Fragmentation of Methyl Hydrogen α-Hydroxyiminophosphonates to Monomeric Methyl Metaphosphate: Stereochemistry and Mechanism

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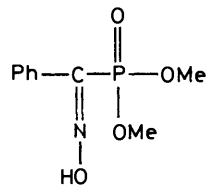
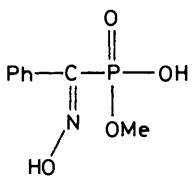
Methyl α-(hydroxyimino)benzylphosphonates [(*E*)-(**2**) and (*Z*)-(**2**)] undergo fragmentation in alcohols to benzonitrile and a (mixed) phosphodiester. Kinetic studies of the behaviour of (*E*)-(**2**) and (*Z*)-(**2**) in a series of alcohols indicate that (*Z*)-(**2**) undergoes acid catalysed isomerization to (*E*)-(**2**) which subsequently undergoes fragmentation *via* a concerted, dissociative bond cleavage to benzonitrile and monomeric methyl metaphosphate (**7**). The latter is trapped by the solvent in the second step of the reaction to give the final phosphodiester product.

Recently we reported the structure determination of dimethyl α-(hydroxyimino)benzylphosphonates [(*E*)-(**1**) and (*Z*)-(**1**)] by *X*-ray crystallography, and described the results of our studies of their thermal behaviour.[1] Based on these results it was also possible to assign the structures of the salts of their monodealkylation products, (*E*)-(**3**) and (*Z*)-(**3**), and to correlate and rationalize their behaviour under alkaline conditions.[1] More recently it was discovered that the two isomers of (**3**) could also be separated, *via* complex formation.[2] Thus it became possible to re-examine our recent preliminary report regarding the fragmentation of methyl α-(hydroxyimino)benzylphosphonate (**2**),[3] using the *E* and *Z* isomers separately and thus elucidate any relationships between reactivity and geometrical structure.


(**1**)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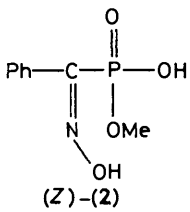
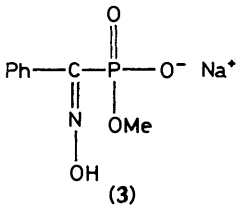
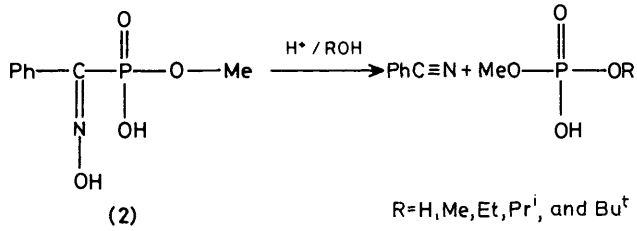

(*Z*)-(**2**)


(**3**)

In this paper we describe in detail the results of our studies of the fragmentation of (*E*)- and (*Z*)-methyl α-(hydroxyimino)-benzylphosphonates [(*E*)-(**2**) and (*Z*)-(**2**)] to benzonitrile, and in the presence of an alcohol, to a (mixed) phosphodiester (Scheme 1).

Experimental

General.—Nuclear magnetic resonance spectra were obtained on a Varian XL-100 or a Bruker WH-300 instrument. Chemical shifts are reported in ppm from external 85% H_3PO_4 in ^{31}P n.m.r. spectroscopy. Positive chemical shifts are at low field with respect to the standard.



(**2**)

Scheme 1.

^{31}P N.m.r. chemical shifts: δ(*E*)-(**2**) 6.42 (q); δ(*Z*)-(**2**) 1.83 (q); δ(dimethyl phosphate) 0.41 (septet); δ(methyl ethyl phosphate) −2.52 (sextet); δ(methyl 2-propyl phosphate) −4.27 (dq); and δ(methyl t-butyl phosphate) −3.51 (q).

Materials. The preparation and characterization of the isomeric mixture of dimethyl α-(hydroxyimino)benzylphosphonates [(*E*) + (*Z*)-(**1**)] and those of the sodium salts [(*E*) + (*Z*)-(**3**)] have been described previously.[1] Pure (*E*)-(**3**) was obtained by acid-catalysed isomerization from the mixture [(*E*) + (*Z*)-(**1**)], followed by dealkylation with sodium iodide.[1] Pure (*Z*)-(**3**) was obtained by treating the mixture [(*E*)-(**3**) + (*Z*)-(**3**)] with $CoCl_2 \cdot 6H_2O$, which resulted in the selective precipitation of (*E*)-(**3**) as described.[2] Methyl α-(hydroxyimino)benzylphosphonates (*E*)-(**2**) and (*Z*)-(**2**) were prepared *in situ* by acidification of the solutions of the corresponding sodium salts, (*E*)-(**3**) and (*Z*)-(**3**).

Kinetic Measurements.—^{31}P N.m.r. kinetic measurements were made using a Bruker WH 300 spectrometer at 121.5 MHz. Reactions were run at 18 °C and the relative quantities of the phosphorus-containing starting materials and products were estimated from the corresponding integrated n.m.r. signals.

Fragmentation of (E) *or* (Z)-*Methyl* α-(*Hydroxyimino*)-*benzylphosphonate* [(E)-(**2**)] *or* [Z)-(**2**)] *in Methanol in the Presence of Different Concentrations of Hydrogen Chloride.*—Either compound (*E*)-(**3**) or (*Z*)-(**3**) (237 mg, 1 mmol) was dissolved in methanol containing hydrogen chloride (0.55, 0.7, or 1.1 mol dm^{-3}; 2 cm^3). The sodium chloride that precipitated was filtered off and the filtrate was monitored by ^{31}P n.m.r. spectroscopy.

Fragmentation of Methyl Hydrogen α-(*Hydroxyimino*)*benzylphosphonate* [(E + Z)-(**2**)] *in Different Alcohols.*—An isomeric mixture of (*E*)- and (*Z*)-(**3**) (*E*:*Z* = 55:45) (237 mg, 1 mmol), was dissolved in the appropriate alcohol (methanol, ethanol,

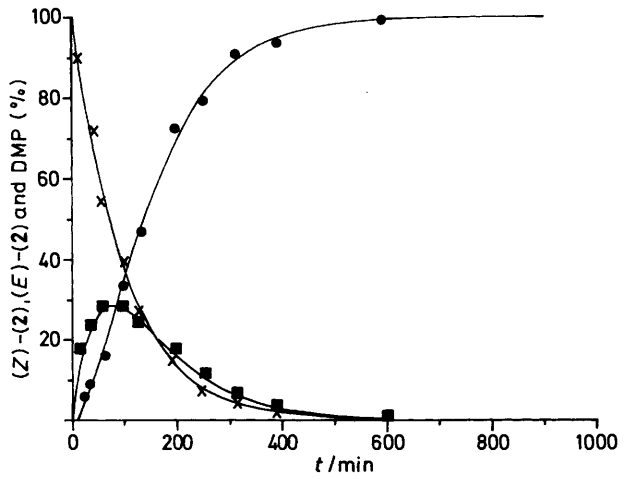


Figure. Concentrations of (*Z*)-(**2**) (×), (*E*)-(**2**) (■), and DMP (●) as a function of time.

propan-2-ol, or t-butyl alcohol, containing 0.55 mol dm^{-3} HCl; 2 cm^3). The sodium chloride formed was filtered off and the filtrate was monitored by ^{31}P n.m.r. spectroscopy.

Fragmentation of (E)-*Methyl α-(Hydroxyimino)benzylphosphonate* [(E)-(**2**)] *with* HCl *in Methanol:Propan-2-ol, 1:1 Mixture.*—Compound (*E*)-(**3**) (237 mg, 1 mmol) was added to a solution of hydrogen chloride (0.7 mol dm^{-3}; 2 cm^3) in equimolar methanol–propan-2-ol. The sodium chloride precipitate was filtered off. Monitoring of the filtrate by ^{31}P n.m.r. spectroscopy showed the concomitant formation of dimethyl phosphate and methyl 2-propyl phosphate in the ratio of 37:35, as evidenced by the ratio of their integrated peaks.

Acid-catalysed Isomerization of (E)- *and* (Z)-*Dimethyl α-(Hydroxyimino)benzylphosphonate* [(E)- *and* (Z)-(**1**)] *in methanol.*—Compound (**1**) (*E*:*Z* = 55:45) (229 mg, 1 mmol) was dissolved in methanolic hydrogen chloride (0.55, 0.7, or 1.67 mol dm^{-3}; 2 cm^3). The reaction mixtures were monitored by ^{31}P n.m.r. spectroscopy.

Results

The fragmentation of methyl α-(hydroxyimino)benzylphosphonate [(*E*)-(**2**)] in methanol, in the presence of hydrogen chloride at three concentrations (Table), follows first-order kinetics (k_2). In contrast, the fragmentation of (*Z*)-(**2**) is consistent with a consecutive-reaction mechanism. This became apparent when the reaction of (*Z*)-(**2**) in methanol was monitored by ^{31}P n.m.r. spectroscopy. In this experiment the appearance and subsequent decay of a signal corresponding to (*E*)-(**2**) was observed, together with the appearance of a signal due to dimethyl phosphate (DMP) (see Figure). The reaction pathway can therefore be represented by Scheme 2.

$$\text{DMP} \xleftarrow{k_3} (Z)\text{-}(\mathbf{2}) \xrightarrow{k_1} (E)\text{-}(\mathbf{2}) \xrightarrow{k_2} \text{DMP}$$

Scheme 2.

The dependence of the concentrations of (*E*)-(**2**) and DMP on time is given by equations (1) and (2), respectively,

$$[(E)\text{-}(\mathbf{2})]/[(Z)\text{-}(\mathbf{2})]_0 = B[\exp-(k_1 + k_3)t] - C\exp(-k_2t) \quad (1)$$

$$[\text{DMP}]/[(Z)\text{-}(\mathbf{2})]_0 = 1 + C\exp(-k_2t) - B\exp-(k_1 + k_3)t \quad (2)$$

where $[(E)\text{-}(\mathbf{2})]/[(Z)\text{-}(\mathbf{2})]_0$ and $[\text{DMP}]/[(Z)\text{-}(\mathbf{2})]_0$ represent the relative concentrations of [(*E*)-(**2**)] and the product DMP, respectively. The symbols B and C represent $(k_2 - k_3)/(k_2 - k_1 - k_3)$ and $k_1/(k_2 - k_3)$, respectively. The values of k_1 and k_3 were calculated by fitting the time-dependent relative concentrations of (*E*)-(**2**) and DMP (Figure) into equations (1) and (2), using non-linear, least-squares analysis, while the value of k_2 was obtained from the kinetics of pure (*E*)-(**2**). From the curve fitting obtained it was deduced that k_3 is negligible, and that the reaction consists solely of the consecutive steps k_1 [isomerization of (*Z*)-(**2**) to (*E*)-(**2**)] and k_2 [fragmentation of (*E*)-(**2**)].

The fragmentation of a 45:55 mixture* of (*Z*)- and (*E*)-(**2**) was also examined in methanol, ethanol, propan-2-ol, and 2-methylpropan-2-ol containing 0.55 mol dm^{-3} hydrogen chloride, by ^{31}P n.m.r. spectroscopy. In each case the formation of the corresponding (mixed) phosphodiester, as a single product, was observed. The identification of the phosphodiesters was based on their ^{31}P n.m.r. spectra. The rate expressions [equations (3) and (4)] were derived to fit Scheme 2, with $k_3 = 0$,

$$\%[(E)\text{-}(\mathbf{2})] = 55\exp(-k_2t) + 45D[\exp(-k_1t) - \exp(-k_2t)] \quad (3)$$

$$\%\text{DMP}\dagger = 45\{[1 - \exp(-k_1t)] - D[\exp(-k_1t) - \exp(-k_3t)]\} + 55[1 - \exp(-k_2t)] \quad (4)$$

where $D = k_1/(k_2 - k_1)$.

In another experiment the rate of fragmentation of pure (*E*)-(**2**) was determined under competition conditions in an equimolar mixture of methanol and propan-2-ol. In this experiment the products were practically equal amounts of dimethyl phosphate (DMP) and methyl 2-propyl phosphate (51.4 and 48.6%, respectively).

In contrast to the hydroxyiminophosphonic monoacids, (*E*)- and (*Z*)-(**2**), diester (**1**) undergoes only $Z \longrightarrow E$ isomerization, but no fragmentation under similar conditions. Starting from the initial composition in solution of (**1**) (*Z*:*E* = 45:55), an equilibrium ratio of 1:9 was reached. Assuming that the equilibrium is established by first-order kinetics

$$(Z)\text{-}(\mathbf{1}) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (E)\text{-}(\mathbf{1})$$

the rates of isomerization (*Z*)-(**1**) ⟶ (*E*)-(**1**) can be expressed by equation (5).

$$\ln\{([EZ]_0 - [Z]_e)/([Z] - [Z]_e)\} = (k_1 + k_{-1})t \quad (5)$$

In equation (5) $[EZ]_0$ stands for the initial concentration of the mixture (*E*)-(**1**) + (*Z*)-(**1**), while $[Z]_e$ and $[Z]$ represent the concentration of (*Z*)-(**1**) at final equilibrium, and at a given time, respectively.

The rate constants calculated by equations (1)–(5) are summarized in the Table.

Discussion

Fragmentation.—By analogy with the various mechanisms proposed in the past for the solvolysis of phosphodiesters,

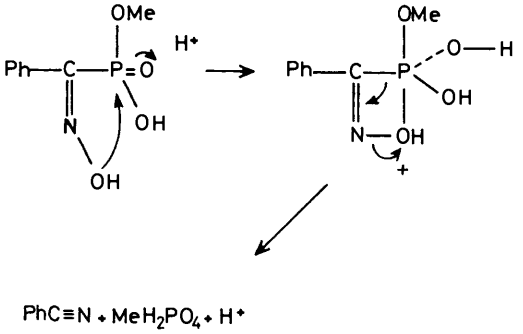
* This is the isomeric composition obtained in the synthesis of (**1**) by the reaction of dimethyl benzoylphosphonate and hydroxylamine.[1] This ratio is observed in the dealkylation of (**1**) by sodium iodide, to afford the isomeric mixture of (**3**).[1]

† Or other phosphodiesters.

Table. Rate constants for acid-catalysed $Z \longrightarrow E$ isomerization of (*Z*)-(**2**) and (**1**) and fragmentation of (*E*) and (*Z*)-(**2**) (18 °C).

Compound	[HCl]/mol dm^{-3}	Solvent	$k_1/10^{-2}$ min^{-1}	$k_2/10^{-2}$ min^{-1}	$k_1/10^{-2}$ dm^3 mol^{-1} min^{-1}	$k_2/10^{-2}$ dm^3 mol^{-1} min^{-1}
(*E*)-(**2**)[a]	0.55	MeOH		0.82		1.48
	0.70	MeOH		1.05		
	1.10	MeOH		1.62		
(*Z*)-(**2**)[b]	0.70	MeOH	0.62	0.95	0.90	1.40
	1.10	MeOH	1.00	1.60		
(**2**)[c]	0.55	MeOH	0.52	0.72		
(*E*:*Z* = 55:45)	0.55	EtOH	0.49	0.69		
	0.55	Pr^{i}OH	0.48	0.68		
	0.55	Bu^{t}OH	0.51	0.71		
(**1**)[d]	0.55	MeOH	0.15		0.37	
	0.70	MeOH	0.26			
	1.67	MeOH	0.62			

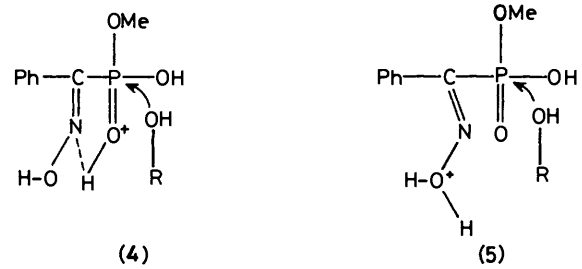
[a] Rate constants calculated according to first-order kinetics. [b] Rate constants derived by non-linear, least-squares curve fitting to equation (3). [c] Rate constants calculated according to equation (3). [d] Rate constants for the isomerization of (*Z*)-(**1**) to (*E*)-(**1**) determined using the *Z* and *E* mixture, and calculated according to equation (5).

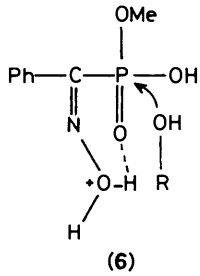


Scheme 3.

several possible routes can be considered for the fragmentation of hydroxyiminophosphonates.

Scheme 3 shows a possible mechanism involving specific acid-catalysed intramolecular nucleophilic attack by the oxime oxygen upon the phosphorus, in which the role of the acid is to promote cyclization by protonation of the phosphoryl oxygen. Although there are precedents for reactions proceeding through analogous intermediates,* this mechanism can be excluded due to the following considerations. (*i*) The mechanism shown in Scheme 3 should operate better with oxime (*Z*)-(**2**) than with the *E* isomer, because of the favourable orientation of the oxime oxygen in the former. However the kinetic results clearly established that of the two isomers only the latter is reactive. (*ii*) The mechanism shown in Scheme 3 also predicts the formation of methyl dihydrogen phosphate (and benzonitrile) regardless of the solvent. However, the products formed clearly depend on the reaction medium, since in each case the alcoholic solvent (methanol, ethanol, propan-2-ol, and 2-methylpropan-2-ol), was incorporated into the product, the corresponding (mixed) phosphodiester. (*iii*) Only methyl α-(hydroxyimino)benzylphosphonate, (**2**), and not dimethyl ester (**1**), undergoes fragmentation under the conditions described; the mechanism does not explain this difference, on the contrary, it predicts identical behaviour for both mono- and di-methyl esters.





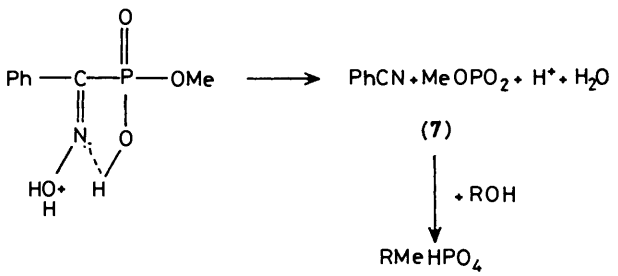
Scheme 4.

The formation of phosphodiesters in the fragmentation of hydroxyiminophosphonates can also be visualized to take place by associative-type mechanisms that involve nucleophilic attack of the alcohol on the phosphorus, prior to the breaking of the C–P bond. It is expected that such reactions would be

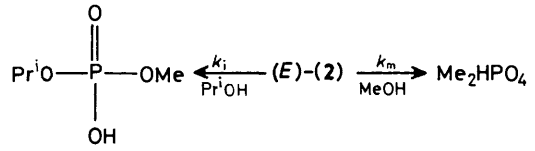
* Previously we have shown that while treatment of (*E*)-(**1**) with sodium hydroxide in boiling methanol leads, by monodealkylation, to (*E*)-methyl sodium α-(hydroxyimino)benzylphosphonate [(*E*)-(**3**)], under the same conditions (*Z*)-(**1**) undergoes fragmentation, by C–P bond cleavage, to benzonitrile and dimethyl phosphate.[1] Control experiments established that the fragmentation of (*Z*)-α-(hydroxyimino)phosphonates involves an intramolecular attack on the phosphorus atom by the ionized *syn*-oriented oxime oxygen. Similar differences in behaviour have been noted between the isomers of the monoanions of α-(hydroxyimino)phosphonates (*E*)- and (*Z*)-(**3**).[1] Intramolecular interaction between an oxime and a phosphoryl group has also been noted in cases where the distance between the functional groups is longer, and the interaction lends assistance to phosphonate hydrolysis *via* five-membered intermediates.[4]

Anchimeric assistance to solvolysis of phosphates by the participation of other functional groups involving five- and six-membered cyclic intermediates have also been reported.[5–8]

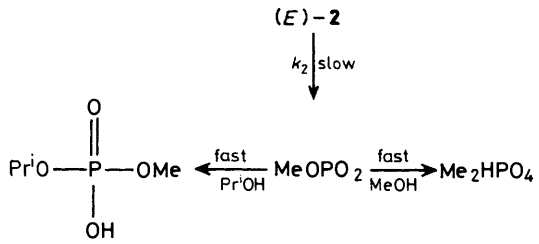
† The role of protonation of the P=O oxygen in acid-catalysed hydrolysis of phosphates or phosphonates is well established.[9]



Scheme 5.



Scheme 6.



Scheme 7.

catalysed by acid.† Scheme 4 presents three alternative products of the protonation of (**2**) that may account for the acid catalysis. (*i*) The hydrogen-bonded structure (**4**) might result either from protonation on the nitrogen or the phosphoryl oxygen atom (P=O) and certainly should be more susceptible to nucleophilic attack on the phosphorus than the unprotonated compound. (*ii*) Protonation on the *N*-hydroxy group might catalyse the reaction by increasing its leaving-group ability [structure (**5**)]. (*iii*) An intermediate of type (**6**) in the reaction would only be likely if the *Z* isomer were found to have been the more reactive species. In any case, the formation of the intermediates in Scheme 4 requires nucleophilic attack by alcohol on the phosphorus atom prior to fragmentation. It is therefore expected that the rate constants with various alcohols should be sensitive to steric effects, and consequently fall in the order: MeOH > EtOH > Pr^{i}OH > Bu^{t}OH, as is observed in the alkaline hydrolysis of phosphonates.[4a,10] This is not seen in the present case. The rate constants found for the fragmentation of (**2**) in the various alcohols (Table) are very similar. Furthermore, comparison of the rate of fragmentation of (*E*)-(**2**) with that of the bimolecular, acid-catalysed hydrolysis of a representative phosphonate, clearly indicates that the two reactions are of quite different types. The fragmentation is far more rapid ($k = 1.62 \times 10^{-2}$ min^{-1} at 18 °C and 1.1 mol dm^{-3} HCl) than the hydrolysis of phenyl hydrogen methylphosphonate ($k = 6.5 \times 10^{-4}$ min^{-1} at 80 °C and in 0.5 mol dm^{-3} H_2SO_4),[11] in spite of the latter having a much better leaving group.

An additional argument against the involvement of intermediates [(**4**)–(**6**), and also against a mechanism involving a Beckmann-type migration of the phosphoryl group from carbon to nitrogen in (**5**)], is that if the reaction were to proceed through any of these, the dimethyl ester (**1**) should not be expected to behave differently from monoester (**2**), and should undergo similar fragmentation.

Finally, a mechanism compatible with all the experimental results, and illustrated in Scheme 5, is a concerted, dissociative bond-cleavage,* initiated by protonation on the oxygen of the hydroxyimino group,† and leading in the first (slower) step to monomeric methyl metaphosphate (**7**). This reactive intermediate is rapidly trapped by the solvent in the second (faster) step. Monomeric metaphosphate esters have been postulated before, mainly in pyrolytic fragmentation reactions,[13] in which such reactive intermediates could be trapped by nucleophilic reagents. The direct observation of metaphosphate esters by mass spectrometry has also been reported.[14]

The monomeric methyl metaphosphate (**7**), that is assumed to be formed in the first step of the present fragmentation, is closely related to the monomeric metaphosphate anion (PO_3^-), the putative intermediate in biological phosphoryl-transfer reactions.[15] Despite some arguments about details, it is now generally agreed that such reactions proceed by a dissociative mechanism, either involving monomeric metaphosphate anion as reactive intermediate, or through an open transition state of dissociative nature, resembling monomeric metaphosphate.[15] In view of recent results[16] that indicate that the monomeric metaphosphate anion may exist in protic solvents, we feel that the existence of the corresponding ester (**7**) in alcohol solvents can also be assumed.

One of the commonly accepted diagnostic tests for the involvement of monomeric metaphosphate as a reactive intermediate is the absence of steric effects in the phosphorylation of a hindered alcohol, as compared with a primary alcohol.[17] The fulfilment of this criterion in the present work is apparent in (*i*) the similarity of rate constants for the formation of the different phosphodiesters [dimethyl phosphate, methyl ethyl phosphate, methyl 2-propyl phosphate, and methyl (2-methyl-2-propyl) phosphate] during alcoholysis of (**2**) in the corresponding alcohols (Table) and (*ii*) the result of a competition experiment, in which (*E*)-(**2**) was allowed to undergo fragmentation in a medium consisting of equimolar methanol and propan-2-ol, which yielded the two phosphodiesters dimethyl phosphate and methyl 2-propyl phosphate in equal amounts.

The latter cannot be the result of two competing, parallel, bimolecular reactions (Scheme 6), in which the attack of methanol and propan-2-ol is rate-determining, because the two products would be expected to form at different rates due to differences in the steric effects of the alcohols. However the first-order rate constants calculated for such an eventuality are equal (in 0.6 mol dm^{-3} HCl: $k_m = k_i = 0.36 \times 10^{-2}$ min^{-1}), and about half the value of those obtained in the pure solvents (Table). In contrast, when the first-order rate constants for the formation of the products are calculated assuming the mechanism in Scheme 7, the results ($k_2 = 0.72 \times 10^{-2}$ min^{-1}) fit the values that were obtained in the pure alcohols (Table), and consequently confirm that the alcohols are not involved in the rate-determining step (see the mechanism in Scheme 5).

With regard to the fragmentation pathway of (*E*)-(**2**) in

* A similar, concerted, *trans*-elimination mechanism has been suggested for the decarboxylative conversion of (*E*)-α-(hydroxyimino)carboxylic acids into nitriles, in which case the *E* isomers were also found to be selectively reactive.[12]

† One of the referees suggested that since the nitrogen of a protonated oxime is not expected to be sufficiently basic to remove a proton from the P–O–H group, a pre-equilibrium between (*E*)-(**2**) and its zwitterion is most likely to be the first step of the reaction. Protonation of the oxime oxygen of this zwitterion, however, would lead to the same internally hydrogen-bonded intermediate, which serves as starting material in Scheme 5.

Scheme 5 two more questions need to be answered. (*i*) Why does the *anti* isomer (*E*)-(**2**), alone, undergo the fragmentation reaction? (*ii*) Why does (*E*)-(**2**) undergo C–P bond cleavage only, and not even partial P–OMe bond fission?

It seems to us that the present course of the reaction can be explained by considering stereoelectronic factors.[18] As shown in Scheme 5, only the *anti* oxime (*E*)-(**2**) is the reactive species, since only in this isomer can the two bonds which are cleaved (P–C and N–O) be oriented antiperiplanar.* Furthermore, the formation of an internal hydrogen-bond between the phosphonic acid proton and the nitrogen in the *E*-oxime (see Scheme 5) will lock the C–P bond in a conformation in which the lone-pairs of the P–O oxygen will become antiperiplanar to the C–P bond and not to the P–OMe bond,† and thus facilitate C–P (but not P–OMe) bond cleavage.

Another factor that may influence the course of the reaction is the relative strengths of the bonds to phosphorus. In an associative hydrolytic reaction of a phosphonate the P–O bond will break in preference to a P–C bond, probably because the former has greater affinity for the apical position than the latter, and also because oxygen is a better leaving group than carbon. This is in spite of the fact that the P–O bond is shorter (*ca.* 1.58 Å) and stronger than the P–C bond (*ca.* 1.82 Å). (In α-oxyiminophosphonates we found bond lengths of 1.538–1.615 Å for P–O and 1.828–1.830 Å for P–C.[1])

The case of the fragmentation of (*E*)-(**2**) however, is quite different. (*a*) This reaction does not proceed through a trigonal-bipyramidal intermediate and it is not required for the carbon to become apically oriented to break the C–P bond. (*b*) The leaving-group ability of the carbon is enhanced (comparable to methoxide) by the departure of the protonated *N*-hydroxy group.

In summary, the mechanism described in Scheme 5 is in accord with all the experimental results. It involves a concerted, acid catalysed, stereoelectronically controlled cleavage of C–P and N–O bonds to form benzonitrile and monomeric methyl metaphosphate, which is subsequently trapped by the solvent (alcohol). The preference for C–P bond fission over P–OMe is governed by intramolecular hydrogen bonding between the phosphoric acid hydrogen and the oxime nitrogen, and by the relative strengths of the two bonds in which breakage may occur. Protonation of the oxime hydroxy group is required to increase its leaving ability. Another feature that should be emphasized is the need for at least one acidic P–O–H group in an α-oxyiminophosphonic acid for such a fragmentation to take place.

A control experiment showed that the dimethyl ester (*E*)-(**1**) was absolutely stable under the reaction conditions. It is also worthy of note in the context of this work, that although we have not so far carried out detailed kinetic and competition experiments, preliminary results suggest that α-hydroxyiminophosphonic diacids behave analogously to the monoacids (**2**), in that under acidic conditions they too undergo dissociative fragmentation to a nitrile and monomeric metaphosphoric acid.[21]

Z ⟶ E *Isomerization.*—The reaction of hydroxylamine with dimethyl benzoylphosphonate gives, under kinetic control, the oxime (**1**) as a mixture of *E*- and *Z*-isomers in a ratio of 55:45.[1] In acidic solution, however, compound (**1**) reaches a new equilibrium of the ratio $E:Z = 9:1$.[1]

From the Table it is seen that the isomerization of the monomethyl ester (*Z*)-(**2**) is faster by a factor of 2.4 than that of the dimethyl ester (*Z*)-(**1**). Although in the absence of equilibrium constants for (*E*)- and (*Z*)-(**2**) one cannot draw conclusions regarding the relative stabilities of *E*- *vs.* *Z*-isomers (**2**) as compared with (**1**), it might be tempting to theorize that internal hydrogen bonding (similar to that in structure (**4**) stabilizes the *anti* isomer (*E*)-(**2**), after the rotation around C–N bond has taken place.

Acid-catalysed isomerization has been observed in oximes[22] as well as in other imines.[23] Such a *Z* ⟶ *E* isomerization may take place by protonation of the nitrogen and rotation about the C–N bond. Alternatively, an addition–elimination mechanism involving the addition of a nucleophilic reagent (alcohol or chloride) to the C=N double bond of the protonated oxime, may also be considered, in view of support for such mechanism in the literature.[23d] ‡

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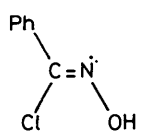
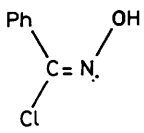
* A case of stereoelectronic control operating across a C=N bond has recently been demonstrated in the reaction of benzoyl chloride oxime (**8**),[19] in which the loss of chloride from the *Z*-isomer was faster by a factor of 10^7 than that from the *E*-isomer. This was ascribed to the lone-pair electrons on the nitrogen, oriented antiperiplanar to the leaving chloride.



(*Z*)-(**8**)



(*E*)-(**8**)

† A similar type of stereoelectronic assistance has been suggested to control the process of C–N bond breaking in the phosphoryl-to-carbonyl migration of amino groups.[20] Calculations carried out by Gorenstein *et al.* showed earlier that the cleavage of a bond at phosphorus in the product-determining step requires *ca.* 11 kcal mol^{-1} less energy when the bond between phosphorus and the departing group is oriented in an antiperiplanar fashion to one of the lone pairs of another heteroatom bound to the phosphorus.[18c].

‡ We thank one of the referees for directing our attention to this literature reference.

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