A kinetic study of competing fragmentation and hydrolyses of phenyl hydrogen α-hydroxyiminobenzylphosphonate—a case of acid mediated inhibition of acid catalysis

Rachel Ta-Shma, Hava Schneider, Mahmoud Mahajna, Jehoshua Katzhendler † and Eli Breuer *†

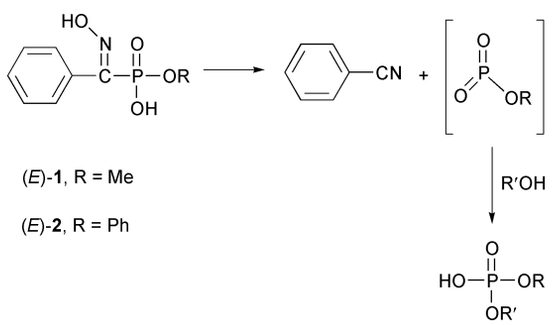
Department of Medicinal Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, P. O. Box 12065, 91120 Israel. E-mail: breuer@cc.huji.ac.il; Fax: 972-2-675-8934; Tel: 972-2-675-8704

Received (in Cambridge, UK) 14th December 2000, Accepted 29th May 2001
First published as an Advance Article on the web 19th June 2001

The behavior of phenyl hydrogen α-hydroxyiminobenzylphosphonate (*E*)-**2** in aqueous hydrochloric acid solution was examined by ^{31}P NMR spectroscopy and by HPLC. Compound (*E*)-**2** was found to undergo two competing acid-catalyzed reactions. 1) Fragmentation to phenyl phosphate (**6**) and benzonitrile, similar to the fragmentation of other hydroxyiminophosphonates to metaphosphate examined previously. The fragmentation of (*E*)-**2** was found to be slower by a factor of 4 than that of hydrogen methyl α-hydroxyiminobenzylphosphonate ((*E*)-**1**). This phenomenon is interpreted in terms of inductive effects on the suggested metaphosphate intermediate. 2) Compound (*E*)-**2** was found to undergo hydrolytic cleavage of the oxime group giving NH_2OH and hydrogen phenyl benzoylphosphonate (**4**), which was found to hydrolyze to phenol and benzoylphosphonic acid (**5**). The latter reacted with the NH_2OH liberated in the previous step to give α-hydroxyiminobenzylphosphonic acid ((*E*)-**3**), which fragmented to benzonitrile and phosphoric acid. The rate of a possible hydrolysis of the phenol group in oxime (*E*)-**2** was shown to be slower by two orders of magnitude than that from ketone **4**. This phenomenon is interpreted in terms of acid mediated retardation of acid catalyzed hydrolysis of phenol due to initial protonation of the oxime nitrogen in (*E*)-**2**.

Introduction

In previous reports from our laboratory, we have shown that a variety of α-hydroxyiminophosphonic acid derivatives undergo fragmentation and are capable of performing phosphorylation of hydroxy compounds (Scheme 1).[1–9] Recently we published a

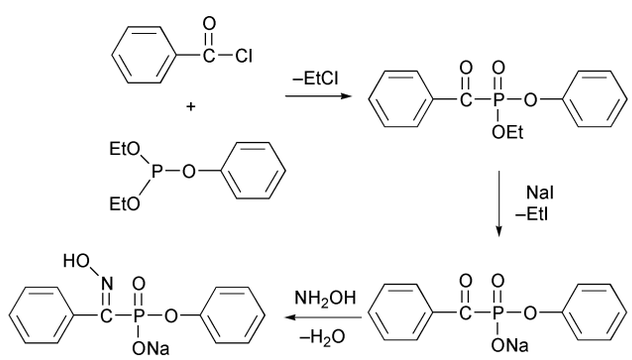


Scheme 1

detailed kinetic investigation of the fragmentation of methyl hydrogen α-hydroxyiminobenzylphosphonate ((*E*)-**1**) and some of its derivatives in water and in mixed alcohol–water solutions under acidic conditions.[10] The results were compatible with a dissociative mechanism ($D_N{}^*A_N$ or $D_N + A_N$). The thermodynamics, and especially the different solvent effects on the fragmentation rate, on the one hand, and on the products on the other, indicated that the rate limiting step and the product determining step do not share a common transition state, and that the reaction coordinate includes at least one reactive intermediate, probably methyl metaphosphate (Scheme 1). Since our previous, synthetically oriented work showed that the propensity of α-hydroxyiminophosphonates to fragment depends considerably on the inductive effect of the esterifying R groups (*e.g.* Breuer and Mahajna[7]), we considered it of interest to subject hydrogen phenyl α-hydroxyiminobenzylphosphonate ((*E*)-**2**) to a careful kinetic study.

Results and discussion

Hydrogen phenyl α-hydroxyiminobenzylphosphonate ((*E*)-**2**) was synthesized by the reaction sequence shown in Scheme 2.



Scheme 2

Arbuzov reaction of benzoyl chloride with diethyl phenyl phosphite gave ethyl phenyl benzoylphosphonate, which was de-ethylated by treatment with NaI in acetone to phenyl sodium benzoylphosphonate. The latter was treated with hydroxylamine to yield sodium phenyl α-hydroxyiminobenzylphosphonate. This salt served as a stable precursor to hydrogen phenyl α-hydroxyiminobenzylphosphonate ((*E*)-**2**).[11]

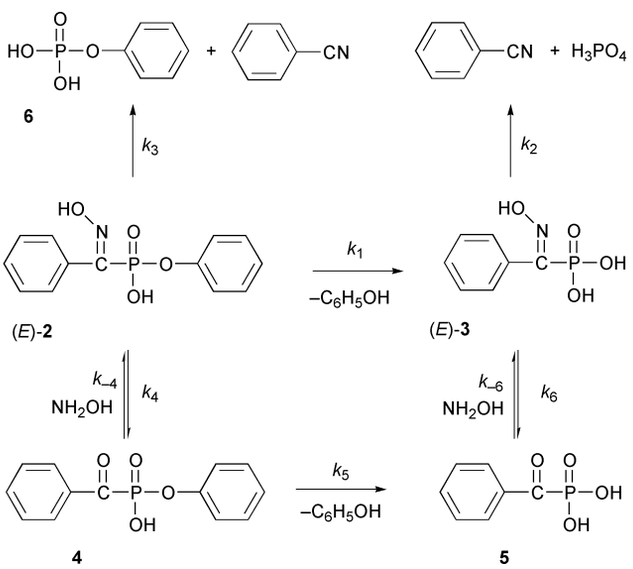
It soon became clear that the behavior of (*E*)-**2** is much more complex than that of the corresponding methyl derivative (*E*)-**1**. While the latter gave in aqueous HCl only methyl dihydrogen phosphate and benzonitrile,[10] examination of a solution of (*E*)-

† Affiliated with the David R. Bloom Center for Pharmacy.

 DOI: 10.1039/b010152o

2 by ^{31}P NMR spectroscopy after 5 days in 1 M HCl at room temperature, showed the presence of two final products: phenyl phosphate (**6**) and phosphoric acid. The HPLC chromatogram of the reaction mixture showed the presence of phenol in addition to the expected **6** and benzonitrile. We ascertained that under the same conditions and time span, **6** does not hydrolyze noticeably to phenol and phosphoric acid. Monitoring (*E*)-**2** in 1 M HCl by ^{31}P NMR spectroscopy revealed after 5 and 19 hours the presence of small amounts (<20%) of three transient products. Two of them were identified by comparing their chemical shifts to those of authentic samples, as phenyl benzoylphosphonate (**4**, $\delta_P = -4.0$ ppm) and benzoylphosphonic acid (**5**, $\delta_P = -1.7$ ppm). The chemical shift ($\delta_P = -2.6$ ppm) of the third one (<5%) is consistent with that of the isomer (*Z*)-**2** (see Experimental section). In a separate experiment **4** was shown by NMR and HPLC to hydrolyze relatively quickly in 1 M HCl to **5** and phenol, while in the presence of an equivalent amount of $NH_3OH^+Cl^-$ it fragmented to benzonitrile, phenyl phosphate (**6**), phosphoric acid and phenol as final products.[12]

Scheme 3 shows three feasible acid catalyzed reaction paths



Scheme 3

for (*E*)-**2**. These are: a) fragmentation of (*E*)-**2** to phenyl phosphate (**6**) and benzonitrile; b) hydrolysis of (*E*)-**2** to phenol and (*E*)-α-hydroxyiminobenzylphosphonic acid ((*E*)-**3**), which in turn fragments to benzonitrile and phosphoric acid; and c) an equilibrium formation of NH_2OH and hydrogen phenyl benzoylphosphonate, **4**, which can subsequently hydrolyze to phenol and benzoylphosphonic acid, **5**, which in turn can then react with NH_2OH liberated in the previous step to give the oxime (*E*)-**3**. The latter could not be observed by NMR due to its relatively fast fragmentation (*vide infra*).[15] The noteworthy phenomena here are: a) the noticeable hydrolysis of the oxime group in (*E*)-**2**; and b) the fact that although the free hydroxylamine concentration formed from the above hydrolysis is necessarily very low in 1 M HCl (<2×10^{-8} M when (*E*)-**2** is 0.03 M), it is sufficient to ensure the complete formation of the oximes **2** and **3** from the ketones **4** and **5**, and their subsequent fragmentation over the reaction time course. For clarity, Scheme 3 does not include the isomerization of oximes (*E*)-**2** and (*E*)-**3** to their geometrical isomers (*Z*)-**2** and (*Z*)-**3** either directly, or through the ketones **4** and **5**.[16]

In order to validate Scheme 3 and unravel the various rate constants in 1 M HCl at 35 °C (a temperature convenient for NMR analysis), we worked in steps. The rate constant for the fragmentation of (*E*)-**3** (k_2) at 1 M HCl and 35 °C could be interpolated from measured values at other temperatures and was found to be 0.073 min^{-1}.[17] Therefore, we first found k_6 and k_{-6} by monitoring through HPLC the formation of benzonitrile

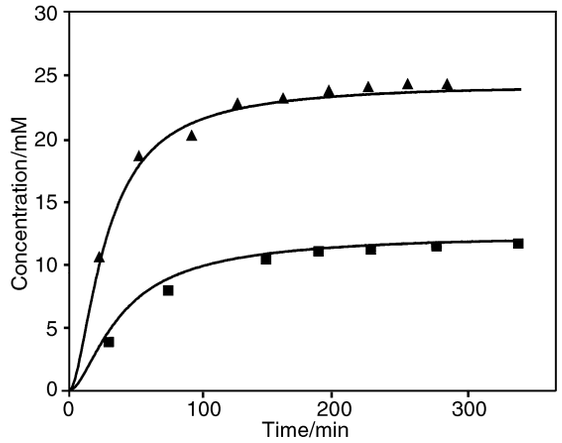


Fig. 1 Formation of benzonitrile from the reaction of **5** with NH_2OH in 1 M HCl at 35 °C. Upper line: [**5**] = 24 mM, [$NH_3OH^+Cl^-$] = 26.6 mM. Lower line: [**5**] = 12 mM, [$NH_3OH^+Cl^-$] = 13.3 mM.

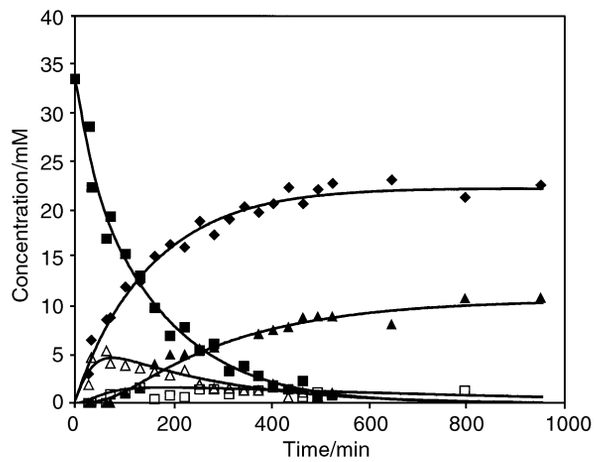


Fig. 2 Intermediates and products from the fragmentation and hydrolysis of (*E*)-**2** (33.4 mM) in 1 M HCl at 35 °C. (*E*)-**2** –■–; **6** –◆–; H_3PO_4 –▲–; **4** –△–; **5** –□–.

from near equivalent amounts of **5** and $NH_3OH^+Cl^-$ in 1 M HCl at 35 °C (Fig. 1). The time–concentration data for two initial concentration sets were analyzed using the non-linear least squares regression program Dynafit[18] and gave $k_6 = 0.0067 \pm 0.014$ min^{-1} and $k_{-6} = (4.9 \pm 1) \times 10^6$ M^{-1} min^{-1}. The latter constant was corrected for the concentration of free NH_2OH using the relation $[NH_2OH] = K_a[NH_3OH^+] / [H^+]$ and $K_a = 6.8 \times 10^{-7}$ for NH_3OH^+ at 25 °C and ionic strength of 0.5 M.[19] The error range in k_6 is uncomfortably large; however, this value decisively gave the best fit to the experimental data, as judged by mean square and standard deviation values. The calculated equilibrium constant for the oxime **3** formation is $k_{-6}/k_6 = 7.3 \times 10^8$ M. Reimann and Jencks[19] obtained 2.3×10^6 M^{-1} min^{-1} for the rate of formation of oxime from *p*-chlorobenzaldehyde and 6.1×10^7 M for the equilibrium constant in 1 M HCl and 25 °C, and more recently Malpica *et al.* observed 5×10^6 M^{-1} min^{-1} for the rate of formation of oxime from *p*-trimethylammoniobenzaldehyde iodide and from *p*-dimethylaminobenzaldehyde and 1.8×10^7 M^{-1} min^{-1} from pyruvic acid, all in 1 M HCl and at 30 °C.[20,21] Our values for **5** are therefore quite in line with relevant literature data.

Next, we monitored by ^{31}P NMR spectroscopy the changes in the concentrations of (*E*)-**2**, **4**–**6** and H_3PO_4 in 1 M HCl at 35 °C. The results are presented in Fig. 2. We again used the Dynafit regression program with fixed values for k_2, k_6 and k_{-6} (stated above). We obtained the following values: $k_1 = 0.00014 \pm 0.00013$ min^{-1}, $k_3 = 0.0049 \pm 0.0001$ min^{-1}, $k_4 = 0.0047 \pm 0.0006$ min^{-1}, $k_{-4} = (2.6 \pm 0.7) \times 10^6$ M^{-1} min^{-1}

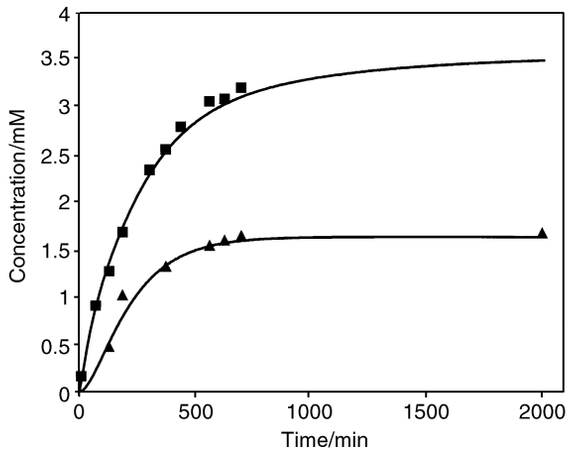


Fig. 3 Fragmentation products from (*E*)-**2** (3.67 mM) in 1 M HCl at 35 °C. Benzonitrile –■–; phenol –▲–.

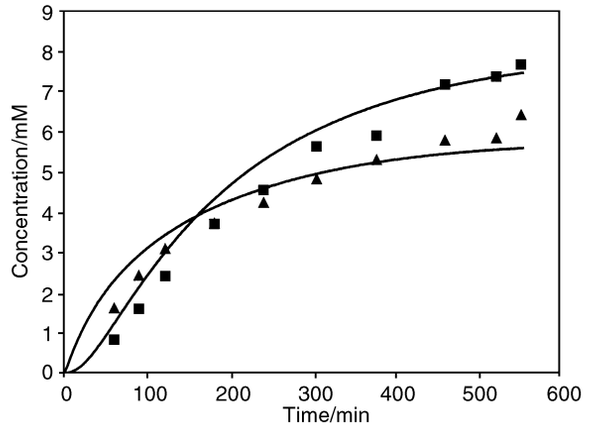


Fig. 4 Fragmentation products from reaction of **4** (8.4 mM) with NH_2OH ([$NH_2OH^+Cl^-$] = 8.7 mM) in 1 M HCl at 35 °C. Benzonitrile –■–; phenol –▲–.

and $k_5 = 0.0072 \pm 0.0008$ min^{-1}. Rate constant k_{-4} was corrected (like k_{-6} above) for the concentration of the free NH_2OH. Both k_4 and k_{-4} are similar to k_6 and k_{-6} and the equilibrium constant for the oxime (*E*)-**3** formation (5.6×10^8 M^{-1}) is identical, within error limits, to that of (*E*)-**2**. The hydrolysis step **4** → **5** was measured separately through HPLC in 1 M HCl at 35 °C and gave $k_5 = 0.0051 \pm 0.001$ min^{-1}, which is not far from the value found by the Dynafit program from the NMR results.

The numeric results found for k_1 and k_5 mean that the acid catalyzed hydrolysis of phenyl hydrogen α-hydroxyiminobenzylphosphonate ((*E*)-**2**) (k_1) is *slower* by around 2 orders of magnitude relative to the hydrolysis of phenyl benzoylphosphonate (**4**) (k_5). This is also apparent from Fig. 2, which shows that H_3PO_4 formation has a long lag period and starts appearing only after meaningful concentrations of **5** have been reached, testifying that **5** is the main precursor of H_3PO_4. It seems reasonable to assume that the hydrolysis of the phenol from both phenyl esters requires protonation of a phosphorus oxygen in the first step.[22] From estimated pK_a values available in the literature for the C=O and P=O groups and of the oxime nitrogen (−7.2, −0.5 and 1.5, respectively[23]), it follows that in **4** the protonation of the P=O oxygen will take precedence over the C=O, while in (*E*)-**2** the oxime nitrogen will be protonated first, and thus *retard* the second protonation on the phosphoryl group, and the subsequent attack by water. *This may be regarded as a case of an acid mediated inhibition of acid catalysis*.[24]

In order to confirm the rate constants found from the NMR data by the non-linear program, the formation of both benzonitrile and phenol from (*E*)-**2** in 1 M HCl at 35 °C was monitored by HPLC. Fig. 3 presents results of a representative experiment. From this figure it can be seen that the experimental points lie close to the predicted progress curves derived from Scheme 3, and the above mentioned rate constants. Finally, we monitored by HPLC the formation of both benzonitrile and phenol from nearly equal amounts of **4** and $NH_3OH^+Cl^-$. The results are presented in Fig. 4. Although the quantitative fit between the experimental points and the calculated progress curves is not very good, they both show the same phenomenon, namely, starting from **4** the phenol is formed initially faster, but after 160–180 min it is overtaken by the benzonitrile. As expected from Scheme 3, the final concentration of phenol is only around two thirds of that of benzonitrile, which equals the initial concentration of (*E*)-**2**. Still, more phenol is formed when starting from **4** and $NH_3OH^+Cl^-$ than when starting from (*E*)-**2** (compare Figs. 4 and 2; note that in the NMR experiment [PhOH] = [H_3PO_4] = one third of the total). In addition, when the initial concentration of (*E*)-**2** is lower, we obtain, as expected, a somewhat higher percentage of PhOH (45% in Fig. 3) because the necessarily lower [NH_2OH] favors the **4** → **5** reaction at the expense of the reverse reaction, **4** + NH_2OH → (*E*)-**2**.

The question arises, why was no sign to such multiple reaction pathways observed in the fragmentation of (*E*)-**1**?[10] One obvious reason is that methanol is a much worse leaving group than phenol, therefore in the case of (*E*)-**1** a reaction analogous to the hydrolysis **4** → **5**, ending in H_3PO_4 formation, would not be expected. However, we should expect equilibrium formation of the ketone, PhCOPO(OH)OMe. Assuming that k_4 and k_{-4} are similar for (*E*)-**1** and (*E*)-**2** and using Dynafit[18] we can calculate that in the concentration range used for NMR analysis in the case of (*E*)-**1** (around 0.04 M),[10] we should expect to see a maximum of 0.0048 M (12%) of the ketone after 70 min but only an easily unnoticeable 0.002 M (5%) after 5 hours when the reaction was actually checked.

Extrapolating from values at other temperatures,[10] we find that in 1 M HCl the fragmentation rate of (*E*)-**1** is 0.020 min^{-1}, namely 4 fold higher than k_3 for (*E*)-**2**. This suggests that the fragmentation of (*E*)-**2** proceeds by a dissociative mechanism, similar to the case of (*E*)-**1**,[10] and leads to phenyl metaphosphate, whose formation should be less favored than that of methyl metaphosphate due to inductive effects. An oxime similar to (*E*)-**1** in which the methoxy group was replaced by the powerful electron withdrawing 2,2,2-trifluoroethoxy group fragmented in 0.6 M HCl in ethanol, at least 10 times slower than (*E*)-**1**.[3,7] In summary, our results show a multifunctional molecule, (*E*)-**2**, which in acidic solution undergoes two competing reactions, fragmentation to metaphosphate and oxime to ketone hydrolysis. Both originate from the oxime-protonated species and are accelerated by acid, while a third reaction, the hydrolysis of the *O*-phenyl group, is apparently retarded by the protonated oxime nitrogen.

Experimental

Materials

Reagent grade inorganic compounds were used. Organic reagents were purified by recrystallization or distillation.

Ethyl phenyl benzoylphosphonate. To benzoyl chloride (14 g, 0.1 mol) placed in a round bottomed flask equipped with an addition funnel was added dropwise diethyl phenyl phosphite in an inert atmosphere with cooling. After the addition was complete, the mixture was allowed to stir at room temperature overnight. The product was distilled *in vacuo*, bp 150–155 °C at 0.4 mmHg. ^1H NMR ($CDCl_3$) 7.41 (10H, m), 4.39 (2H, m), 1.38 (3H, t) ppm.

Phenyl sodium benzoylphosphonate. Ethyl phenyl benzoylphosphonate (29 g, 0.1 mol) was added to a solution of sodium iodide (16.6 g, 0.11 mol) in dry acetone (70 ml) and the reaction mixture stirred at ambient temperature for 24 h. The precipitate was filtered, washed with acetone and dried under vacuum to yield 15.6 g (55%) sodium phenyl benzoylphosphonate sufficiently pure for the next step. ^{31}P NMR (D_2O) 2.26 ppm (s). Anal. Calcd. for $C_{13}H_{10}O_4PNa$: C, 54.92; H, 3.52. Found, C, 54.67; H, 3.78%.

Phenyl sodium α-hydroxyiminobenzylphosphonate. To a solution of sodium phenyl benzoylphosphonate (28.4 g, 0.1 mol) was added hydroxylamine (3.9 g, prepared from $NH_2OH{\cdot}HCl$ by the addition of an equimolar amount of sodium methoxide in methanol and filtration of the precipitated NaCl) and the mixture was stirred for 72 h at ambient temperature. After evaporation of the solvent the residue was washed with dry acetone (50 ml) and dried under vacuum. Yield 41%.^{31}P NMR (D_2O) 4.70 ppm (s). Anal. Calcd. for $C_{13}H_{11}NO_4PNa$: C, 52.17; H, 3.68; N, 4.68. Found, C, 51.97; H, 3.65; N, 4.26%. This sodium salt served as a stable storable precursor of (*E*)-**2** and was converted to it by acidification of its solution *in situ*.

Kinetic measurements

Reactions were initiated by dissolving the desired amount of the sodium salt of (*E*)-**2** or **5**, or the lithium salt of **4**, with or without the desired amount of $NH_3OH^+Cl^-$, in a few milliliters of 1 M HCl at 35 °C. The reactions of (*E*)-**2** were monitored by ^{31}P NMR using a Varian VXR-300S instrument. All spectra were recorded using repetition times sufficiently long for complete relaxation. The relative quantities of the starting material, intermediates, and products were determined by integrating and normalizing the appropriate NMR signals. The chemical shifts were measured relative to an external standard (85% H_3PO_4). They depended on the acidity of the solution. In 1 M HCl we observed the following: (*E*)-**2** $\delta_P = 2.1$, **4** $\delta_P = -4.0$, **5** $\delta_P = -1.7$, **6** $\delta_P = -4.6$, (*Z*)-**2** $\delta_P = -2.6$, H_3PO_4 $\delta_P = 0$ ppm. The NMR peaks of **3–5** and **6** were assigned by comparison with authentic samples.[2,25] The peak of (*Z*)-**2** was assigned by its relative chemical shift (4.7 ppm upfield from that of (*E*)-**2**) that fits the usual differences between the geometric isomers in α-hydroxyiminophosphonates $\Delta\delta_P = 4.3$–4.8 ppm).[7,9,10,26] The reactions of (*E*)-**2**, **4** and **5** (with or without added $NH_3OH^+Cl^-$) were monitored through HPLC by using Hewlett Packard's HP1090 system with Diode Array, the column was a Waters μ-bondapak RP-18, 5 mm × 30 cm, mobile phase: 40 : 60 acetonitrile–water, $\lambda = 230$ nm. The peaks of phenyl phosphate, phenol and benzonitrile were identified by comparing their retention times with those of authentic samples. The concentrations of the latter two compounds were calculated by comparing peak areas with external standards.

References

1 E. Breuer, R. Karaman, H. Leader and A. Goldblum, *J. Chem. Soc., Chem. Commun.*, 1987, 671.
2 E. Breuer, R. Karaman, D. Gibson, H. Leader and A. Goldblum, *J. Chem. Soc., Chem. Commun.*, 1988, 504.
3 J. Katzhendler, R. Karaman, D. Gibson, H. Leader and E. Breuer, *J. Chem. Soc., Perkin Trans. 2*, 1989, 589.
4 A. Schlossman, D. Gibson and E. Breuer, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1990, **49/50**, 81.
5 L. D. Quin, X. P. Wu, E. Breuer and M. Mahajna, *Tetrahedron Lett.*, 1990, **31**, 6281.
6 E. Breuer, M. Mahajna, L. D. Quin and G. S. Quin, *J. Org. Chem.*, 1991, **56**, 4791.
7 E. Breuer and M. Mahajna, *Heteroat. Chem.*, 1992, **3**, 251.
8 M. Mahajna and E. Breuer, *J. Org. Chem.*, 1993, **58**, 7822.
9 M. Mahajna and E. Breuer, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1847.
10 J. Katzhendler, H. Schneider, R. Ta-Shma and E. Breuer, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1961.
11 The present route is preferred over the alternative sequence in which the reaction of hydroxylamine precedes the nucleophilic de-ethylation. In the latter method the yield of the oxime formation was considerably lower, because of competing C–P bond cleavage due to the relatively good leaving group characteristics of the ethyl phenyl phosphonate anion.
12 Benzoylphosphonates are known to give readily, in water or alcohols, hydrates or hemiketals[13,14] that can subsequently undergo fission of the C–P bond to yield benzoic acid or esters and H-phosphonates. The fission is base catalyzed and should be negligible in 1 M HCl (a rate below 10^{-5} min^{-1} can be estimated from results at lower acidities[13]), however, some hydrate could have been formed in an equilibrium process from either **4** or **5**, obviously in quantities too small to be observed in NMR spectra.
13 K. S. Narayanan and K. D. Berlin, *J. Am. Chem. Soc.*, 1979, **101**, 109.
14 J. Katzhendler, I. Ringel, R. Karaman, H. Zaher and E. Breuer, *J. Chem. Soc., Perkin Trans. 2*, 1997, 341.
15 A preliminary communication from our laboratory reported the fragmentation of (*E*)-**3** to metaphosphate some years ago;[2] a detailed account of this reaction is in preparation.
16 When monitoring the reaction through NMR we observed an additional small peak, which was assigned as (*Z*)-**2**. This amounted to 3 ± 2% of the initial oxime concentration and persisted up to 90% reaction. The quality of the NMR data did not permit us to reach quantitative conclusions regarding the oxime isomerization, but the percentage seen agrees with an *E*/*Z* equilibrium ratio of 10–20, which is consistent with the value of 9 found for dimethyl α-hydroxyiminobenzylphosphonate[3] and that of 4–7 found for the monomethyl ester.[10]
17 H. Schneider, PhD Thesis, The Hebrew University of Jerusalem, 1999.
18 P. Kuzmic, *Anal. Biochem.*, 1996, **237**, 260.
19 J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, 1966, **88**, 3973.
20 A. Malpica, M. Calzadilla, T. C. Cordova, S. Torres and G. H. Saulny, *Int. J. Chem. Kinet.*, 1999, **31**, 387.
21 A. Malpica, M. Calzadilla and T. Cordova, *J. Phys. Org. Chem.*, 2000, **13**, 162.
22 (*a*) A. J. Kirby and S. G. Warren, *The organic chemistry of phosphorus*, Elsevier, Amsterdam, 1967, pp. 322–324; (*b*) E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards and M. Isaks, *J. Org. Chem.*, 1970, **35**, 3063.
23 Arnett and coworkers (E. M. Arnett, E. J. Mitchell and T. S. S. R. Murty, *J. Am. Chem. Soc.*, 1974, **96**, 3875) give values of −7.2 for acetone and −0.5 for trimethylphosphine oxide. Recently, Modro and Modro (A. M. Modro and T. A. Modro, *Can. J. Chem.*, 1999, **77**, 890) estimated that the P=O group is about 100-fold more "effective" in hydrogen bonding than the carbonyl group in a similar molecular structure. Although there is no general linear correlation between hydrogen bonding energies and those of protonation valid for different functional groups, qualitatively they are related. In our case, the proximity of the two electron withdrawing groups P=O and C=O may be expected to result in lowering of the basicity of both. However, since the phosphoryl is more strongly electron withdrawing ($\sigma^* = 2.65$, J. Katzhendler, I. Ringel, R. Karaman, H. Zaher and E. Breuer, *J. Chem. Soc., Perkin Trans. 2*, 1997, 341) than the carbonyl ($\sigma^* = 1.65$ for the acetyl group), the basicity of the latter should be affected more than that of the former. The pK_a of the oxime nitrogen in acetoxime was estimated to be around 1.54 (J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi and J. M. Wilson, *J. Org. Chem.*, 1977, **42**, 1593).
24 One of the referees has argued that protonation of the oxime nitrogen in (*E*)-**2** lowers the pK_a of the phosphonic acid thus readily forming a zwitterion, in which the ionized phosphonic group will be relatively resistant to the attack of water. We view this as another way of acid mediated inhibition of the hydrolysis. In addition, in our previous paper[10] we have estimated the pK_a's of the POH group in protonated (*E*)-**1** to be around 0.6, which means that in 1 M HCl only about 20% of it will be present as a zwitterion. The same should apply to (*E*)-**2**. Therefore, the zwitterion alone cannot account for the lack of phenyl ester hydrolysis.
25 R. Karaman, A. Goldblum, E. Breuer and H. Leader, *J. Chem. Soc., Perkin Trans. 1*, 1989, 765.
26 E. Breuer, R. Karaman, A. Goldblum, D. Gibson, H. Leader, B. V. L. Potter and J. H. Cummins, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3047.