Z*-**6a**); $\delta_H(D_2O)$ 7.4 (3 H, m), 7.3 (2 H, m), 4.0 (2 H, quintet) and 2.72 (2 H, t, *J* 6).

Lithium p-*nitrophenethyl α-hydroxyiminobenzylphosphonate* **6b**. Yield 32 g (90%), ν(KBr)/cm^{-1} 3150, 1635, 1600, 1220 and 1087; $\delta_P(D_2O)$ 4.8 (t); $\delta_H(D_2O)$ 8.1 (2 H, m), 7.4 (5 H, m), 7.1 (2 H, m), 4.1 (2 H, quintet) and 2.9 (2 H, t, *J* 6.7) (Found: C, 48.4; H, 3.8; N, 7.3. Calc. for $C_{15}H_{14}Li{\cdot}N_2O_6H_2O$: C, 48.12; H, 4.19; N, 7.48%).

Lithium 2-*Cyanoethyl Methoxyiminobenzylphosphonate* **8a**.—Methoxylamine free base was prepared by neutralizing methoxylamine hydrochloride (10.2 g, 0.12 mol) in methanol with sodium methoxide (6.5 g, 0.12 mol). The precipitated sodium chloride was filtered off and lithium 2-cyanoethyl benzoylphosphonate **7a** (24.5 g, 0.1 mol) was added to the filtrate. The reaction mixture was stirred for 3 h at room temperature, the solvent evaporated and the solid residue was washed with diethyl ether and then dried to give the title compound **8a** (24 g, 89%), $\delta_P(D_2O)$ 4.1 (t, *E*-**8a**) and −0.5 (t, *Z*-**8a**); $\delta_H(D_2O)$ 7.4 (3 H, m), 7.3 (2 H, m), 4.0 (2 H, quintet), 3.8 (3 H, s) and 2.7 (2 H, t, *J* 6) (Found: C, 48.1; H, 4.4; N, 10.3. Calc. for $C_{11}H_{12}LiN_2O_4$: C, 48.18; H, 4.38; N, 10.22%).

Lithium p-*nitrophenethyl methoxyiminobenzylphosphonate* **8b**. The procedure used to prepare compound **8a** was followed to give title compound **8b** (31.5 g, 85%), $\delta_P(D_2O)$ 4.0 (t); $\delta_H(D_2O)$ 8.0 (2 H, m), 7.3 (5 H, m), 7.1 (2 H, m), 4.1 (2 H, quintet), 3.8 (3 H, s) and 2.9 (2 H, t, *J* 6) (Found: C, 51.7; H, 4.3; N, 7.2. Calc. for $C_{16}H_{16}LiN_2O_6$: C, 51.90; H, 4.31; N, 7.56%).

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