Fragmentation of methyl hydrogen α-hydroxyiminobenzylphosphonates—kinetics, mechanism and the question of metaphosphate formation †

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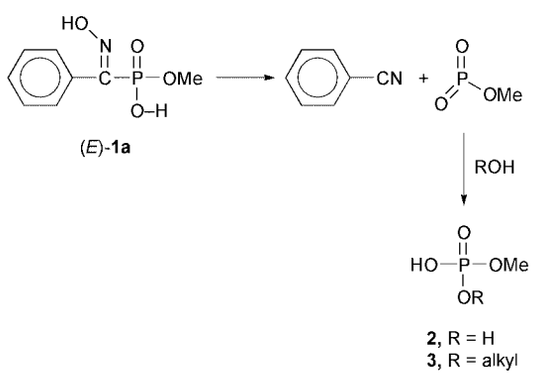
The thermodynamics, pH dependency and solvent effects of the fragmentation reaction of a series of α-oxyiminobenzylphosphonate monomethyl esters [(*E*)-**1a**–**f**] were examined in water and other hydroxylic solvents by UV and by ^{31}P NMR spectroscopy at pH 0–3.1. The fragmentation of compounds (*E*)-**1a**–**f** was found to be a first-order reaction in substrate over the acidity range studied, while the dependence on the acidity is more complex, with rate constants k_1 and k_2. The ρ values corresponding to the first and second order rate constants were −1.12 and −0.835, respectively, indicating that the reaction is facilitated by electron-donating substituents, which probably enhance the protonation of the oxime OH group. Activation parameters for k_1 and k_2 reactions were also calculated. The near-zero values of the entropies of activation obtained are consistent with a dissociative transition state with almost no bonding to a nucleophilic solvent. Monitoring the fragmentation reaction of (*E*)-**1a** in several binary alcohol–water mixtures at different acidities showed that the reaction rate is enhanced by the alcohol's acidity and not hampered by the steric requirements of the alcohol molecule. This rules out in our opinion, the likelihood for nucleophilic solvent assistance in the rate-determining step. On the other hand, product studies show that both the nucleophilicity and the steric requirements of the alcohol are of importance in determining the product formed in the fragmentation of (*E*)-**1a**. The highest selectivity (*S*) value was found for MeOH, while *S* values of <1 were observed for 2,2,2-trifluoroethanol and the sterically hindered alcohols. The divergence between the effects of the solvent on the rate, on the one hand, and on the products on the other, indicates 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. The results are compatible with a dissociative mechanism (D_N*A_N or D_N + A_N), in which the solvating water molecules pull the departing water molecule into the hydration shell, while the solvated phosphonic group becomes a metaphosphate without nucleophilic assistance. The fragmentation of oxyiminobenzylphosphonates to metaphosphate is perceived as a special case of the "abnormal" Beckmann reaction.

Introduction

Previous reports from our laboratory have shown that α-hydroxyiminophosphonic derivatives (*e.g.* (*E*)-**1a**) undergo fragmentation and are capable of performing phosphorylation of hydroxy compounds to yield phosphates **2** and **3** (Scheme 1).[1]

In these papers the versatility of α-hydroxyiminophosphonic derivatives was demonstrated by using a variety of specific types of ester, which could be induced to undergo fragmentation under acidic or basic, thermal or photolytic conditions. While the composition and nature of the phosphorylated products obtained in α-hydroxyiminophosphonate fragmentations pointed to a unimolecular dissociative mechanism involving monomeric metaphosphate species, prior to the present report only a limited kinetic study had been carried out on this reaction.[1b] In view of the importance of the question of the metaphosphate species' existence, both to mechanistic organophosphorus chemistry and to bioorganic chemistry,[2] and in view of the utility of α-hydroxyiminophosphonates as versatile metaphosphate precursors,[3] we felt that a rigorous kinetic–mechanistic study of the fragmentation of some representative α-hydroxyiminophosphonates was needed. In this paper we report kinetic studies of the fragmentation of α-hydroxyiminobenzylphosphonic acid monomethyl ester [(*E*)-**1a**], some of its ring-substituted derivatives [(*E*)-**1b**–**e**] and the corresponding oxime methyl ether [(*E*)-**1f**] (Scheme 2) in water and in mixed alcohol–water solutions under acidic conditions.



Scheme 1

† UV spectra, pH–rate profiles and rate constants for the fragmentations of some of (*E*)-**1a**–**f** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b002267p

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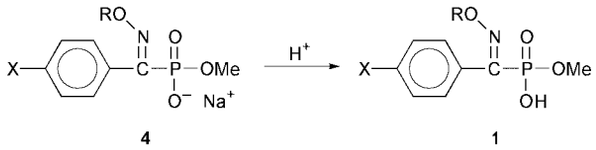


4 **1**

a, R = X = H; **b**, R = H, X = OMe; **c**, R = H, X = Me; **d**, R = H, X = Cl; **e**, R = H, X = CF_3; **f**, R = Me, X = H.

Scheme 2

Experimental

Materials

Reagent grade inorganic compounds were used. Organic reagents were purified by recrystallization or distillation. Substituted dimethyl α-hydroxyiminobenzylphosphonates were obtained as mixtures of (*E*) and (*Z*)-isomers by reacting dimethyl (substituted) benzoylphosphonates with hydroxylamine or methoxylamine as described previously.[4] Treatment of the (*E*) + (*Z*) isomeric mixtures with methanolic HCl, followed by recrystallization, afforded the pure (*E*)-isomers, which were monodemethylated to give compounds **4** by treatment with sodium iodide in acetone, as described previously.[4] Compounds **4** served as stable storable precursors of compounds **1**, which were the subject of the kinetic studies, and to which they were converted *in situ*.

Kinetic measurements

The rates for the fragmentation reaction of (*E*)-**1a**–**f** in aqueous solution were determined by monitoring the decrease in their absorbance at 240–250 nm and the increase in the absorbance of the evolving benzonitrile at 220–230 nm at 30 or 50 ± 0.1 °C and ionic strength of 1.0 M (KCl) (see Figure S1). Reactions were monitored by ultraviolet spectroscopy using a Varian DMS 80 UV-visible recording spectrophotometer equipped with an automatic cell changer. Constant temperature was maintained by the use of a thermostated cell compartment. Reactions were initiated by adding 50 μl of 1 mg ml^{-1} (stock solution) of the appropriate hydroxyiminobenzylphosphonate sodium salt (**4**) to 3.0 ml of solution containing buffer or HCl. The rates were measured at a pH of 0–3.1. Hydrochloric acid was used for pH control at a pH below 1.5 and above it two buffer systems were employed, glycine ($pK_a = 2.45$) and chloroacetic acid ($pK_a = 2.7$). The first order rate constants k_{obs} were determined at five buffer concentrations (0.1–0.5 M) for each buffer ratio. Plots of k_{obs} against total buffer concentration occasionally showed slight linear changes. The pH of each run was determined before and after its completion using Metrohm 633 Titroprocessor pH meter equipped with a combined glass electrode. The pD values for reactions carried out in D_2O were obtained by adding 0.40 to the observed pH of the solution.[5] Experiments in binary solvent systems (alcohol–water mixtures) were carried out in 1 M and 0.1 M HCl.

Product studies

Solutions of compounds (*E*)-**4a**–**f** (5 mg ml^{-1}) in various alcohol–water mixtures (20–80%) containing 1 M HCl were allowed to stand for 24 h at room temperature and were then analyzed by ^{31}P NMR spectroscopy using a Varian VXR-300S instrument. The ratios of the products from the reaction with water (methyl dihydrogen phosphate **2**) and those from the reaction with alcohols (alkyl methyl hydrogen phosphate, **3**) were determined by integrating the appropriate NMR signals. Peaks of the reaction products were identified by their multiplicities. The chemical shifts depended on the solvent compositions. The ranges of chemical shifts were: **2** $\delta_P = 2.03$–2.18, **3g**, (R = Et) $\delta_P = 0.05$–0.6, **3h**, (R = 2-Pr) $\delta_P = [-0.6]$–$[-1.25]$, **3i** (R = 2,2,2-trifluoroethyl) $\delta_P = [-0.53]$–$[-1.0]$, **3j** (R = *t*-Bu) $[-0.7]$–$[-0.96]$ ppm. All spectra were recorded using repetition times long enough for complete relaxation. The percentage values of the components of the reaction mixtures are raw data obtained from the integrated ^{31}P NMR spectra and thus, possibly, they are not a precise representation of the actual molar ratios of the components.

Activation parameters

These were determined from the temperature dependence of the rate constants (2 or 3 temperatures) using the Eyring equation: $k = \Delta T/h \, (\exp -\Delta H^{\ddagger}/RT)(\exp \Delta S^{\ddagger}/R)$.

Dissociation constants

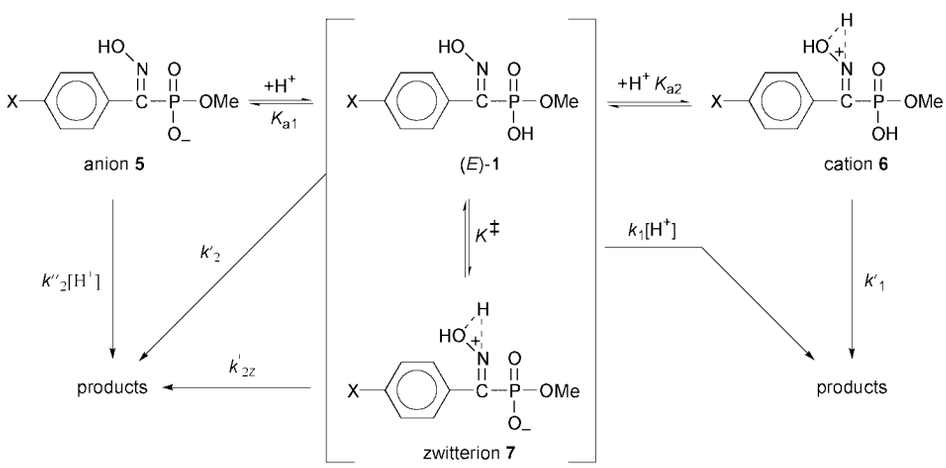
The dissociation constants of **1a**–**e** in water were determined by potentiometric titration of **4a**–**e** (0.25 mmol) up to 50% acidification. The pK_a values thus obtained were 1.86–2.0. The pK_a of (*E*)-**1a** in D_2O was found to be 2.30.

Results

Scheme 3 outlines the various feasible kinetic pathways for the fragmentation of **1a**–**f**.

pH–rate profiles

The fragmentation of compounds **1a**–**f** is first order in substrate over the acidity range studied. The rate constants as function of pH are collected in Table S1 (30 °C) and Table S2 (50 °C) and are shown in Fig. 1 and Fig. S2. The lines in Figs. 1 and S2 have been fitted to eqn. (1), which was derived from Scheme 3. Eqn. (1) delineates the dependence of the first order rate constants on the pH.



anion **5** (*E*)-**1** cation **6** zwitterion **7** products products

Scheme 3

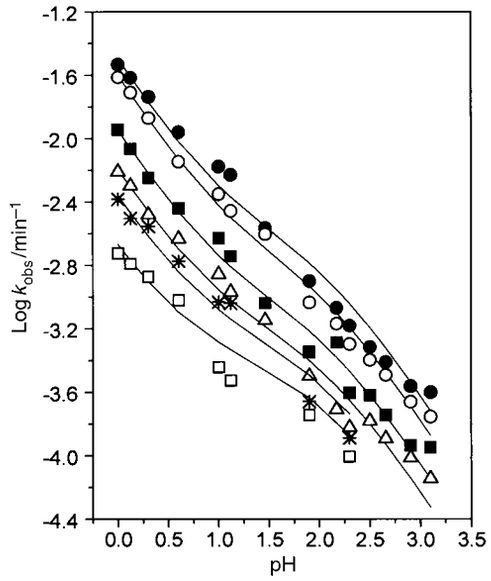


Fig. 1 pH–rate profiles for the hydrolysis of *p*-substituted methyl (*E*)-α-hydroxyiminobenzylphosphonates at 30 °C. (*E*)-**1a**, (X = H, R = H) -■-; (*E*)-**1b**, (X = OMe, R = H) -●-; (*E*)-**1c**, (X = Me, R = H) -○-; (*E*)-**1d** (X = Cl, R = H) -Δ-; (*E*)-**1e** (X = CF_3, R = H) -⁎-; (*E*)-**1f**, (X = H, R = Me) -□-.

$$k_{obs} = \frac{k_1[H^+]^2 + [k'_2 + k''_2K_{a1}][H^+]}{K_{a1} + [H^+]} = \frac{k_1[H^+]^2 + k_2[H^+]}{K_{a1} + [H^+]} \quad (1)$$

Where: $k_2 = k'_2 + k''_2K_{a1}$

The fragmentation of (*E*)-**1** may proceed either *via* a specific acid-catalyzed reaction $k_1[H^+]$ or through a non-catalyzed reaction pathway k'_2. The specific acid-catalyzed fragmentation of the anion **5** ($k''_2[H^+]$) is kinetically equivalent to the latter (k'_2) route. As no reaction was observed above pH 6 for any of the compounds, even after a month, the uncatalyzed fragmentation of **5** must have a very low rate constant (< 10^{-7} min^{-1}) and need not be considered. The kinetic data at various pH values were fitted to eqn. (1) by means of a non-linear least squares regression program PCNONLIN version 4 (SCI software). The independent parameters k_1 and k_2 were introduced without any constraint. The dissociation constant, K_{a1}, was taken as 0.01 M.

The mechanistic scheme for the hydronium catalyzed and uncatalyzed fragmentation of (*E*)-**1a**–**f** (Scheme 3) can be expanded to involve a rapid pre-equilibrium formation of the reactive cationic and zwitterionic forms, **6** and **7** (Scheme 3) which proceed to products. In such a case the rate constants k'_1 and k'_{2Z} will equal approximately k_1K_{a2} and $k_2K^‡$ respectively, where k'_1 and k'_{2Z} correspond to the rate constant of the cation **6** and zwitterion **7**. The calculated rate constants are presented in Table S3.

The σ–ρ plots for k_1 and k_2, obtained from the data listed in Table S3, are presented in Fig. 2. The corresponding ρ values were −1.12 and −0.835, respectively. It can be seen that the reaction is facilitated by electron-donating substituents, which probably enhance the protonation of the oxime group. Activation parameters for k_1 and k_2 reactions are displayed in Table 1. The near-zero values of the entropies of activation obtained are consistent with a dissociative transition state with almost no bonding to a nucleophilic solvent. The solvent isotope effects ($k^H_1/k^D_1 = 0.55$, and $k^H_2/k^D_2 = 0.71$, Table 1) observed indicate that the reaction proceeds *via* specific acid catalysis and that fragmentation of the neutral species, (*E*)-**1**, is in accord with a pre-equilibrium proton transfer in the ground state.[6]

Buffer effect

It was of interest to clarify whether the fragmentation reaction is subject to general acid catalysis. However, attempts to correlate k_{obs} with the total buffer concentrations of 0.1–0.5 M of glycine ($pK_a = 2.45$) or chloroacetic acid ($pK_a = 2.7$) at pH 1.9–3.1, failed to give a definitive answer. At pH <2.5 a modest linear increase of k_{obs} against the total buffer concentration (up to 70% at 0.5 M buffer) was usually observed, but the slopes of the lines at different pH's showed only a qualitative fit with the free acid percentage. At pH >2.5 the occasional increases were very small. Therefore, we cannot say with any certainty that the fragmentation reaction is subject to general acid catalysis. In addition, several measurements in various 0.5 M buffers in the pH range 4.5–9.2 showed no general acid or base catalysis of the unmeasurably slow fragmentation rate at this range.[7]

Exceptionally, cacodylic acid ($pK_a = 6.15$) displayed a substantial effect on both the fragmentation and isomerization rate of (*E*)-**1a**. The reaction was carried out using a cacodylate buffer concentration of 0.5 M at 25 °C on both the pure (*E*)-**1a** and a mixture of 55% (*E*)-**1a** and 45% (*Z*)-**1a**. The reactions were monitored by ^{31}P NMR and the results are presented in Table S4. Fig. 3 shows the percentage–time curves for the mixture. The time–percentage data presented in Table S4 were fitted to eqn. (2) using the program PCNONLIN version 4 (SCI

$$(Z)\text{-}\mathbf{1a} \underset{k_{EZ}}{\overset{k_{ZE}}{\rightleftharpoons}} (E)\text{-}\mathbf{1a} \overset{k_f}{\rightleftharpoons} \mathbf{2} \quad (2)$$

software). This program can deal with fitting simultaneously the observed concentrations of (*Z*)-**1a**, (*E*)-**1a**, and MeH_2PO_4 (**2**) to the series of differential kinetic eqns. (3) derived from eqn. (2).

$$d[(Z)\text{-}\mathbf{1a}]/dt = -k_{ZE}[(Z)\text{-}\mathbf{1a}] + k_{EZ}[(E)\text{-}\mathbf{1a}] \quad (3a)$$

$$d[(E)\text{-}\mathbf{1a}]/dt = k_{ZE}[(Z)\text{-}\mathbf{1a}] - (k_{EZ} + k_f)[(E)\text{-}\mathbf{1a}] \quad (3b)$$

Table 1 Activation parameters for the fragmentation of (*E*)-**1a** and (*E*)-**1b** and the solvent isotope effect for (*E*)-**1a** at 50 °C[a]

Compound	$\Delta H^‡(k_1)$ $\Delta S^‡(k_1)$	$\Delta H^‡(k_2)$ $\Delta S^‡(k_2)$	$\Delta H^‡(k'_1)$ $\Delta S^‡(k'_1)$	k^H_1/k^D_1	k^H_2/k^D_2
(*E*)-**1a**	21.2	26.7	21.2	0.55	0.71
	−6.4	7.0	1.8		
(*E*)-**1b**	21.0	24.0	21.0		
	−4.8	−0.15	2.3		

[a] $\Delta H^‡$ values are in kcal mol^{-1} and $\Delta S^‡$ values are in e.u.

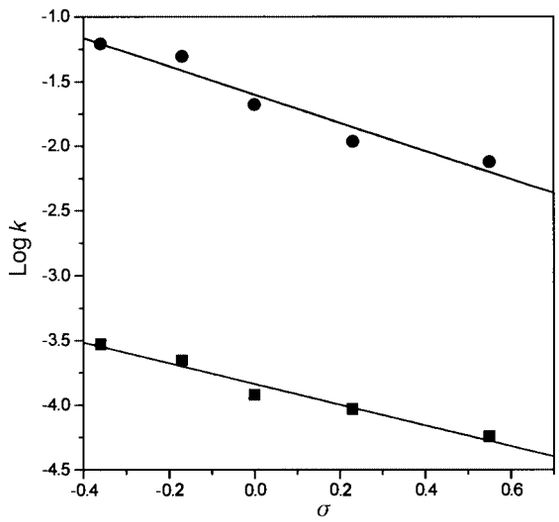


Fig. 2 Hammett plots for the specific acid-catalyzed fragmentation of *p*-substituted methyl hydrogen (*E*)-α-hydroxyiminobenzylphosphonates (*E*)-**1a**–**e**, k_1 -●-; and for the non-catalyzed fragmentation of the neutral species, k_2 -■-, at 30 °C.

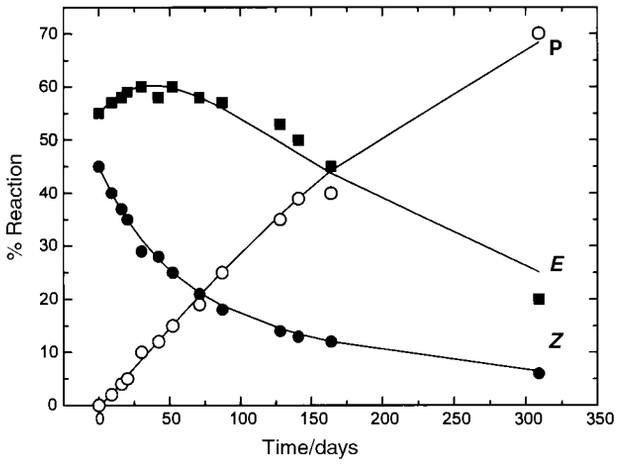


Fig. 3 Percentage–time curves for (*Z*)-**1a**, ●, (*E*)-**1a**, ■, and methyl dihydrogen phosphate, **2**, ○, in 0.5 M cacodylate buffer pH = 6.21 at 25 °C. The points represent observed values. The solid curves were obtained by introducing the rate constants to the differential eqns. (3a), (3b) and (3c).

$$d[\mathbf{2}]/dt = k_f[(E)\text{-}\mathbf{1a}] \quad (3c)$$

where k_{EZ} and k_{ZE} are the rates of isomerization between the (*E*) and (*Z*) forms of **1**, and k_f is the rate of fragmentation of **1** to give **2**.

The rate constants k_{ZE}, k_{EZ} and k_f derived from the kinetic data for the pure (*E*)-**1a** are: $k_{ZE} = 1.68 \times 10^{-5}$ min^{-1}, $k_{EZ} = 2.48 \times 10^{-6}$ min^{-1} and $k_f = 3.45 \times 10^{-6}$ min^{-1}. The corresponding rate constants derived from the (*E*) + (*Z*) mixture of isomers are: $k_{ZE} = 1.23 \times 10^{-5}$ min^{-1}, $k_{EZ} = 2.47 \times 10^{-6}$ min^{-1} and $k_f = 3.43 \times 10^{-6}$ min^{-1}. Inspection of the determined rate constants reveals that k_{ZE} is 4–7 times greater than the rate constants k_f and k_{EZ}. This implies that, at the initial stage of the fragmentation process of the mixture, isomer (*E*)-**1a** will be accumulated along the reaction course. Indeed the time–concentration curve of (*E*)-**1a** in Fig. 3 shows that the concentration of latter rises up to 60% after 42 days and then it descends with the reaction's progression. The (*Z*)–(*E*) interconversion does not reach an equilibrium state, since such a case would require that k_{EZ} should be significantly larger than k_f, which is not the case. It is worthy of note that, in contrast to the specific acid catalysis in methanol,[1b] in the case of cacodylic acid as catalyst in water, it was possible to follow the rate of the interconversion of (*E*)-**1a** to (*Z*)-**1a**. This is probably due to the fact that cacodylic acid catalyzed both the fragmentation reaction of (*E*)-**1a** to **2** and the isomerization of (*E*)-**1a** to (*Z*)-**1a** (k_f and k_{EZ}, respectively, in eqn. (2)) so that they proceed at similar rates (see above). In contrast, the rate constant of the specific acid catalyzed fragmentation in methanol is around 14 times greater than k_{EZ}.[8]

Solvent effect

The fragmentation reaction of (*E*)-**1a** was monitored in several binary alcohol–water mixtures (v/v) at different acidities. The results are summarized in Tables S5 and S6 and presented graphically in Figs. 4 and S3. The main observations were as follows:

(*a*) In 1 M HCl in water, in 20–90% ethanol–water (EtOH–W), 90% methanol, 90% propan-2-ol (IPA) and 90% *tert*-butyl alcohol (TBA), practically the same observed rate constant of $(1.15 \pm 0.05) \times 10^{-2}$ min^{-1} was obtained (Tables S1 and S5). In contrast, in 10–90% 2,2,2-trifluoroethanol (TFE) in water, a gradual increase of the rate (up to 4 fold) was seen (Fig. 4 and Table S6). The observation that in 1 M HCl the rate was enhanced only by TFE suggests that it is the alcohol acidity which is important, as this is the only factor which distinguishes TFE from the other alcohols and from water (pK_a of TFE = 12.4[9]). This, and the insensitivity of the rate to the steric

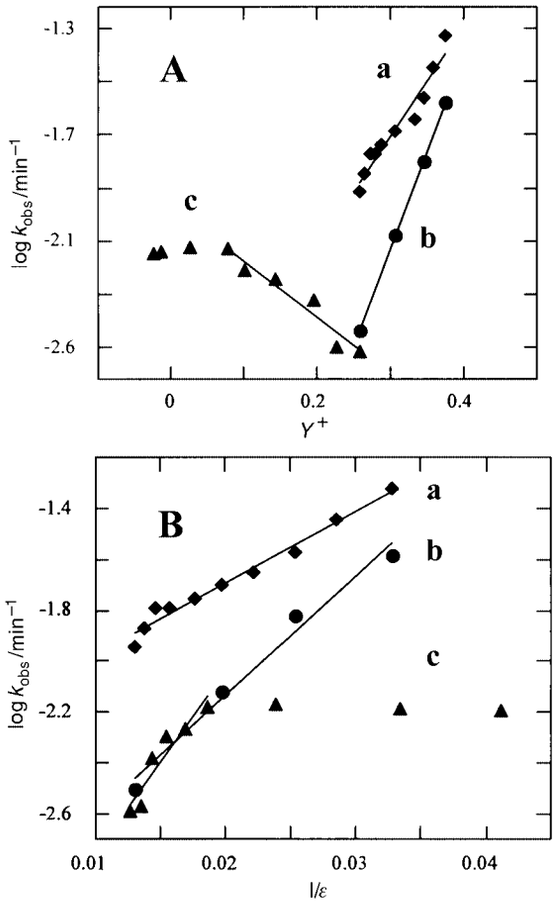


Fig. 4 Log k_{obs} for the fragmentation of (*E*)-**1a** in (a) TFE–W, 1 M HCl, 30 °C; (b) TFE–W, 0.1 M HCl, 30 °C and (c) EtOH–W, 0.1 M HCl, 25 °C against (A) Kevill and Anderson Y^+ values (D. N. Kevill and S. W. Anderson, *J. Am. Chem. Soc.*, 1986, **108**, 1579); (B) The inverse of the relative permittivities (1/ε). Values for TFE–W interpolated from J. Murto and E. L. Hieno, *Suom. Kemistil.*, 1966, **B39**, 263. Values for EtOH–W are from Y. Y. Adhadov, in *Dielectric Properties for Binary Solutions*, 1981, Pergamon, Oxford, p. 278. For slopes and correlations see text.

requirements of the alcohol molecule, seems to rule out the likelihood of nucleophilic solvent assistance in the rate-determining step. The same conclusion had been reached previously for the fragmentation of (*E*)-**1a** in pure MeOH, EtOH, IPA and TBA in 0.55 M HCl, as in all these alcohols similar rate constants were obtained.[1b]

(*b*) In 0.1 M HCl, for both EtOH and TFE the rate increased up to 50% ROH; however the increase with TFE did not "flatten" above 50% alcohol as it did with EtOH (Fig. 4 and Table S6).

(*c*) The rate increase with %TFE was twice as steep in 0.1 M HCl as in 1M (Fig. 4 and Table S6).

(*d*) The rate in ethanol–water mixtures above 80% EtOH and [HCl] > 0.045 M does not change significantly with the HCl concentration (Table S5). This probably fortuitous constancy could be because EtOH, like TFE, enhances the reaction more when the acidity is lower.

Several attempts were made to correlate the values in Table S6 with various known solvent parameters. The correlations with Grunwald–Winstein Y values[10] or with Schadt, Bentley and Schleyer Y_{AdOTs} values[11] were only reasonable with negative m values (Fig. S3). A better correlation was achieved with Kevill and Anderson Y^+ values,[12] which are based on the solvolysis of 2-AdSMe$_2^+$, and reflect only the solvent's ionizing power (Fig. 4A). The m values in 0–90% TFE–W are large and positive, 4.5 ($r = 0.9707$) with 1 M HCl and 7.8 ($r = 0.9998$) with 0.1 M HCl, however in 0–50% EtOH–W and 0.1 M HCl, m is negative, −2.3 ($r = 0.9682$). The best correlation was achieved against

Table 2 Selectivity[a] in product formation in the acid (1 M HCl) catalyzed fragmentation of (*E*)-**1a** in several binary alcohol–water mixtures at 25 °C

	Selectivity values					
ROH–H_2O[b]	MeOH E_s[e] = 0	EtOH $E_s = -0.07$	TFE	IPA $E_s = -0.47$	2-BuOH[c] $E_s = -1.13$	3-PeOH[d] $E_s = -1.98$
80:20	1.54	1.13	0.64	0.75	0.58	0.46
60:40	2.36	1.29	0.72	0.78	0.45	0.66
40:60	3.50	1.38	0.61	0.68	0.52	
20:80	3.26	1.95	0.65	0.68	0.50	

[a] Calculated using eqn. (4). [b] Molar ratio. [c] Butan-2-ol. [d] Pentan-3-ol. [e] The definition of E_s and the numerical values are given by R. W. Taft, Jr., in *Steric effects in organic chemistry*, ed. M. S. Newman, John Wiley & Sons, New York, 1956, pp. 598–599.

the inverse of the relative permittivity (Fig. 4B) and the slopes were all positive, namely 28 ($r = 0.9880$), 47 ($r = 0.9903$) and 71 ($r = 0.9453$), for the three solvent systems mentioned above.

Product distribution

Methyl hydrogen α-hydroxyiminobenzylphosphonate, (*E*)-**1a**, was allowed to undergo fragmentation in 1 M HCl in several binary alcohol–water mixtures. The ratios of the two phosphates, **2** and **3**, obtained were determined by ^{31}P NMR spectroscopy. Selectivity values, *S*, were calculated as shown in eqn. (4). The results are summarized in Table 2.

$$S = [\mathbf{3}][W]/[\mathbf{2}][ROH] \quad (4)$$

In addition, product ratios were determined and selectivities calculated in three ternary solvent systems: In EtOH–IPA–W 44:31:24 (molar ratios), the selectivity values found were 1.38:1:1, in MeOH–IPA–W 42:33:25 the values found were 2.2:0.67:1 and in MeOH–TFE–W 30:30:40 they were 1.53:0.48:1. The selectivity between 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP, $pK_a = 9.3$[9]) and water (W) was measured. HFIP was found to be almost completely unreactive. In 80% and 60% HFIP the water product (**2**) was obtained almost exclusively (94% and 100%, respectively).

The results clearly show that both the nucleophilicity and the steric requirements of the solvent are of some importance in determining the product formed in the fragmentation of (*E*)-**1a**. The highest *S* value was found for MeOH, while *S* values of <1 were observed for TFE and the sterically hindered alcohols. However, the differences are moderate and MeOH is only 2–5 times more reactive than TFE or IPA, both in binary ROH–W mixtures, relative to W, and in the ternary systems. The *S* values of the three secondary alcohols are not as different from each other as could be expected from their E_S factors (Table 2). The *S* values in the binary mixtures MeOH–W and EtOH–W increase markedly when the alcohol's molar percentage decreases. This phenomenon is well documented and most probably stems from changes in the activity coefficients of the solvent components.[13]

Discussion

Because of the bifunctional nature of hydroxyiminophosphonates (phosphonates on the one hand and oximes on the other hand) the results will be discussed first in the context of phosphate and phosphonate chemistry, and then in the context of the chemistry of oximes.

As a result of extensive studies over the past decades, it has become recognized that several types of mechanism may be involved in the hydrolysis of phosphates.[14] Phosphomonoester monoanions generally undergo hydrolysis faster than the phosphodi- and -tri esters, and also faster than the other protoionic species, such as the dianion (except for those derived from phenols having a pK_a <5.5) and the neutral acid. Consequently, it was suggested that phosphate monoesters hydrolyze *via* a dissociative mechanism ($D_N + A_N$) involving a metaphosphate-like transition state.[14–17] Metaphosphate anion was suggested as a reaction intermediate in phosphate hydrolyses in which two or more of the following characteristics were observed. 1) The reactivity of the phosphate monoanion is greater than that of the neutral species and, with good leaving groups, the reactivity of the dianion is greater still, arguing against a rate limiting nucleophilic attack on the phosphorus. 2) There is a large dependence of reactivity on the pK_a of the leaving group. 3) The hydrolysis has near-zero values of $\Delta S^{\ddagger}$. 4) The solvent deuterium isotope effect is small, but the leaving oxygen (^{18}O) isotope effect is substantial. 5) The products in alcohol–water mixtures show little selectivity towards the nucleophilicities or steric requirements of the solvent components.

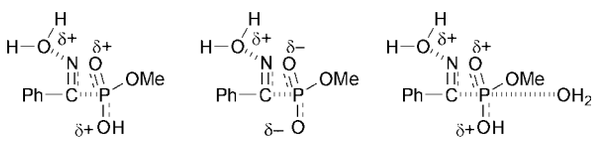
Phosphodiesters[18] and phosphonate monoesters[19] hydrolyze mainly through a concerted, A_ND_N (S_N2 (P)) type process with a transition state resembling phosphorane, although in some cases an $A_N + D_N$ mechanism (*via* a pentacoordinated phosphorane intermediate) may operate.[20] In addition, phosphodiester hydrolysis can be catalyzed intramolecularly by nucleophiles such as carboxy,[21] hydroxy,[21d,22] and amino[23] groups. In the case of phosphate diesters the appropriate physical parameters reflecting the nature of the transition state (S_N2-like) are: a) entropy of activation $\Delta S^{\ddagger} = -14$ to -26; b) $\beta_{lg} = -0.9$ to -1.0[24] (a value of $\beta_{lg} = -1.25$ was found for the intramolecular aminolysis reaction of arylphosphorylethanolamines[23a] and for aryl 2-carboxyphenyl phosphates[21a]), and $\beta_{nuc} = 0.3$–0.47 (for some intramolecular reactions β_{nuc} approaches a value of 0.7[21a]); and *c*) solvent isotope effect of 1.0–1.55.[18a,b,21a]

In the case of phosphodiester hydrolysis, the heavy atom isotope effects clearly indicate an S_N2 process with a slightly higher bond order of the nonbridging atom, suggesting a slight dissociative character.[18c] Hydrolyses of phosphodiesters and phosphonate monoesters do not proceed *via* a metaphosphate intermediate or a similar transition state, presumably, since they possess only one oxyanion of low basicity, which is inadequate to serve as an internal nucleophile. This is in contrast to phosphomonoesters, in which the driving force for the dissociation comes from the two negatively charged oxygens, which contribute a push to the departing group.

α-Hydroxyiminobenzylphosphonic acid monoesters (*E*)-**1a**–**f**, having also only one ionizable oxygen, resemble ordinary alkylphosphonate monoesters, in so far as their anion form, **5**, is not reactive. At low pH however (Table S1, Table S2, Fig. 1 and Fig. S2), they resemble phosphomonoester monoanions in the ease of their fragmentation. As shown in previous work, (*E*)-**1a** can act as phosphorylating agent of hydroxy compounds, and the composition and nature of the phosphorylated products formed suggest the operation of a unimolecular dissociative mechanism involving methyl metaphosphate.[1] Comparison between the rate constant for the acid-catalyzed fragmentation of compound (*E*)-**1a** and those for the acid-catalyzed hydrolyses of phosphodiesters and phosphonate monoesters reveals that the former has an enhanced rate constant even when the latter have very good leaving groups. The

rate constants for acid-catalyzed hydrolysis (k_1 M^{-1} min^{-1}) of bis(2,4-dinitrophenyl) phosphate,[18a] 4-nitrophenyl 2-pyridylphosphonate,[23b] 4-nitrophenylphenylphosphonate,[23b] 2-carboxyphenyl phenylphosphate,[21a] are: 2.8×10^{-4} (25 °C), 2.1×10^{-3} (60 °C), 2.8×10^{-3} (60 °C), and 2.9×10^{-4} (40 °C), respectively, while the corresponding rate constant (k_1) of compound (*E*)-**1a** is 9.7×10^{-2} M^{-1} min^{-1} at 50 °C. The fragmentation of compound (*E*)-**1a** is faster than the acidic hydrolysis of methyl dihydrogen phosphate (**2**).[25] The same trend was observed in the uncatalyzed fragmentation of (*E*)-**1a**. The neutral species, **2**, hydrolyzes[15c] with a rate constant of 3×10^{-5} min^{-1} (100 °C), whereas compound (*E*)-**1a** fragments with a rate constant of $k_2 = 15.7 \times 10^{-3}$ min^{-1} at 50 °C. This increased reactivity of (*E*)-**1a,** as compared to the phosphate and phosphonate esters, is probably caused by the thermodynamically favored, synchronized, irreversible two (N–O and C–P) bond cleavage.[26]

The two types of transition state structures considered for the fragmentation of (*E*)-**1a** are illustrated by structures **8** and **9**. Transition states **8a** and **8b** show a dissociative process with a



8a **8b** **9**

high degree of P–C and N–O bond breaking and an incipient methyl metaphosphate. In structure **9** a water molecule is partially bound to the methyl metaphosphate-like transition state, and provides nucleophilic assistance to the leaving group departure. In another feasible transition state similar to **9** (not shown), the preassociated water molecule does not interact covalently with the incipient methyl metaphosphate. It serves as a spectator within the solvation shell, and is rapidly captured by the discrete methyl metaphosphate molecule, before it escapes from its solvation sphere.

A salient feature of the transition states shown is that all three of them require a synchronized (concurrent) cleavage of two bonds, ruling out the possibility of a reverse reaction. Thermodynamically, this feature provides a strong impetus towards product formation. Protonation of the oxime OH group of compounds (*E*)-**1a**–**e** appears to render a strong pull to P–C bond cleavage, so that only a small internal push by a weakly nucleophilic phosphoryl oxygen anion is required to complete the reaction. In such a case transition states **8** will predominate. Indeed, the near-zero entropy of activation values ($\Delta S^{\ddagger}$ (k_1) = −6.4 and −4.8 and $\Delta S^{\ddagger}(k_2)$ = 7.0 and −0.15 e.u.) obtained for the fragmentation of compounds (*E*)-**1a** and (*E*)-**1b** respectively (Table 1) are consistent with a dissociative pathway. In this regard it is noteworthy that α-hydroxyiminobenzylphosphonate diesters, in which the phosphorus oxygen atoms are not able to serve as internal nucleophiles, do not undergo this type of fragmentation at all.[4,27]

The assumption that the compounds (*E*)-**1a**–**f** fragment through an intermediate is supported by the opposing effects of the solvent components on the rate and the products in binary alcohol–water mixtures. An increase in the proportion of TFE in the medium (in 1 M HCl) causes an increase in the rate, but the selectivity for the TFE-derived product is only around 0.65. In contrast, the more basic (nucleophilic) alcohols, like MeOH and EtOH (in 1 M HCl) do not have any effect on the rate, but the selectivity for MeOH or EtOH-derived products is greater than 1 (Tables 2, S5 and S6). This clear divergence between the effect of the solvent components on the rate and on the products in hydroxyiminophosphonate fragmentation is an indication 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.

In transition state **8a** the positive charge is dispersed over several atoms, while in **8b** both the positive and negative charges are dispersed and partially cancelled. This explains the linear positive dependence of the log k_{obs} on the inverse of the relative permittivities, which was found for both TFE–W and EtOH–W mixtures at 0.1 M HCl (Fig. 4B). The large positive slopes against Y^+ in TFE–W and the negative one in EtOH–W attest also to the greater importance of charge dispersion here than in the Y^+ model system with $AdSMe_2^+$. Yet, the need to protonate the oxime hydroxy is no less important, and might be the reason why the k_{obs} values in 0.1 M HCl did not change above 50% EtOH, and why in 1 M HCl only the relatively acidic alcohol TFE still enhanced the reaction, while even 90% of the more basic alcohols (methanol, ethanol, propan-2-ol and *tert*-butyl alcohol) did not (Table S5). It is possible that no change is seen in the k_{obs} values in 1 M HCl, because the effect of alcohols promoting the fragmentation by reducing the relative permittivity is offset by their basicity and competition for the proton against the oxime hydroxy. As the oxime protonation is endothermic, it is reasonable that an EtOH molecule, being more basic than water, would be a worse mediator, while TFE would be a better one.

At first glance it might seem irreconcilable that EtOH does not accelerate the reaction in the presence of 1 M HCl, but does so in the presence of 0.1 M acid (Table S5 and Table S6). This implies that at higher acidity the reaction is impeded to a greater extent by competition with the basic solvent than it is at lower acidity. Two factors might contribute to this effect: a) The protonation of the oxime is expected to be easier (lower $\Delta H^{\ddagger}$ and higher pK_a) when the phosphoryl group is anionic (structure **5**), rather than neutral.[28] b) The fragmentation of the anionic (*E*)-**1a** proceeds through transition state **8b**, in which there is cancellation of charges and not merely dispersion of charge like in **8a**, so it is more sensitive to changes in relative permittivity. Therefore, in more dilute acid (0.1 M), where more ionized (*E*)-**1a** reacts through **8b**, the total effect of adding EtOH might be more noticeable than in stronger acid (1 M). Furthermore, when [H^+] decreases from 1 M to 0.045 M and there is a continuous increase in the fraction of fragmentation through **8b**, the beneficial effect of high EtOH concentration increases and compensates for the lower acid concentrations, resulting, above >50% EtOH, in k_{obs} values which effectively do not change with the pH (Table S5). Rough calculations, taking into account the ratio $k_1 \sim 10k_2$ (Table S3), suggest that the experimental observations, upon changing the medium from water to 99% EtOH, are in accord with a 6–7-fold increase in k_2, coupled with a 2-fold decrease in k_1.

Having concluded that product formation is from the unstable metaphosphate, we may consider whether the product distribution in binary and ternary solvent systems can further unravel the nature of the metaphosphate. Can this intermediate be regarded as a free one with a short but sufficient life time to discriminate between the solvent molecules ($D_N + A_N$), or is it trapped faster than it can diffuse away from the solvent cage in which it was formed ($D_N{*}A_N$)?

In our opinion, the selectivity results presented earlier show a clear preference of the metaphosphate for the more nucleophilic solvent component. *S* values for EtOH are 2–3 times higher than for TFE (Table 2) and while in HFIP–W in 80 : 20 molar ratio we obtained only 6% of the alcohol product, 2-PrOH gave, under similar conditions, 75% of the alcohol product. Moreover, the preference for MeOH or EtOH over W cannot be attributed to solvent sorting of the starting material, as (*E*)-**1a** is quite hydrophilic, especially when it is protonated or ionized, and should prefer water over alcohol in its immediate surroundings. The sensitivity of product formation to the size of the nucleophile is moderate, as expected for a reactive planar intermediate.

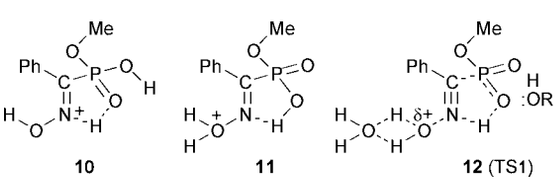
The Hammett ρ parameters are consistent with a dissociative type mechanism. The values of $\rho(k_1) = -1.12$, $\rho(k_2) = -0.835$

were derived from the Hammett plot (Fig. 2) for the acid-catalyzed fragmentation of *para*-substituted methyl α-hydroxyiminobenzylphosphonates [(*E*)-**1a**–**e**]. The negative values obtained indicate that the reaction is enhanced by electron donating substituents. This electron donating effect tends, on the one hand, to decrease the electrophilicity of the phosphorus atom and, on the other hand, to assist the departure of the protonated oxime OH group. If transition state **9** is involved, the two effects will operate in opposite directions (the rate of a nucleophilic attack on phosphorus will decrease and that of the departure of H_2O will increase) and as a result, the apparent ρ value should be close to zero, which is not the case. The Hammett coefficients for the acid hydrolysis of benzaldehyde dimethyl acetal and for acetophenone dimethyl acetal were reported to be $\rho = -3.3$[29] and $\rho = -3.6$,[30] respectively. The much smaller negative value of $\rho = -1.12$ observed for the fragmentation of **1a** indicate that the reaction had proceeded a considerable way along the reaction coordinate, a large amount of charge had diminished and the transition state had become more product-like (late TS). The same arguments are valid also for the neutral species of compounds **1a**–**e**. The fragmentation of these uncharged species probably proceeds *via* the corresponding zwitterions, **7** (Scheme 3).

The deuterium isotope effect is not a good criterion for differentiation between the dissociative and the associative mechanisms, since it reflects only the degree of proton transfer in a termolecular transition state. Reactions subjected to general catalysis will display large solvent isotope effect values (>2), whereas the value of about 1 is associated with specific catalysis (acid and base). The ratios of $k^{H}_1/k^{D}_1 = 0.55$ and of $k^{H}_2/k^{D}_2 = 0.71$ found for the fragmentation of (*E*)-**1a** agree with a specific acid-catalyzed reaction. The solvent isotope effect for the acid catalyzed hydrolysis of ethyl acetate[31] was found to be: $k^{H}/k^{D} = 0.5$. However, nucleophilically-catalyzed hydrolysis of phosphate diesters[18a,b,21a] and phosphonates[19b] exhibit somewhat higher values, $k^{H}/k^{D} = 1$–1.55. The question whether the fragmentation of the neutral species (*E*)-**1a** proceeds *via* a pre-equilibrium proton transfer or is controlled by an intramolecular general acid catalysis is still open.

Comparison between the fragmentation rate constant of the oxime, (*E*)-**1a**, with that of the oxime ether, (*E*)-**1f** (Table S3) reveals that the reaction of the latter is suppressed by a factor of 5.9 [calculated from the ratio k_1(**1a**)/k_1(**1f**)] and 2.4 [calculated from the ratio k_2(**1a**)/k_2(**1f**)] relative to the former. At first glance this result may be puzzling, since MeOH ($pK_a = 15.5$–15.7) should serve as a slightly better leaving group than H_2O ($pK_a = 15.74$). MeOH is also a better proton acceptor (pK_a of $MeOH_2^+ \approx -1.45$) than H_2O (pK_a of $H_3O^+ \approx -1.74$).[9] Thus, the opposite could be expected, namely that the ratio k(**1a**)/k(**1f**) should be <1, or at least close to 1. However, the observed rates are in accordance with a late transition state. In such a case the leaving water molecule will be more solvated and more stabilized than a methanol molecule.

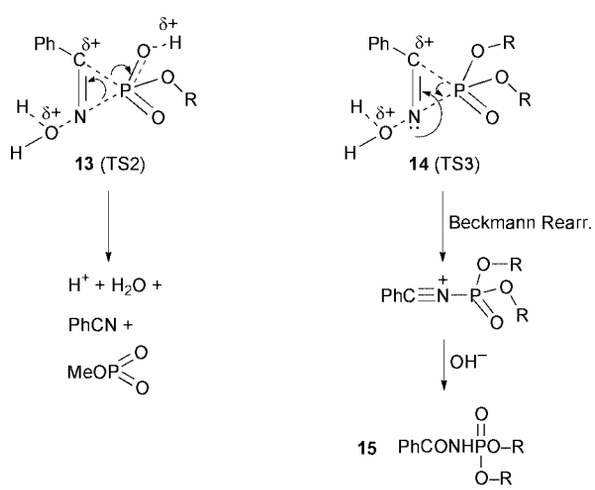
All the experimental results are compatible with a dissociative bond cleavage mechanism ($D_N{}^*A_N$), in accordance with transition state **8**. Transition state **12** illustrates some more possible features of the reaction process. TS **12** is assigned to



the fragmentation of the cationic form **6** (Scheme 3) where the water molecules in the solvation shell surrounding the leaving group pull the departing water molecule into the hydration shell. On the other hand, the nucleophilically-solvated phosphorus is not covalently bound to the solvent molecules, hence the solvent is not involved in nucleophilic assistance to the kinetic behavior of the reaction, but remains a spectator. The solvation shell around the leaving group and the electrophilic phosphorus center is not necessarily of the same composition. The ground state of the above fragmentation reaction can be described by **11**. In structure **10** protonation takes place on the nitrogen, while **11** illustrates an oxime-oxygen protonated species. In the case of the Beckmann rearrangement reaction, MO *ab initio* calculations[32] indicate implicitly that the *N*-protonated isomer is the most stable form and a 1,2-proton shift (from N to O) takes place along the reaction course. The two protonated species **10** and **11** may be stabilized through internal hydrogen bonds linking the P–O to the nitrogen. Structures having features similar to **10**–**12** can also be drawn for the fragmentation of the zwitterionic form, **7** (Scheme 3).

Finally, our results are compatible with a mechanism according to which the fragmentation of oxyiminophosphonates follows the path of the Beckmann reaction.[32,33] A well known complication of the Beckmann rearrangement is the Beckmann fragmentation, also referred to as the "abnormal" Beckmann reaction. This occurs usually in cases in which the migrating groups have a tendency to form stable carbocations, which split off as such, instead of migrating from the C to N.[33]

In a series of previous papers from our laboratory, over the past decade, we have reported that α-hydroxyiminophosphonate diesters,[34] α-hydroxyiminophosphinate,[34] and α-hydroxyiminophosphonamidate[35] monoesters undergo facile Beckmann rearrangement upon heating. In contrast, acidic α-hydroxyiminophosphonate monoesters (*e.g.* (*E*)-**1**) fragment to give a metaphosphate-like phosphorus species and nitriles under acid catalysis. We can view the fragmentation of oxyiminophosphonates as taking place *via* a Beckmann type transition state **13** (TS2), which fragments to give metaphosphate,



proton, water and benzonitrile. The analogy to the Beckmann fragmentation is based on the similarity between metaphosphates and carbocations, which have features in common: both are electrophilic, planar, and frequently formed in dissociative-type reactions, as in the present case. Such a fragmentation is blocked for diesters. In this case the transition state **(14)** (TS3) can only continue along the Beckmann rearrangement path to the final benzoylphosphoramidate diester product, **15**.[27]

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8 The fragmentation of (*E*)-**1a**, and the interconversion of (*Z*)-**1a** to (*E*)-**1a** in HCl–methanol gave, at 18 °C, the rates 1.4×10^{-2} min^{-1} M^{-1} and 0.9×10^{-2} min^{-1} M^{-1} respectively.[1b] The interconversion of (*E*)-**1a** to (*Z*)-**1a** was not observed, and was not considered in the non-linear kinetic analysis for the fragmentation of pure (*E*)-**1a**, pure (*Z*)-**1a** and their mixture.[1b] However, for the analogous diester, dimethyl α-hydroxyiminobenzylphosphonate, the equilibrium ratio of (*E*) to (*Z*) was found to be 9.[1b] Assuming a similar ratio for **1a** we can conclude that, with specific acid catalysis in methanol, the fragmentation of (*E*)-**1a** is 14 times faster than its isomerization.
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26 In this regard our system resembles solvolysis reactions of diazonium ions leading to carbocations formed by the loss of N_2.
27 In contrast, the fragmentation is not blocked for the unionizable alkyl hydroxyiminophosphonamidates, in which, presumably, back-donation from N to P supplies electrons for C–P bond cleavage.[35c] This paper reports that methyl α-hydroxyiminobenzyl-*N*-*tert*-butylphosphonamidate underwent Beckmann rearrangement when refluxed in toluene, but fragmentation to a phosphoramidate when refluxed in a high boiling alcohol, *e.g.* butan-1-ol or pentan-3-ol. Fragmentation carried out in a 1 : 1 mixture of the two alcohols gave the two products in a 65 : 35 molar ratio, resulting in the selectivity value of ≈ 0.54 (consistent with the value of 0.46–0.66 found in the present work for pentan-3-ol, while assuming a selectivity value of 1 for 1-BuOH), thus compatible with a metaphosphoramidate intermediate. These and other results reported in this paper were interpreted in terms of similar transition states for the rearrangement and the fragmentation.
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