Micellar Acceleration of Organophosphate Hydrolysis by Hydroximinomethylpyridinium Type Surfactants

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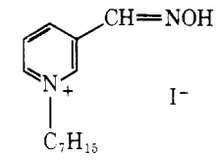
Micellar 1-*n*-dodecyl-3-(hydroximinomethyl)pyridinium salts (**2a–f**) were found to be much more effective nucleophilic reagents for the reaction with two neutral organophosphates, diethyl *p*-nitrophenyl phosphate (**3**) and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**), than nonmicellar 1-alkyl-3-(hydroximinomethyl)pyridinium salts. However, the micellar pyridinium compounds are practically ineffective in accelerating the reaction of the oximate ion with positively charged organophosphates, such as the protonated form of *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**) and *O,O*-diethoxyphosphinylthiocholine iodide (**5**). The influence of solution pH and comicellizing surfactants on the reactivity of 1-*n*-dodecyl-3-(hydroximinomethyl)pyridinium iodide (**2a**), a micellar oxime, is reported. It is concluded that the rate increase observed between micellar and nonmicellar oximes can be explained by differences in the solubility of the substrate in the micelle.

Within the past decade, a number of micelle–substrate systems have been investigated in which reactive functional groups have been incorporated into the micelle-forming molecules.[2-7] In the present work, we present our studies on the acceleration of the reaction between organophosphorus esters and an oximate ion which has been covalently bound to the backbone of a micelle. Most of the studies concerned the reaction between diethyl *p*-nitrophenyl phosphate (**3**), as the organophosphorus substrate, and 1-*n*-dodecyl-3-pyridiniumaldoxime iodide (**2a**), as the functional micellar component. However, some studies were conducted using 1-*n*-heptyl-3-hydroximinomethylpyridinium iodide (**1**). In addition, the reaction between **2a** and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**), a fully substituted



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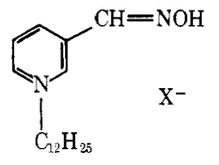
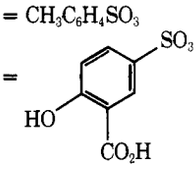
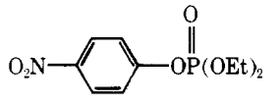


2a, X = I
2b, X = Cl
2c, X = Br
2d, X = CH_3SO_3
2e, X = $CH_3C_6H_4SO_3$
2f, X =





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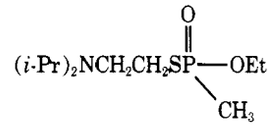

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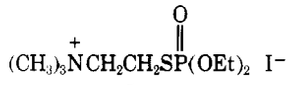

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phosphonate which exists in the neutral, protonated, or mixture of the two forms depending upon the solution pH (pK_a of **4** = 8.6), was examined.

Selection of the oxime function as an integral part of the micelle was based on three reasons:

First, the well-documented high reactivity of the oximate ion with organophosphorus esters and the irreversibility of the reaction[8,9] make possible examination of the micellar effects in neutral or slightly alkaline pH where hydroxide ion catalysis is likely to be negligible. Under these circumstances, interpretation of the results is less ambiguous.

Second, the oxime function is present in many pharmaceutical agents used for the treatment of organophosphorus poisoning.[10] The results of this study could potentially be useful for the design of more effective organophosphorus antidotes.

Third, some anionic nucleophiles, such as hydroxamates, thiolates, and alkoxides, have significant reactivity in cationic micelles.[11] The molecular combination of an anionic nucleophile and a cationic surfactant could enhance the nucleophilicity of the anion by a "charge effect".[9]

It was found that an analogous combination, an imidazole–cationic surfactant micelle,[12] resulted in a significant increase in the hydrolysis rate of *p*-nitrophenyl esters. In these cases, it was postulated[12,13] that the imidazole anion and not the neutral imidazole moiety was the catalytic center.

The choice of a pyridinium micelle was based upon the known reactivity and therapeutic utility of pyridinium oximes. In addition, the availability of information on the micelles of dodecylpyridinium iodides[14] made them particularly attractive.

In the course of this work, Fendler et al.[15] concluded that benzophenone was solubilized in the micelle interior of hexadecylpyridinium chloride near the Stern layer in a polar environment. Similarly, the substrates used in these studies could be expected to be located in close proximity to the oximino group. The studies were conducted near the pK_a of the micellar oximes, pH 9.3.

As a standard for comparing the relative susceptibilities to nucleophilic attack of the organophosphates **3** and **4**, the hydrolysis–pH rate profile for **3** and **4**[16] in the absence of any surfactant was determined, Figure 1.

The susceptibility of **4** to nucleophilic displacement is pH dependent since the reactivity of the protonated and unprotonated forms of **4** is quite different. If the leaving group is the protonated dialkylaminoethyl mercaptan,[16] the hydrolysis rate is approximately ten times that of **3**. On the other hand, if the leaving group is the unprotonated dialkylaminoethyl mercaptan, the hydrolysis rate is approximately one-fourth that of **3**.

At pH 9.3, the half-life of **3** in the absence of detergent was 10 500 min; in 3×10^{-3} M cetyltrimethylammonium bromide (CTAB: cmc 2.5×10^{-3} M), the half-life was reduced only to

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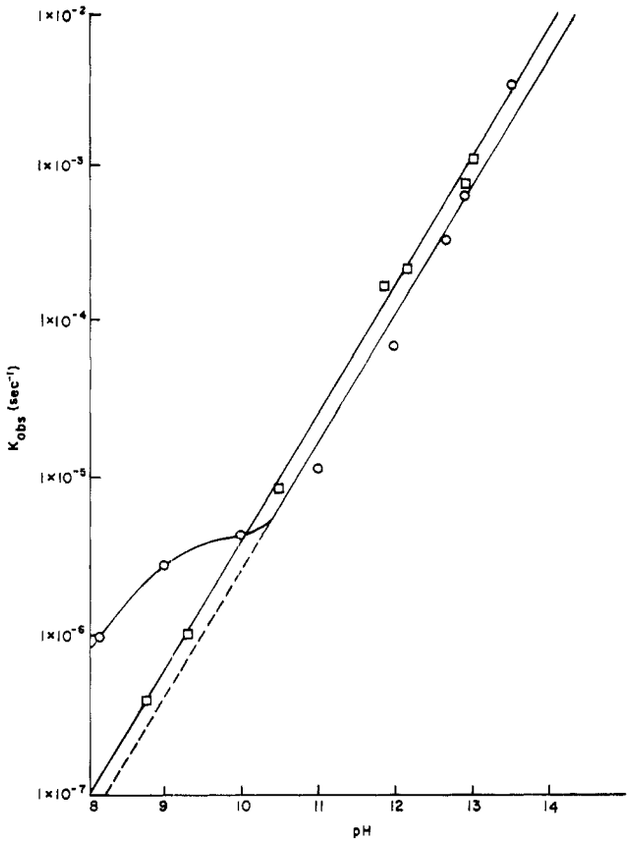

Figure 1. pH–rate profile for the hydrolysis of *p*-nitrophenyl diethyl phosphate (**3**, □) and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**, ○).

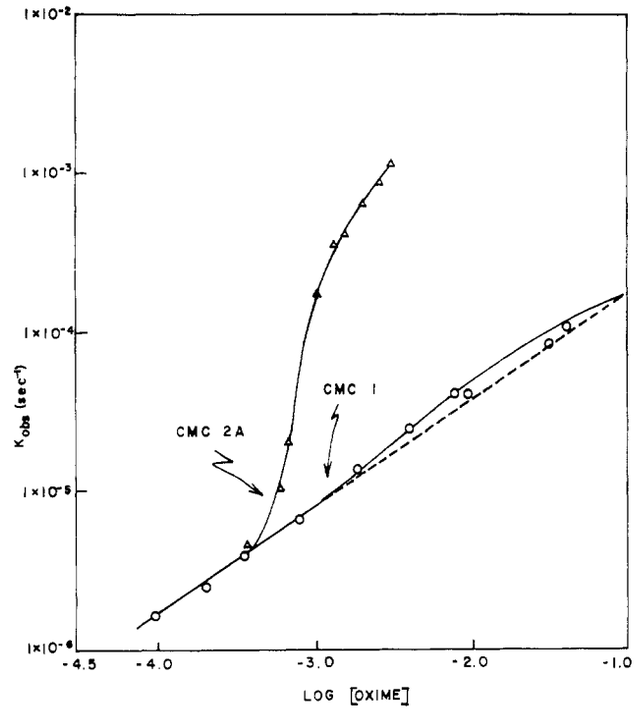

Figure 2. First-order rate constants (s^{-1}) of reaction of **3** with **1** (○) and **2a** (△) at 25 °C, pH 9.3 ($Na_2CO_3/NaHCO_3/NaCl$ buffer = 0.5): cmc of **1** = 1.95×10^{-3} M; cmc of **2a** = 6.30×10^{-4} M.

8700 min. At pH 10.5, the half-life of **3** was reduced from 1200 to 1165 min by CTAB. Thus, the effect of micelles on catalysis of the hydroxide ion reaction with **3** is very small. Similarly, there was only a small increase in the hydroxide ion catalyzed hydrolysis of **4** by micelles of CTAB.

Results

Kinetics. A plot of the observed first-order rate constants (corrected for hydrolysis) for the reaction of **3** with different concentrations of **1** and **2a** in carbonate–bicarbonate buffer, pH 9.3, μ = 0.5, is shown in Figure 2. The critical micelle concentration (cmc) for the two oximes in the reaction medium were 2×10^{-3} and 6×10^{-4} M, respectively. There is a linear increase in the observed first-order rate constant with increasing concentration of **1** to approximately 4×10^{-2} M. The bimolecular rate constant, $k_2' = k_{obsd}/[1]$, over the concentration range 10^{-4}–4×10^{-2}, is $1.2 \times 10^{-2} \pm 0.0008$ M^{-1} s^{-1}. In contrast, there is a marked deviation from linearity in the concentration–rate profile for **2a.** At concentrations of **2a** less than or equal to 2×10^{-4} M, the bimolecular rate constant for **2a** is equal to that of **1** within experimental error. At a concentration of **2a** equal to 6×10^{-4} M, the bimolecular rate constant is equal to 1.5×10^{-2} M^{-1} s^{-1}. The observed rate increase is coincident with the formation of micelles as evident from the cmc (6×10^{-4} M) for **2a** in this medium. A plot of $1/(k_0 - k_{obsd})$ vs. $1/(C_d - C_{cmc})$, where k_0 is the first-order rate constant at the critical micelle concentration (C_{cmc}) and k_{obsd} is the first-order rate constant at the experimental concentration (C_d), is linear (correlation coefficient = 0.99) as predicted from mathematical micellar models.[2] Values of K/N, where K is the binding constant and N is the aggregation number, and k_m, the reaction rate constant for the reaction between **3** and **2a** in the micellar phase, calculated from the slope and intercept are 56 M^{-1} and 1.06×10^{-2} s^{-1}, respectively.

Mechanism of the Reaction. The reaction between **3** and **2a** was examined for stoichiometry and the effect of solution pH. In nonmicellar reactions, 1 mol of the organophosphorus agent is consumed per mol of oxime reacting and the reaction rate is dependent upon the oximate ion concentration.[8] The pseudo-first-order rate constant for the reaction between **2a** and **3** was determined at a concentration of **2a** well above its cmc and using a relatively low concentration of **3** ([**2a**] ≥ 50[**3**]). In order to establish that the oxime **2a** is a true catalyst or a reagent, the reaction of **2a** with **3** was followed at a relative concentration of [**2a**] ≃ 5[**3**]. Following complete destruction of **3,** an additional quantity of **3** was added to the reaction mixture and the reaction rate was determined. Under these circumstances, the concentration of **2a** was greater than its cmc but lowered sufficiently such that the initial rate and the reaction rate were appreciably less than that determined in the first case. After repeating the process several more times, concentrations of **2a** were estimated from the observed second-order rate constant. Following this procedure, the stoichiometry in the micellar reaction between **2a** and **3** was demonstrated to be 1:1 and the regeneration of the oxime from the product by hydrolysis is a much slower process. The oxime **2a** is not a true catalyst but a nucleophilic reagent which deactivates the organophosphate by the formation of the corresponding oxime phosphate.

The influence of pH on the reactivity of **2a** with **3** is shown in Table I. As in the reaction of nonmicellar oximes with organophosphorus compounds,[8] the reactive species in micellar medium is the oximate ion. This thesis is substantiated by the fact that the quotient of the observed rate constant corrected for hydrolysis, k_{obsd}, and the oximate ion concentration is a constant.

Studies with More Soluble Salts and Mixed Micelles. Effect of Cosurfactants on Reaction Rates. Based on the k_m value determined for the reaction between **2a** and **3,** the maximum rate obtainable with this system corresponds to a

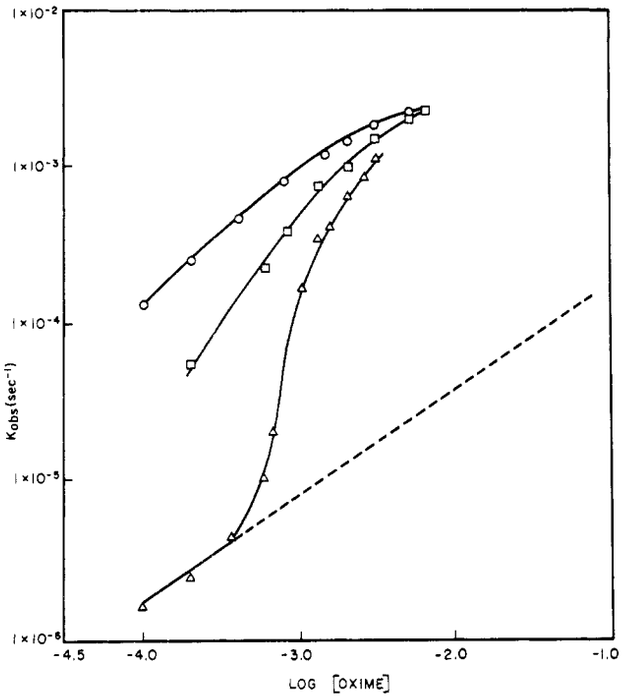

Figure 3. First-order rate constants (s^{-1}) of reaction of **3** with **2a** at 25 °C; pH 9.3 ($Na_2CO_3/NaHCO_3/NaCl$ buffer = 0.5): (△) **2a**; (○) **2a** + 3×10^{-3} M CTAB; (□) **2a** + 3×10^{-3} M Brij.

reaction half-life of 1.1 min. This value is approximately an order of magnitude less than that observed with **2a.** In addition, the fraction (α) of **3** incorporated into the micellar region at the saturation concentration of **2a** (3×10^{-3} M), estimated from eq[2] 1, is 12.7%.

$$K/N = \frac{\alpha}{(1-\alpha)(C_d - C_{cmc})} \quad (1)$$

The difference between the observed rate and the maximum theoretical rate based on k_m can be attributed to the solubility of **3** in the **2a** micelle at its saturated concentration level.

Studies were conducted to determine the effect of (1) mixed micelles of 1-alkyl-3-hydroximinomethylpyridinium iodides, (2) more water soluble salts of **2a,** and (3) mixtures of **2a** with cosurfactants CTAB and polyoxyethylene 20-cetyl ether (Brij) on the reaction rate.

The effect of mixed micelles on the reaction rate of **3** is described in Table II. In mixtures of **1** and **2a,** where the mole fraction of the mixture is weighted greatly in the direction of **1,** the observed rate is close to that obtained with an equivalent concentration of only **1.** When the mole fraction is weighted greatly toward **2a,** the rate is close to that obtained with an equivalent concentration of **2a.** However, the individual contribution of each component in the micellar phase cannot be ruled out. Thus, when approximately equal concentrations of **1** and **2a** are used, the rate is equal approximately to the sum of the individual rates.

The effect of additional cosurfactants, CTAB or Brij, at a constant concentration of 3×10^{-3} M, on the first-order rate constants of the reaction of **3** with different concentrations of **2a** is shown in Figure 3. At a concentration of **2a** equal to 1×10^{-4} M, the addition of CTAB increases the rate by a factor of 82. At a concentration of **2a** equal to 1×10^{-3} M, the increase is a factor of 3 and at a concentration of 3×10^{-3} M the rate increase is less than 2. Similar qualitative data are obtained if Brij is used as the cosurfactant. The relative rate increase tends to decrease with increasing concentrations of **2a.**

A plot of the first-order rate constants for the reaction of **3** with different concentrations of various salts (**2b–f**)[17] of **2a** is shown in Figure 4. It is interesting to note that the first-order rate constants for the various salts fit very well the plot determined for **2a.** At high **2b** concentrations the curve is leveling off at a value corresponding to a half-life of approximately 1.5 min. This value approaches the half-life calculated from the maximum theoretical rate of **2a.**

Table I. Rates of Reaction of 2a (2×10^{-3} M) with 3 at Different Solution pH

pH	$(Ox^-)^a \times 10^3$	$k_{obsd} \times 10^4$	$k_{obsd}' \times 10^4$	k_{obsd}'/Ox^-
8.3	0.16	2.12	2.12	1.32
9.3	0.96	6.60	6.59	0.69
10.6	1.88	12.7	12.6	0.67
11.5	1.98	14.4	13.4	0.68
12.2	2.0	17.8	15.3	0.77

[a] Calculated from equation $(Ox^-) = [K_a/(H^+ + K_a)](Ox)_0$, where $K_a = 4.6 \times 10^{-10}$.

Table II. Half-Lives of 3 in Mixtures of 1 and 2a

[1]	[2a]	$t_{1/2}$, min
4×10^{-2}		40
	2×10^{-3}	10
4×10^{-2}	2×10^{-3}	40
4×10^{-4}		3090
	1.4×10^{-3}	28
4×10^{-4}	1.4×10^{-3}	26
9.1×10^{-4}		2238
	6×10^{-4}	2490
9.4×10^{-4}	5.9×10^{-4}	1273

Studies Using *O*-Ethyl *S*-2-Diisopropylaminoethyl Methylphosphonothiolate (4). The reaction of **2a** with **4** at various solution pH is shown in Table III. The hydrolysis pH–rate profile exhibits a pH–rate dependence similar to that observed in the reaction of **3** with **2a.** This observation is consistent with the thesis that the oximate ion is the reactive functional group in the displacement reaction. However, the relative rate of reaction between **2a** and **3** and **2a** and **4** is 4:1. This observation suggests that the micellar reaction in the case of **2a** and **4** is between **2a** and the unprotonated form of **4.** Since the reaction was examined in a pH range where **4** exists in both the protonated and unprotonated forms, it would appear that the protonated species is barred from entrance into the micelle. In support of this conclusion are the studies of the reaction between **2a** and *O,O*-diethoxyphosphinylthiocholine iodide (**5**), a model for the protonated form of **4.**

The half-life of **5** in water at pH 9.3 is 1690 min. By contrast, the half-life of **3** under the same conditions is approximately 10 000 min. The bimolecular rate constant for the reaction of a nonmicellar oxime with **3** at pH 9.3 was 0.72 M^{-1} min^{-1}. Assuming that the ratio of reactivity for the two substrates toward hydroxide ion is the same as that toward the oximate ion, the half-life of **5** in a 6×10^{-4} M solution of a nonmicellar oxime should be approximately 300 min.

The half-life of **5** in the presence of 3×10^{-3} M **2a** was found to be greater than 500 min. Thus, all the reactions occurring in a system 6×10^{-4} M with respect to oxime concentration in the aqueous phase and 24×10^{-4} M with respect to oxime concentration in the micellar phase can be accounted for by the aqueous phase reaction.

Discussion

The rate of the reaction between the oximate ion of **2a** at a concentration below its cmc and **3** is qualitatively what would be predicted from published data[10,11] for the reaction

Table III. First-Order Decomposition Rates of 4 at Different Solution pH with 3.1 ± 0.1 × 10^{-3} M 2a at 25 °C ($NaHCO_3$–Na_2CO_3 Buffer)

pH	k_{obsd}, s^{-1} × 10^4	pH	k_{obsd}, s^{-1} × 10^4
8.0	0.45	10.1	2.90
9.0	1.52	11.1	4.7
9.3	1.63		

of 1-methyl-3-hydroximinomethylpyridinium with organophosphates. The dramatic effect upon the rate coincident with the cmc and the excellent agreement of the data to a micellar model strongly support the conclusion that the increase in reactivity is due to micelles. Exclusion of the protonated form of **4** from the cationic micelle is also reasonable and the observed level of reactivity with the free base form is consistent with a micellar millieu.

The main factors affecting the rate of reaction at a given pH include the solubility of the substrate in the micelle, the association constant of the substrate with the micelle, and the geometry and aggregation number of the micelle. The latter value is important to the oximate ion concentration as well as to the association constant. Concerning the solubility of the substrate in a micelle, approximately 12% of **3** is partitioned into the micellar phase of a saturated solution of **2a.** Several experiments on the reactivity of **4** with different concentrations of **2a**[18] allow an estimate of the solubility of **4** in a saturated solution of **2a.** It was concluded that the solubility of the free base form of **4** in the micelle is similar to that of **3.** Hydrophilic organophosphorus esters may be expected to show less of an enhancement in reactivity due to micelles relative to **3.** Consistent with this hypothesis, the rate of reaction of isopropyl methylphosphonofluoridate, a very hydrophilic organophosphorus ester,[19] with micellar concentrations of **2a,** is no greater than its rate using equivalent concentrations of the nonmicellar 1-methyl-3-hydroximinomethylpyridinium iodide.[18]

The rates obtained with mixed micelles and cosurfactants are consistent with the thesis that the dominant factor in determining the rate is the solubility of the substrate in the micelle. In mixtures of **1** and **2a** which are higher in one component, the "effective cmc" of the mixture will be heavily weighted toward the richer component.[20] It is anticipated that the micelles produced from such mixtures would be very similar to the micelles of the richer component and behave as the micelle of the pure component. For mixtures in which the component compositions do not differ greatly, the micellar component will contain fractions of the two micelles in accordance with Raoults law and each micelle will contribute to the observed rate.

The results for the effect of added surfactants on the rate are consistent with the hypothesis that the reaction rate is directly proportional to the amount of substrate incorporated into the micelle and that the amount is directly proportional to the micellar volume. To a solution containing 1 × 10^{-3} M **2a,** the micellar concentration of **2a** is approximately 4 × 10^{-4} M. Addition of 3 × 10^{-3} M CTAB to the solution of **2a** provides an additional micellar concentration of approximately 5 × 10^{-4} M. Thus, the contribution of the added CTAB more than doubles the micellar volume and a corresponding increase in the reaction rate is observed. For a solution containing 3 × 10^{-3} M **2a,** the percentage increase in micellar volume upon the addition of CTAB is less and likewise its effect upon the reaction rate is decreased.

In a 3 × 10^{-2} M **2b** solution, it can be assumed that most of **3** is in the micellar phase, since using eq 1 the fraction of **3** in the micelles is approximately 63%. Assuming a density of approximately 0.8 g/mL for the 3-hydroximinomethylpyridinium micelle, the volume of a 3 × 10^{-2} M solution of **2b** is

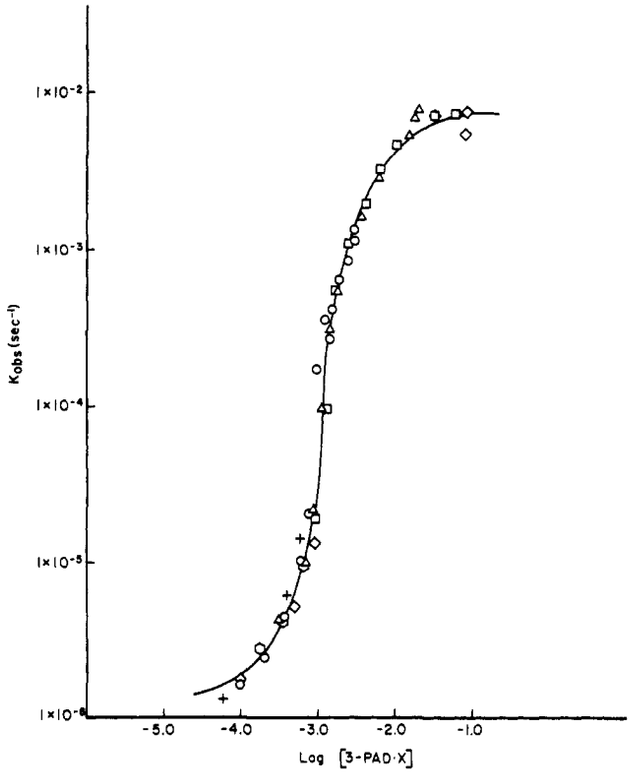

Figure 4. First-order rate constants (s^{-1}) of reaction of **3** with various 3-PAD salts at 25 °C, pH 9.3 (Na_2CO_3/$NaHCO_3$/NaCl, buffer = 0.5): (○) **2a**; (□) **2b**; (△) **2c**; (◇) **2d**; (○) **2e**; (+) **2f.**

Table IV. The pK_a of 2a at 25 °C Under Different Conditions

2a	Conditions	pK_a ± S.E.
5 × 10^{-5} M	Below cmc	9.18 ± 0.07
2 × 10^{-3} M	Above cmc	9.34 ± 0.1
5 × 10^{-5} M	3 × 10^{-3} M CTAB added[a]	9.15 ± 0.03
5 × 10^{-5} M	3 × 10^{-3} M Brij added	9.65 ± 0.15

[a] cmc of CTAB is 2.5 × 10^{-3} M.

15 mL. Therefore, the substrate concentration is 70 times greater in the micellar phase than in the aqueous phase. The first-order rate constants for the reaction between **2b** and **3** and a nonmicellar oxime and **3** are the same when the concentration of **2b** is 3 × 10^{-2} M and the concentration of the nonmicellar oxime is 1.6 M. Therefore, the reaction is 50–60 times more rapid in the micelle relative to the solution and the extent of acceleration can be wholly accounted for on the basis of the concentration effect.

Other factors which could accelerate the reaction between oximes and uncharged substrates were also considered. For example, a cationic micelle could promote ionization of the oximino hydrogen by a field effect without significant reduction in the basicity (nucleophilicity) of the anion in displacement reactions on phosphorous esters.[9] Thus, by producing more of the ionized specie without reducing its intrinsic reactivity, one could achieve a substantial rate enhancement over that observed under conditions where the field effect is not operative. The variation of the pK_a determined for **2a** in various media can be explained by a dielectric effect and an electrostatic field effect each operating in opposing directions, Table IV. With an increase in the hydrocarbon character of the medium, the ionization constant of the oximino hydrogen would be expected to decrease. However, the ionization constant would be expected to increase as the concentration of a quaternary ammonium ion increases. Thus, the normal pK_a

of 8.19 in the nonionic, hydrophobic medium provided by Brij is raised to 9.65, while in the presence of a relatively high concentration of CTAB, the pK_a is virtually unaltered. However, for concentrations of **2a** above its cmc and in the absence of CTAB, it would appear that the effect on the dielectric constant is stronger than the effect of an accumulation of the pyridinium charges. The field effect may be attenuated by a charge transfer reaction with iodide ion. Regardless, the effects, if any, are rather small and are not considered to have a large influence on the reactivity.

Experimental Section

I. Synthesis. 1-*n*-Heptyl-3-hydroximinomethylpyridinium Iodide (1). 3-Hydroximinomethylpyridine (2.44 g; 0.02 mol) and 4.61 g (0.02 mol) of *n*-heptyl iodide were mixed and heated at 120–130 °C for 0.75 h. Upon cooling to room temperature, anhydrous ether was added to the residue. Trituration in anhydrous ether gave 4.5 g (0.019 mol), 99%, of 1-*n*-heptyl-3-hydroximinomethylpyridinium iodide: mp 103–105 °C; IR (KBr) 3220, 3020, 2920, 1640, 1500, 1410, 1280, and 970 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.80 (t, 3 H), 1.2 (bs, 8 H), 1.9 (3 H), 4.6 (t, 2 H), and 7.8–9.15 (5 H).

Anal. Calcd for $C_{13}H_{21}IN_2O$: C, 44.84; H, 6.08; N, 8.05. Found: C, 44.76; H, 5.97; N, 7.94.

Using the procedure described for the preparation of **1**, 1-*n*-dodecyl-3-hydroximinomethylpyridinium iodide (**2a**) was prepared.

1-*n*-Dodecyl-3-hydroximinomethylpyridinium iodide (2a): mp 118–120 °C; IR (KBr) 3180, 2920, 2840, 1500, 1470, 1290 and 1000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.8 (t, 3 H), 1.2 (bs, 18 H), 1.9 (2 H), 4.7 (t, 2 H), and 8.9–9.6 (5 H). Anal. Calcd for $C_{18}H_{31}IN_2O$: C, 51.67; H, 7.47; N, 6.70. Found: C, 51.38; H, 7.41; N, 6.43.

The preparations of 1-*n*-dodecyl-3-hydroximinomethylpyridinium chloride (**2b**), bromide (**2c**), methane sulfonate (**2d**), *p*-toluene sulfonate (**2e**) and 5-sulfosalicylate (**2f**) have been described previously.[17]

II. Physical–Chemical Parameters. a. Solubility. Various weights of each oxime (1 and **2a–f**) were placed in screw-capped 2 dram glass vials; 7-mL quantities of the appropriate buffer solution were added and the vials were sealed (Teflon liners). They were then shaken in a water bath thermostated at 25 °C for periods up to 7 days. Samples were taken at various intervals to ensure that equilibrium conditions had been attained.

At 25 °C, samples were filtered using a Millipore Swinnex adaptor (Millipore HAWD01300 0.45 μm filter) and diluted in a vehicle of ethanol/pH 9.3 carbonate buffer[21] (50:50 v/v) to approximately $0.1–1 \times 10^{-4}$ M. The absorbance of the resulting solutions at 290 or 295 nm was measured and the solubilities were calculated based on the respective molar absorptivities: **1**, $\epsilon_{295} = 1.21 \times 10^4$ M^{-1} cm^{-1}; **2a**, $\epsilon_{295} = 1.29 \times 10^4$ M^{-1} cm^{-1}; **2b**, $\epsilon_{290} = 1.17 \times 10^4$ M^{-1} cm^{-1}; **2c**, $\epsilon_{290} = 1.22 \times 10^4$ M^{-1} cm^{-1}; **2d**, $\epsilon_{290} = 1.07 \times 10^4$ M^{-1} cm^{-1}; **2e**, $\epsilon_{290} = 1.03 \times 10^4$ M^{-1} cm^{-1}; and **2f**, $\epsilon_{295} = 1.54 \times 10^4$ M^{-1} cm^{-1}.

b. Critical Micelle Concentration (cmc). A concentrated solution of each oxime (1 and **2a**) in buffer[21] was prepared, assayed, and serially diluted to produce a range of concentrations. The solutions were equilibrated at 25 ± 0.2 °C. Using a Hitachi Perkin-Elmer MPF-2A spectrophotofluorimeter to excite the solutions at a wavelength of 410 nm, the intensity of the Raman peak of water occurring at 478 nm was recorded. This intensity was plotted against oxime concentration and the inflection point in the curve determined the critical micelle concentration (cmc). The critical micelle concentration of 1 and **2a** was 1.95×10^{-3} and 6.30×10^{-4} M, respectively.

c. pK_a Determination of 1-*n*-Dodecyl-3-hydroximinomethylpyridinium Iodide (2a). The pK_a of 1-*n*-dodecyl-3-hydroximinomethylpyridinium iodide (**2a**) above and below the critical micelle concentration (cmc) and in the presence of 3×10^{-3} M cetyltrimethylammonium bromide (CTAB) and Brij was determined spectrophotometrically. Carbonate–bicarbonate buffers ranging in pH from 5.8 to 12.8 were prepared and used to prepare the following solutions: (1) 5×10^{-5} M **2a**, below cmc; (2) 2×10^{-3} M **2a**, above cmc; (4) 5×10^{-5} M **2a** in 3×10^{-3} M CTAB; and (4) 5×10^{-5} M **2a** in 3×10^{-3} M Brij.

The absorption spectra of these solutions were determined from 220 to 450 nm. The absorbance at 295 nm was plotted against the pH of the buffer solutions. Sigmoidal curves were obtained and the pK_a values were calculated based on three determinations around the point of half neutralization using the equation

$$pK_a = pH_{obsd} + \log \frac{[A_{max} - A_{obsd}]}{[A_{obsd} - A_{min}]}$$

where A_{max}, A_{min}, and A_{obsd} are the absorbance values for the dissociated, undissociated, and the partly dissociated (at pH_{obsd}) solutions of **2a**.

III. Chemical Kinetics. a. Kinetic Studies using *p*-Nitrophenyl Diethyl Phosphate (3). All reactions were carried out in a carbonate buffer system (prepared using 0.1 M sodium carbonate and 0.1 M sodium bicarbonate) of ionic strength 0.5 (added sodium chloride).[21] The concentration of **3** was 3.63×10^{-5} M. The formation of the *p*-nitrophenolate ion was followed spectrophotometrically at 400 nm using a Cary 14 spectrophotometer equipped with an automatic sampling accessory thermostated at 25 ± 0.2 °C.

The reactions were started by adding 25 μL of a 1% v/v solution in dioxane of the phosphate ester to 25 mL of oxime solution equilibrated for 1 h at the temperature investigated.

The reactions were followed for a minimum of 3 half-lives and always obeyed first-order kinetics. Rate constants were calculated from half-lives obtained from semilogarithmic plots of $A_\infty - A_t$ against time (A_∞ is the absorbance at the end point of the reaction and A_t is the absorbance at any time t).

b. Kinetic Studies Using *O*-Ethyl *S*-2-Diisopropylaminoethyl Methylphosphonothiolate (4). Solutions containing approximately 0.1 M Na_2CO_3, 0.1 M $NaHCO_3$, 0.2 M NaCl, 3×10^{-3} M **2a**, and 10^{-3} M CTAB were prepared by dissolving the appropriate quantities of materials in about 45 mL of distilled water. The pHs of the solutions were adjusted with concentrated NaOH or HCl solutions and the volumes raised to 50 mL. The solutions were placed in a water bath at 25 °C for about 15 min and 5 μL of **4** (ca. 86%) was added. The solutions were vigorously shaken for about 10 s and returned to the water bath. Aliquots were removed by a rapid-fill 5-mL syringe and put into 5 mL of CCl_4 and shaken 5 s; on separation the bottom layer was collected. This CCl_4 layer was placed in a 10-mL volumetric flask containing a small amount of anhydrous K_2CO_3 to absorb any water present in the CCl_4 solution. The **4** was assayed by VPC: 10 μL; 5% UCW-98 on W.H.P. 100–120 mesh; 2 min at 200 °C; 16 in./min up to 270 °C; 270 °C for 2 min-He 50 psi; 3 3.6 min; disulfide 6.5 min.

The peak heights of **4** were linear with concentration and referenced to a 1000-ng sample. Less than 1 ng could be detected. The **4** was extracted into the CCl_4 with close to 100% efficiency.

c. Kinetic Studies Using (2-Mercaptoethyl)trimethylammonium Iodide *O,O*-Diethylphosphorothioate; Phospholine Iodide (5). All reactions were carried out in a carbonate buffer system (prepared by use of 0.1 M sodium carbonate and 0.1 M sodium bicarbonate) of ionic strength 0.5 (added sodium chloride).[21] The concentration of **5** was 7.38×10^{-5} M.

The hydrolysis product of **5**, thiocholine, can react with 5,5-dithiobis(2-nitrobenzoate) (DTNB) to produce a yellow colored anion. The rate of this color formation may be measured at 412 nm.[22] Because phospholine iodide is moderately stable in neutral and acidic solution, the reaction could be quenched at time intervals and immediately put into 4 mL of phosphate buffer, pH 7. DTNB (0.2 mL) was added to each sample just before recording the absorbance at 412 nm. The A_∞ was calculated from the initial concentration of phospholine iodide using the known molar absorptivity of 1.35×10^4 M^{-1} cm^{-1}. Only the initial slopes of semilogarithmic plots of $A_\infty - A_t$ against time were taken to calculate the reaction rate constants.

In the case where **2a** was present in the solution, the reaction solution was diluted using a 4:1 water–ethanol mixture.

Registry No.—**1**, 66290-87-7; **2a**, 66290-86-6; **2b**, 66290-85-5; **2c**, 66290-84-4; **2d**, 66290-91-3; **2e**, 66290-90-2; **2f**, 66290-89-9; **3**, 311-45-5; **4**, 50782-69-9; **5**, 513-10-0; 3-pyridinealdoxime, 1193-92-6; heptyl iodide, 4282-40-0.

References and Notes

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(2) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975.

(3) (a) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Phys. Chem.*, **71**, 1961 (1967); (b) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 1333 (1968).

(4) (a) A. Ochoa-Solvano, G. Romero, and C. Gitler, *Science*, **156**, 1243 (1967); (b) C. Gitler and A. Ochoa-Solvano, *J. Am. Chem. Soc.*, **90**, 5004 (1968).

(5) T. E. Wagner, C. Hsu, and C. S. Pratt, *J. Am. Chem. Soc.*, **89**, 6366 (1967).

(6) W. Tagaki, T. Amada, Y. Yamashita, and Y. Yano, *Chem. Commun.*, 1131 (1972).

(7) C. A. Bunton, L. Robinson, and M. Stam, *J. Am. Chem. Soc.*, **92**, 7393 (1970).

(8) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stanfield, *J. Chem. Soc.*, 1583 (1958).
(9) J. Epstein, P. L. Cannon, Jr., H. O. Michel, B. E. Hackley, Jr., and W. A. Mosher, *J. Am. Chem. Soc.*, **89**, 2937 (1967).
(10) (a) R. I. Ellin and J. H. Wills, *J. Pharm. Sci.*, **53**, 995 (1964); (b) R. I. Ellin and J. Henry Wills, *ibid.*, **53**, 1143 (1964); (c) N. Bodor, E. Shek, and T. Higuchi, *Science*, **190**, 155 (1975); (d) N. Bodor, E. Shek, and T. Higuchi, *J. Med. Chem.*, **19**, 102 (1976); (e) E. Shek, T. Higuchi, and N. Bodor, *ibid.*, **19**, 108 (1976); (f) *ibid.*, **19**, 113 (1976).
(11) (a) C. A. Bunton and L. G. Ionescu, *J. Am. Chem. Soc.*, **95**, 2912 (1973); (b) K. Martinek, A. V. Levashov, and I. V. Berezin, *Tetrahedron Lett.*, 1275 (1975); (c) Tabushi, Y. Kuroda, and S. Kita, *ibid.*, 643 (1974); (d) T. Kunitake, U. Okahata, and T. Sakamoto, *Chem. Lett.*, 459 (1975).
(12) R. A. Moss, R. C. Nahas, S. Ramaswami, and W. J. Sanders, *Tetrahedron Lett.*, 3379 (1975).
(13) U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 771 (1976).
(14) (a) A. Ray and P. Mukerjee, *J. Phys. Chem.*, **70**, 2138 (1966); (b) J. E. Adderson and H. Taylor, *J. Pharm. Pharmacol.*, **16**, 147T (1964); (c) G. C. Kresheck, E. Hamori, G. Davenport, and H. A. Scheraga, *J. Am. Chem. Soc.*, **88**, 246 (1966); (d) B. C. Bennion and E. M. Eyring, *J. Colloid Interface Sci.*, **32**, 286 (1970).
(15) J. H. Fendler, E. J. Fendler, G. A. Infante, P. S. Shih, and L. K. Patterson, *J. Am. Chem. Soc.*, **97**, 89 (1975).
(16) J. Epstein, J. J. Callahan, and V. E. Bauer, *Phosphorus*, **4**, 157 (1974).
(17) J. J. Kaminski, K. W. Knutson, and N. Bodor, *Tetrahedron*, in press.
(18) We are indebted to Dr. G. T. Davis and M. M. Demek for supplying these data.
(19) C. Tanford, "The Hydrophobic Effect", Wiley, New York, N.Y., 1973, p 81.
(20) The partition coefficients of isopropyl methylphosphonofluoridate between nonpolar solvents such as hexane and carbon tetrachloride and water are less than one (R. W. Rosenthal, R. Proper, and J. Epstein, *J. Phys. Chem.*, **60**, 1596 (1956)).
(21) G. E. Delory and E. J. King, *Biochem. J.*, **39**, 245 (1945).
(22) G. L. Ellman, K. D. Courtney, V. Anders, Jr., and R. M. Featherstone, *Biochem. Pharmacol.*, **7**, 88 (1961).

The Intermediate from the Triphenylphosphine–Tetrachloromethane–Alcohol Reaction: Relative Rates of Intermediate Formation, Kinetics, and Mechanism of Intermediate Decomposition

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The rate of formation of the phosphorylated intermediate formed by reacting triphenylphosphine, carbon tetrachloride, and an alcohol is only slightly influenced by steric effects. The relative rates of intermediate formation are primary > secondary > neopentyl. The relative rates of intermediate decomposition follow the order primary > secondary > neopentyl. Thus neopentyl alcohol reacted with the phosphorylating agent at room temperature to form an intermediate without concomitant decomposition to neopentyl chloride. The structure of the intermediate was elucidated by ^1H NMR and ^{31}P decoupling. Rates of decomposition to the respective alkyl chlorides of the phosphorylated intermediates formed from neopentyl alcohol and from 1,1-dideuterio-2,2-dimethylpropanol were run at various temperatures. Clean first-order kinetics were obtained as well as the energetics for the decomposition reaction. A small positive α hydrogen kinetic isotope effect was obtained and the various mechanisms of intermediate decomposition to chloride product are discussed in terms of rate constants, the energetics, and the isotope effects.

The reaction of triphenylphosphine, carbon tetrachloride, and alcohols gives rise to an elegant method for the synthesis of primary and secondary alkyl chlorides.

$$(C_6H_5)_3P + CCl_4 + ROH \rightarrow RCl + (C_6H_5)_3PO + CHCl_3 \quad (1)$$

In 1966, the preparation of acyl chlorides[1] by the reaction of a carboxylic acid with triphenylphosphine and carbon tetrachloride was extended to the preparation of alkyl chlorides from alcohols, triphenylphosphine, and carbon tetrachloride.[2]

Similarly, tri-*n*-octylphosphine and carbon tetrachloride were used to convert primary and secondary alcohols to the corresponding chlorides with inversion of configuration; the production of tertiary chlorides gave very poor yields, possibly due to elimination being the primary reaction.[3] The use of carbon tetrabromide, trialkyl- or triarylphosphines, and primary or secondary alcohols led to alkyl bromides. Again, inversion of configuration seemed to predominate in this synthetic procedure.[3] The ease with which chlorides were formed with inversion of configuration was explored by R. G. Weiss and E. I. Snyder in several papers.[4a-c]

The various pathways for intermediate formation have been investigated by Appel and have been summarized in an excellent review article by the same author.[5] The overall mechanism of the reaction is presumed to proceed via eq 2.[5]

$$(C_6H_5)_3P + CCl_4 \rightarrow [(C_6H_5)_3PCl]^+CCl_3^-$$

$$[(C_6H_5)_3PCl]^+CCl_3^- + ROH \rightarrow [(C_6H_5)_3POR]^+Cl^- + HCCl_3$$

$$[(C_6H_5)_3POR]^+Cl^- \rightarrow RCl + (C_6H_5)_3PO \quad (2)$$

In more detail, the formation of the intermediate can be formulated in part as follows:[5]

$$(C_6H_5)_3\overset{\delta+}{P}\cdots Cl\cdots\overset{\delta-}{C}Cl_3 \rightarrow [(C_6H_5)_3POR]^+Cl^- + HCCl_3 \quad (3)$$

(R–O–H)

Appel[5] has also described other minor routes to the phosphorylated intermediate involving $(C_6H_5)_3PCl_2$ and $(C_6H_5)_3PCCl_2$, but they will not be discussed in this manuscript.

There are a number of gaps in this mechanistic picture that need to be filled and clarified: First, it must be noted that nowhere is there any mention of the relative rates of formation and decomposition of the intermediate. Second, it will be noted that the intermediate has been described as an ion pair with a phosphorus–oxygen–carbon bond. At present there is no hard evidence for this assumption. Third, it must be emphasized that although the intermediate has been described as undergoing a first-order decomposition to product, there is no concrete evidence to date that this implied kinetic order is a reality.

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