Nucleophilic Addition and Subsequent Oxime-Assisted Ester Hydrolysis of Diethyl β-Ketopropylphosphonate

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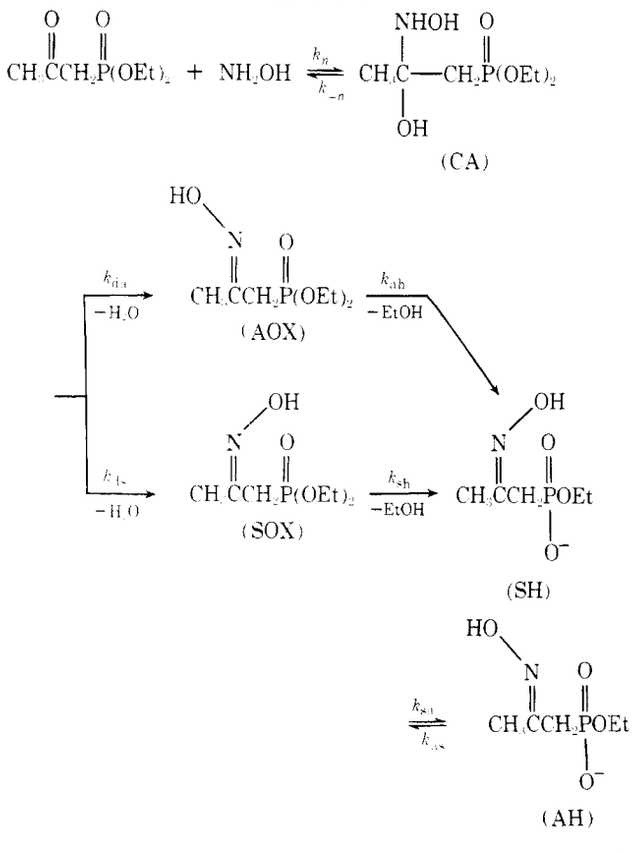
The nucleophilic addition of NH_2OH to the keto carbonyl group of diethyl β-ketopropylphosphonate (DKP) in aqueous solution around pH 7 was studied at 30 °C using ^1H and ^{31}P nuclear magnetic resonance spectroscopy. During the reaction, it was possible to detect the carbinolamine (CA) resulting from addition of NH_2OH to the keto carbonyl group, the syn and anti isomers of the oxime of the diester, and the syn and anti isomers of the oxime of the monoester. The addition involves the rapid equilibrium, DKP + NH_2OH ⇌ CA, for which the rate constants of the forward and reverse steps were calculated from line width data (obtained by continuous flow ^1H NMR) of a signal that is the coalescence of signals due to DKP and CA. These rate constants, which are independent of pH between pH 6.8 and 9.0, have average values, 2.2×10^3 M^{-1} s^{-1} and 4.5×10^3 s^{-1}, for the forward and reverse steps, respectively. Using the time dependence for each of the various signals obtained either by stopped flow or static NMR methods, rate constants have been calculated for a variety of steps, including: (1) dehydration of CA; (2) the separate formation of the syn and anti isomers of the oxime of the diester; (3) the separate ester hydrolysis steps for these isomers; and (4) the equilibration of the syn and anti isomers of the oxime of the monoester. The ester hydrolysis appears to involve internal assistance by the OH group of the oxime, since no hydrolysis was detected after 2143 h for a solution containing the *O*-methyloxime of DKP and acetone oxime. This assistance could involve nucleophilic addition to phosphorus by the OH oxygen to form pentacovalent phosphorus. The lack of pH dependence for this step may indicate that OH–proton transfer is occurring either prior to or concerted with addition. Although unrelated to the kinetic study, it is interesting to note that there is a long-range ^{31}P coupling with $CH_3C(=NOH)$– but not with $CH_3C(=O)$–.

Continuous flow and stopped flow proton nuclear magnetic resonance spectroscopy (NMR) have been used to study a variety of reaction steps associated with the nucleophilic addition of hydroxylamine (HYD) to diethyl β-ketopropylphosphonate (DKP) in aqueous solution. Because of the detailed information available in the NMR spectrum, it is possible to measure the rate constants for the reaction steps indicated in Scheme I.

Between pH 6.8 and 9.0, equilibration between the carbinolamine intermediate (CA) and DKP is rapid relative to the dehydration step in which both the syn and anti oximes (SOX) and (AOX) are formed. Both isomers undergo phosphonate ester hydrolysis with the syn oxime being faster by a factor of about 40 at pH 6.8, indicating that the anti to syn isomerization is the rate-limiting step for ester hydrolysis of the anti isomer. The fact that the syn oxime of the diester hydrolyzes faster than the anti oxime indicates that intramolecular assistance by the oxime oxygen is involved. The absence of any detectable ester hydrolysis of the *O*-methyloxime of DKP after three months under the same conditions supports this conclusion. This assistance probably involves addition to phosphorus to form a pentacovalent intermediate similar to that suggested previously to explain the intramolecular assistance to phosphonate ester hydrolysis caused by an amide[2] and an oxime.[3] For the latter, the mechanism differs from Scheme I in that monoester formation occurs via O–N rather than O–P bond scission. For the former, the rate of amide assisted hydrolysis becomes appreciable only in highly acidic solutions and, consequently, amide assistance appears to be less effective than oxime assistance, which induces hydrolysis in neutral solution. In the pH range employed, hydrolysis of the monoester was not studied since it is substantially slower than that for the diester. The syn oxime of the monoester isomerizes to attain an equilibrium anti/syn ratio of 1.6.

Scheme I



Experimental Section

Chemicals. Diethyl β-ketopropylphosphonate (DKP) was prepared as described previously.[4] A fraction with bp 75 °C (0.2 mm) was used for the kinetic studies. The *O*-methyloxime of DKP was prepared by addition of methoxyamine hydrochloride to an aqueous solution of DKP. Purification was by vacuum distillation, bp 110–112 °C (1.0 mm). Acetone oxime was prepared by reaction of acetone with a twofold excess of hydroxylamine hydrochloride in a pyridine–ethanol solution. The oxazolidine of DKP was prepared according to the procedure of Keana[5] using 2-amino-2-methylpropan-1-ol. The oxazolidine was purified by vacuum distillation, bp 96 °C (0.25 mm). All other chemicals were obtained commercially.

Equilibrium and Kinetic Measurements. Flow NMR and stopped flow NMR spectra at 100 MHz were measured using a Varian HA-100 as described previously.[6] The ^{31}P NMR spectra were obtained at 24.3 MHz using a Bruker WP60. The equilibrium constant K_n for

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Table I. Chemical Shifts and ^1H–^{31}P Coupling Constants in H_2O at 30 °C

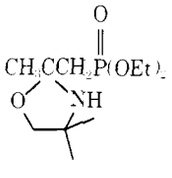
compd and nucleus	Registry no.	δ_H,[a] ppm	δ_P,[b] ppm	$J_{H,P}$, Hz
CH_3 $COCH_2$**P**$O(OCH_2CH_3)_2$	1067-71-6	2.27	21.08	
CH_3CO**CH_2**$PO(OCH_2CH_3)_2$		3.34		21.5
$CH_3COCH_2PO(OCH_2$**CH_3**$)_2$[c]		1.245		
CH_3 $C(NOH)CH_2$**P**$O(OCH_2CH_3)_2$				
syn (a)	66417-82-1	1.909	23.92	3.0
anti (a)	66417-83-2	1.909	25.38	3.0
$CH_3C(NOH)$**CH_2**$PO(OCH_2CH_3)_2$				
syn (e)		3.12		23.5
anti (f)		2.90		21.8
$CH_3C(NOH)CH_2PO(OCH_2$**CH_3**$)_2$[c]				
syn		1.245		
anti		1.245		
CH_3 $C(NOH)CH_2$**P**$O_2(OCH_2CH_3)^-$				
syn (c)	66417-84-3	1.896	15.98	2.8
anti (c)	66417-85-4	1.896	17.39	2.8
$CH_3C(NOH)$**CH_2**$PO_2(OCH_2CH_3)^-$				
syn (g)		2.82		22.0
anti (h)		2.57		20.5
$CH_3C(NOH)CH_2PO_2(OCH_2$**CH_3**$)^-$[c]				
syn		1.245		
anti		1.245		
CH_3 $C(NOCH_3)CH_2$**P**$O(OCH_2CH_3)_2$				
syn	66417-86-5	1.90	22.62	3.0
anti	66417-87-6	1.87	24.12	2.8
$CH_3C(NOCH_3)$**CH_2**$PO(OCH_2CH_3)_2$				
syn		2.81		23.5
anti		2.60		22.0
$CH_3C(NOCH_3)CH_2PO(OCH_2$**$CH_3$**$)_2$[c]		1.245		
Oxazolidine of DKP	66417-88-7			
$CH_3C(O)(N)(C)$		1.467		1.4
CH_2P		2.178	25.83	18.3
OCH_2**CH_3**		1.245		
CH_3 CH_2OH (b)		1.095		

[a] Relative to tetramethylsilane. [b] Relative to H_3PO_4; positive values indicate signals are at lower field relative to the reference signal. [c] Ethoxy-CH_2 resonance is too close to the H_2O signal, which is used as the lock signal, to be observed.

the addition step, DKP + HYD ⇌ CA, was measured by means of flow UV using a Cary 118 as described previously.[6a] At pH 6.8, 8.2, and 9.0, the value for K_n is 0.55 ± 0.06, 0.46 ± 0.05, and 0.45 ± 0.09, respectively.

Results

Figure 1 illustrates 100 MHz proton spectra obtained at two stages in the reaction: before DKP has disappeared (upper spectrum); and after DKP has disappeared but with AOX, SOX, AH, and SH present (lower spectrum). The lower spectrum, which was measured at pH 6.8, illustrates the CH_2 and CH_3 proton resonances due to these oximes as well as one-half of the CH_2 quartet (labeled j) due to ethanol. For assignments, see Table I. The unlabeled singlet near a–c is the CH_3CO resonance due to ethyl acetate, which is used as a line width and chemical shift reference. As indicated in Figure 1, the CH_2 resonances due to the oximes (labeled e, f, g, and h) are well resolved and are split into doublets because they are magnetically coupled to ^{31}P (see Table I for the coupling constants). Likewise ^{31}P is also coupled to the CH_3 resonances (a–c) of the oximes. However, the CH_3 resonances due to AOX and SOX have identical chemical shifts (similarly for AH and SH). Consequently the time dependence of the concentration for each of these oximes was obtained either from the CH_2 resonances or the ^{31}P resonances (see Table I), which also can be resolved for each isomer. The upper spectrum, which was obtained at pH 8.2 and twice the sweep width of the lower, illustrates only the CH_3 region of the spectrum. Resonance a is in common with the lower spectrum, and the unequal intensity of the doublet signals as well as the presence of a shoulder indicates that some phosphonate ester hydrolysis has occurred. The presence of the triplet b due to ethanol is an additional indication of ester hydrolysis. The larger triplet near b is due to the ethoxy CH_3 protons of the mono- and diester for the oximes as well as DKP and CA, i.e., the chemical shift for this type of proton is the same for all of the compounds (see Table I). The signal (D + I), which is somewhat broader than the others, indicates the presence of DKP and CA. This signal is upfield (to the right of) from the keto CH_3 resonance of DKP, and its position depends on the concentration ratio HYD/DKP, moving upfield as this ratio increases. This change in chemical shift is accompanied by line width changes, indicating a CH_3 proton exchange process,[6a] which is ascribed to the first equilibrium in Scheme I. Using K_n and the concentration dependence of the D + I chemical shift, the chemical shift of the **CH_3**$C<$ resonance of CA relative to the keto CH_3 resonance of DKP is calculated to be 0.795 and 0.788 ppm at pH 9.0 and 7.5, respectively. The corresponding chemical shift for the oxazolidine of DKP, which has a structure similar to CA, is 80.3 Hz (see Table I). From the line width of D + I, values for k_n and k_{-n} are obtained as described previously[6a] using spectra measured while continuously flowing at a rate that is fast (usually 20 mL/min) relative to the rate of dehydration of CA so that a steady state



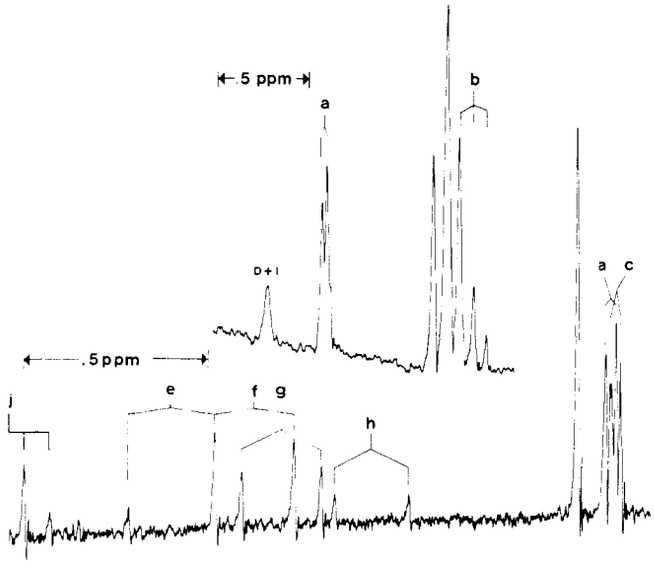


Figure 1. Portions of the static 100 MHz proton magnetic resonance spectra of reaction mixture containing 0.1 M DKP and 0.25 M NH_2OH (total, initially after mixing) obtained at pH 8.2 (upper, 30 min after mixing) and pH 6.8 (lower, 40 min after mixing). The sweep widths differ as indicated and the upper spectrum, which is obtained without spinning the sample, overlaps the lower one with doublet (a) being common in both. Signal D + I, which is not observed in the lower spectrum, is a coalescence of two signals, one due to the $\mathbf{CH_3}CO$ protons of DKP and the other due to the corresponding CH_3 protons of the carbinolamine intermediate (CA, see Scheme I). The unlabeled triplet is due to the CH_3 protons of the ethoxy group present in DKP, CA, SOX, AOX, SH, and AH. Signals labeled j are part of the quartet due to the CH_2 protons of ethanol. For assignments of the other signals see Table I.

concentration of DKP and CA is maintained and no oxime formation occurs. For this purpose, the line width for CA in the absence of exchange is assumed to be the same as that for the oxazolidine of DKP, freshly prepared to avoid the presence of nitroxide radicals. All of the other rate constants indicated in Scheme I are obtained from the time dependence of the appropriate signals (^1H or ^{31}P) determined after the flow has been stopped. An example of the time dependence for the oximes at pH 6.8 is given in Figure 2. The decay of D + I follows a time dependence that corresponds to the one for the growth of AOX and, consequently, is not included in this figure. Data were obtained at pH values ranging from 6.8 to 9.0.

Discussion

The values of k_n listed in Table II were calculated from line width data in the manner described previously.[6a,7] The value for k_{-n}, which is also listed, is not obtained independently, i.e., it is obtained from the relation $K_n = k_n/k_{-n}$. For all pH values, k_n is independent of $[NH_2OH]$, the total concentration of HYD, indicating that the addition step is first order in HYD, in agreement with Scheme I. In addition, k_n is essentially independent of pH in the range 6.8 to 9.0. For a number of other systems, k_n is independent of pH and the buffer concentration, indicating that the rate-determining step for this exchange process is the unassisted addition of the nucleophile to the ketocarbonyl carbon to form the zwitterion $>C(O^-)(NH_2OH^+)$.[6-8] The value for k_n in Table II is very close to those for acetone[6a] and ethyl acetoacetate.[8] Consequently, replacing hydrogen by a carboethoxy or phosphonate diester group has little effect on the reactivity of the keto carbonyl toward HYD.

Because of the number of consecutive and parallel steps occurring during the reaction, none of the rate constants indicated in Scheme I can be obtained by a simple first-order kinetic treatment. Consider the decay of the coalescence signal D + I, which provides the value for the dehydration rate constant k_d, which is equal to $k_{ds} + k_{da}$ (Scheme I). This decay cannot be treated according to simple first-order or second-order kinetics because DKP and CA are present in appreciable amounts. However, k_d can be obtained as the slope in a linear least-squares fit of ln (d + i) vs. βt in which (d + i) is the intensity of D + I, t is time in seconds, and β is $K_n[N]/(K_n[N] + 1)$ in which [N] is the equilibrium concentration of nucleophile free base.[7] Although this treatment does not result from an exact solution of the differential equation, the error is less than 10% for the concentration ratio HYD/DKP employed.[7] Each value of k_d listed in Table III is an average of two to four runs. A linear least-squares fit of k_d with respect to the concentration of phosphate buffer provides the slopes and intercepts listed. Although the slope increases with decreasing pH, as might be expected for general acid catalysis by phosphate buffer, it is not linearly related to the fraction of general acid. Consequently, the general acid and general base catalytic rate constants were not calculated. In addition, the intercept does not appear to exhibit a systematic dependence on hydronium or hydroxide ion concentration. As a cross check of the reliability of the NMR determination of k_d, this rate constant was also obtained by UV measurements, which show good agreement with the NMR data (Table III).

As indicated by the values of k_{ds} and k_{da} (Table IV), AOX

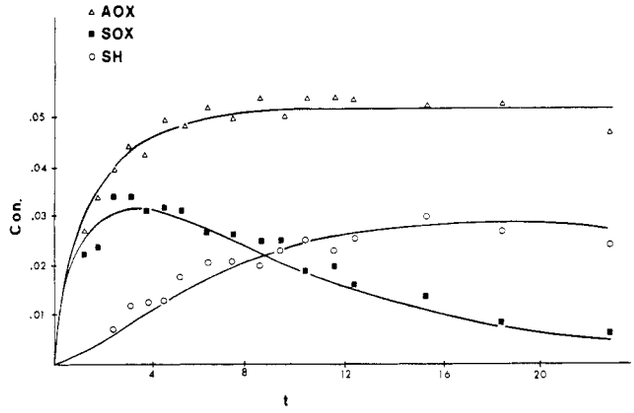


Figure 2. Molar concentration of AOX, SOX, and SH as a function of time in minutes for an aqueous solution of 0.10 M DKP and 0.125 M HYD (initially) at pH 6.8 and 30 °C. The solid lines represent the simulated time dependences based on rate constants obtained by an iterative technique in which the data for the three species are treated simultaneously (see text).

Table II. Values for k_n and k_{-n} at 30 °C in H_2O (μ = 1.6 M (KCl))

pH	$[NH_2OH]^a$	$k_n \times 10^{-3}$, $M^{-1}s^{-1}$	$k_{-n} \times 10^{-3}$, s^{-1}	M^b
9.00[c]	0.55	1.9	4.2	18
	0.45	1.8	3.9	18
	0.36	1.8	3.9	18
	0.25	1.7	3.8	18
	0.10	1.7	3.8	18
7.50[d]	0.51	2.0	4.4	20
	0.45	2.2	4.8	20
	0.36	2.6	5.6	20
	0.275	2.5	5.4	20
	0.10	2.5	5.4	20
6.80[d]	0.36	3.0	5.5	8
	0.10	2.7	4.9	12

[a] Total concentration of NH_2OH. [b] Number of measurements. [c] 0.2 M diazabicyclooctane. [d] 0.2 M sodium phosphate.

Table III. Kinetic Parameters for the Dehydration of CA in H_2O at 30 °C (μ = 1.6 M (KCl) [a])

pH	[buffer],[b] M	$k_d \times 10^2$, s^{-1}	slope,[c] $M^{-1}\ s^{-1}$	int $\times 10^3$, s^{-1}
6.80	0.20	6.7		
	0.25	8.5		
	0.30	11.0	0.34	2
		11.0[d]		
	0.40	13.6		
		13.5[d]		
7.00	0.10	4.2		
	0.15	5.4		
	0.20	4.9	0.14	30
	0.30	8.1		
	0.40	8.4		
7.3	0.10	2.4		
	0.15	2.9		
	0.20	3.8		
	0.25	3.9	0.12	13
	0.32	5.0		
	0.39	5.8		
7.5	0.05	1.2		
	0.10	1.6		
	0.15	1.9		
	0.20	2.8		
	0.25	3.6	0.12	3
	0.32	4.1		
	0.36	5.0		

[a] 0.10 M DKP and 0.25 M HYD. [b] Sodium phosphate buffer. [c] Slope and intercept of a linear least-squares fit of k_d with respect to [buffer]. [d] Measured by flow UV.

and SOX are formed from CA at equal rates at pH 6.8 and 9.0. Whether this represents kinetic or thermodynamic control of the formation of these isomers cannot be ascertained because SOX converts to SH simultaneously. These values for k_{ds} and k_{da} as well as k_{sh} and k_{sa} were obtained by a simultaneous fit of the time dependence of the concentrations of AOX, SOX, and SH by means of an iterative method programmed using Fortran IV for an IBM 370 computer. In essence, the program performs a numerical integration of the differential equations (eq 1) to provide calculated time dependences for AOX, SOX, and SH concentrations (indicated by brackets).

$$\frac{d[CA]}{dt} = -(k_{ds} + k_{da})[CA]$$

$$\frac{d[AOX]}{dt} = k_{da}[CA]$$

$$\frac{d[SOX]}{dt} = k_{ds}[CA] - k_{sh}[SOX]$$

$$\frac{d[SH]}{dt} = k_{sh}[SOX] - k_{sa}[SH] \quad (1)$$

The last equation is valid for small concentrations of AH. This program starts with "guessed values" for all of the rate constants and then adjusts them to give a "best fit" of all three time dependences simultaneously. The criterion for the best fit is the minimization of the sums of the squares of all of the residuals, each of which is defined as the difference between the observed and calculated concentration. This approach was used to calculate k_{ds}, k_{da}, k_{sh}, and k_{sa} at pH 6.8 and 9.0 (Table IV). The calculated time dependences at pH 6.8 are indicated by the solid lines in Figure 2. The reliability of the rate constants calculated in this manner is indicated by the good agreement between k_d and ($k_{ds} + k_{da}$) at pH 6.8 (see Tables III and IV).

The rate constant k_{sh} for the hydrolysis step SOX → SH appears to be pH independent between pH 6.8 and 9.0. A similar behavior was observed for the ester hydrolysis of alkyl α-hydroxyimino-*p*-nitrobenzyl alkylphosphonates in almost the same pH region.[3] In fact, the rate constant for this system ($1.2 \times 10^{-3}\ s^{-1}$) is almost identical to that for SOX even though the mechanism for monoester formation is probably different in the two cases, i.e., via N–O bond cleavage for the hydroxyimino compound. This similarity in rates could mean that the rate-determining step in the ester hydrolysis is the intramolecular nucleophilic addition of the oxime oxygen to phosphorus. However, the details of the addition may differ in these two reactions. Thus, the estimated pK_a for the OH proton of the hydroxyimino compound appears to be sufficiently low so that deprotonation is complete between pH 8 and 9, and the lack of pH dependence has been explained in terms of intramolecular addition of the hydroxyiminate anion to phosphorus.[3] On the other hand, the pK_a for the OH proton of SOX is unlikely to be low enough for complete deprotonation in the pH range 6.8 to 9.0. The pK_a for *p*-nitrobenzaldoxime[3] is 10, and the value for SOX is probably no lower since the $CH_2PO(OEt)_2$ group is unlikely to be more strongly electron withdrawing than the *p*-nitrophenyl group. Consequently, the lack of pH dependence for ester hydrolysis of SOX may indicate that the hydroxyl proton of the oxime group is transferred to the oxygen of the phosphoryl group either prior to or concerted with nucleophilic addition to phosphorus. Protonation of the phosphoryl oxygen prior to nucleophilic addition has been suggested for the amide case,[2] which is compared with our system below.

The value for k_{sa} obtained by the iterative method described above is semiquantitative because only a small amount of SH has converted to AH over the time period used for the calculation (see, for example, in Figure 2). Quantitative values for k_{sa} as well as k_{as} and k_{ah} were obtained from the time dependence of the concentrations for AOX, SH, and AH after SOX could no longer be detected (not illustrated). Under these conditions, the rate for each reaction step can be considered to have a first-order concentration dependence, and an integrated expression for the time dependence of the concentration for either SH or AH can be readily obtained. Although this expression contains all three rate constants, the number of unknowns for the fit is reduced to one by determining k_{ah} from the first-order decay of AOX and measuring the equilibrium concentration ratio AH/SH (found to be 1.6 ± 0.14), which is equal to k_{sa}/k_{as}. Values for k_{ah}, k_{as}, and k_{sa} calculated from the time dependence of the CH_2 proton signals for the appropriate compounds at pH 6.8 are listed in Table IV along with values calculated using the corresponding ^{31}P resonances at pH 9.0. Although they are less accurate, values for k_{ah} obtained from ^{31}P NMR at other pH values are also listed to illustrate that they appear to have no dependence on pH and that ^1H and ^{31}P data are in agreement at pH 6.8. Values for k_{as} and k_{sa} obtained by the least-squares method are considered more accurate than those obtained by the iterative approach, which used data for a time period in which only a small amount of SH has converted to AH. The change in pH from 6.8 to 9.0 causes a decrease in k_{as} and k_{sa}; however, in view of the accuracy of the ^{31}P measurements this must be considered a tentative observation. On the other hand, the ^1H data at pH 6.8 are sufficiently reliable to conclude that k_{as} is larger than k_{ah}, indicating that the isomerization of the anti isomer of the monoester occurs at a faster rate than that for the diester. This conclusion is based on the supposition that k_{ah} represents the rate constant for the isomerization of AOX, which seems reasonable since k_{sh} is larger than k_{ah} by a factor of about 40, and no SOX is detected during the period that AOX decays. Thus, the steady state approximation is applied to SOX, and the forward and reverse steps of the isomerization are assumed to have comparable rate constants, as is the case for SH and AH (Table IV).

Table IV. Kinetic Parameters for Formation of Syn and Anti Isomers, Ester Hydrolysis, and Syn–Anti Isomerization in H_2O at 30 °C (μ = 1.6 M (KCl))[a]

pH	[buffer]	$k_{ds} \times 10^2$, s^{-1}	$k_{da} \times 10^2$, s^{-1}	$k_{sh} \times 10^3$, s^{-1}	$k_{ah} \times 10^5$, s^{-1}	$k_{sa} \times 10^4$, s^{-1}	$k_{as} \times 10^4$, s^{-1}
6.8	0.3[b,c]	6.5	7.0	1.8		6.5	
	0.2[b,d]				4.7	2.5	1.7
	0.2 (^{31}P)[b]				6.4		
8.2	0.3 (^{31}P)[e]				3.6		
9.0	0.2[f,c]	0.32	0.32	1.3		3.0	
	0.2 (^{31}P)[g,d]				4.2	1.1	0.66
	0.2 (^{31}P)[e]				3.0		

[a] Obtained by means of ^{1}H NMR unless otherwise indicated. [b] Sodium phosphate buffer. [c] Iterative method of calculation; see text. [d] Nonlinear least-squares method of calculation, see text. [e] Boric acid buffer. [f] *p*-Hydroxybenzoic acid buffer. [g] Diazabicyclooctane buffer.

To compare the intramolecular assistance of ester hydrolysis with the intermolecular process, the hydrolysis of 0.075 M *O*-methyloxime of DKP in the presence of 0.075 M acetone oxime at pH 7.5 (0.2 M phosphate) was studied. After 2143 h no ester hydrolysis was detected, although about 16% of the acetone oxime had hydrolyzed. Since about 5% ester hydrolysis could have been detected, the effective molarity[9] of the oxime hydroxyl group is $>10^4$ M. It would appear that this group is more effective in assisting phosphonate ester hydrolysis than the amide group, which requires strongly acidic conditions to promote conveniently rapid rates of hydrolysis[2] and presumably has a very slow rate at neutral pH. This difference in effectiveness may be due in part to the presence of the oxime OH proton, which can be transferred to the phosphoryl oxygen as described above. Finally, hydrolysis of the monoester SH is not observed, probably because the presence of the negative charge makes the phosphorus in this compound much less reactive than in the diester. Presumably, removal of the negative charge by lowering the pH would promote monoester hydrolysis as has been observed for the amide case.[2]

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Registry No.—CA, 66417-89-8; methoxyamine hydrochloride, 593-56-6; acetone oxime, 127-06-0; acetone, 67-64-1; hydroxylamine hydrochloride, 5470-11-1.

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A Useful, Regiospecific Synthesis of Isoxazoles

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Isoxazoles have been obtained in excellent yield by acylation of *syn*-1,4-dilithio oximes with amides (DMF, ArCONMe$_2$) followed by a mineral acid induced cyclization–dehydration. The process is exemplified by the conversion of cyclohexanone oxime to 3,4-tetramethyleneisoxazole in 87% yield by successive treatment with *n*-butyllithium, DMF, and acid and by the similar isolation of 5-*p*-anisyl-3,4-trimethyleneisoxazole (67% yield) from cyclopentanone oxime and *N*,*N*-dimethyl-*p*-anisamide. Acylation with DMF of the dilithio salt from (*E*)-benzylacetone oxime afforded 3-(2-phenylethyl)isoxazole in 91% yield uncontaminated by the isomeric 4-benzyl-3-methylisoxazole. An extension of the general scheme permitted the preparation of the latter in 82% yield from acetone oxime. By these procedures, classes of isoxazoles, previously among the most difficult to synthesize (3-substituted, 5-unsubstituted, or aryl), are now among the easiest to make.

Today, the isoxazole ring system is generally considered to be the most broadly useful heteroaromatic precursor and intermediate in preparative organic chemistry.[2] However, the synthetic potential of isoxazoles has not yet been realized fully because of limitations in the structural variations now readily available.[3]

Classically, isoxazoles are made by reaction of 1,3-dicarbonyl compounds (**1**) with hydroxylamine followed by dehydrative cyclization of an intermediate monooxime.[3] When R and R″ in **1** are not the same, two isomeric isoxazoles (**2**) are possible. Both are obtained when R and R″ are similar, a complication which usually leads to major separation prob-

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