Catalysis of Reactions of p-Nitrobenzoyl Phosphate by Functional and Nonfunctional Micelles[1]

Clifford A. Bunton* and Michael McAneny

Department of Chemistry, University of California, Santa Barbara, California 93106.

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Cationic micelles of cetyltrimethylammonium bromide (CTABr), (n-$C_{16}H_{33}N^+Me_2)_2(CH_2)_6$ $2Br^-$ (I), and n-$C_{16}H_{33}N^+Me_2CH_2CH_2OH$ Br^- (II) catalyze the spontaneous hydrolysis of p-nitrobenzoyl phosphate dianion by factors of up to 6, with little effect upon spontaneous hydrolysis of the monoanion. Nonfunctional micelles of CTABr and I catalyze attack of OH^- upon the dianion by factors of up to 10, but at high pH micelles of II are partially ionized and the zwitterion of II is an effective reagent. Choline is a more effective reagent than OH^- at high pH in the absence of surfactant. In micelles of CTABr n-octyloxyamine effectively deacylates p-nitrobenzoyl phosphate monoanion; and n-alkylamines, especially n-dodecylamine, react readily with the dianion. 1-Decylguanidinium bromide doubles the rate of attack of OH^- upon the dianionic substrate in CTABr, but it, and other guanidinium salts, have little effect on the other reactions.

The rate of hydrolysis of primary aryl phosphates ($RCOOPO_3H_2$ and their salts) in water or aqueous organic solvents is pH sensitive.[2-4] The reaction is acid catalyzed, and at pH >2 three reactions can be observed under appropriate conditions: (1) spontaneous decomposition of the monoanion with elimination of PO_3^-; (2) spontaneous decomposition of the dianion with elimination of PO_3^-, and (3) deacylation.

The relative importance of these reactions depends upon the substituents, and electron-withdrawing groups favor spontaneous reaction of the dianion over that of the monoanion.[4] Nucleophiles other than the lyate ion can attack either the mono- or dianion, and the rates of all these reactions should be affected by micelles.[5]

Micellar catalysis of reactions of phosphate esters has the following pattern: (1) the spontaneous decomposition of the dianion, but not the monoanion, of a monosubstituted phosphate ester is catalyzed by cationic micelles;[9,10] (2) attack of anionic nucleophiles upon di- and trisubstituted phosphate esters is catalyzed by cationic micelles and inhibited by anionic and nonionic micelles,[10,11] and (3) micelles of surfactants which contain nucleophilic or basic groups are good reagents toward di- and trisubstituted phosphate esters.[12,13] Deacylation of an acyl phosphate should be similar to reactions of carboxylic esters which are catalyzed by cationic micelles,[6-8] and functional mcelles are good reagents in this reaction.[6-8,14-16]

The aim of the present work was to compare micellar catalysis of reactions of p-nitrobenzoyl phosphate in the pH range 2–13 with that of uni- and bimolecular reactions of carboxylic and phosphoric esters and unimolecular decarboxylation.[17] Micelles can control reaction rates and products,[6-8,18-20] and our system is a model for acylation and phosphorylation,[2-4,21,22] and illustrates control of the mechanisms of reaction of acyl phosphates by a submicroscopic aggregate.

The surfactants were cetyltrimethylammonium bromide (CTABr), n-$C_{16}H_{33}N^+Me_3Br^-$; hexamethylenebis(hexadecyldimethylammonium) dibromide (I), n-$C_{16}H_{33}N^+Me_2(CH_2)_6N^+Me_2n$-$C_{16}H_{33}$, $2Br^-$; and hexadecyl(2-hydroxyethyl)dimethylammonium bromide (II), n-$C_{16}H_{33}N^+Me_2CH_2CH_2OH$ Br^-. As nucleophiles we used n-alkylamines, 1-octyloxyamine, and hydroxide ion and the reactions were

$$\begin{array}{l} ArCOOPO_3H^- \longrightarrow ArCO_2H + PO_3^- \\ \quad III \quad \llcorner N \longrightarrow ArCON + Pi \\ ArCOOPO_3^{2-} \longrightarrow ArCO_2^- + PO_3^- \\ \quad IV \quad \llcorner N \longrightarrow ArCON + Pi \end{array}$$

Ar = O_2N–C$_6$H$_4$–; N = nucleophile

The hydroxyethyl moiety in II is a model for an enzymic serine residue.[12,15,16]

Experimental Section

Materials. p-Nitrobenzoyl phosphate was prepared as the dilithium salt from silver dihydrogen phosphate and p-nitrobenzoyl chloride by standard methods,[22] and the preparation and purification of the surfactants has been described.[11,12] 1-Octyloxyamine hydrochloride was prepared from benzohydroxamic acid and 1-bromooctane. After recrystallization (EtOH–EtOAc) it had mp 147–149 °C (lit.[23] 147–149 °C). 1-Decylguanidine hydrobromide was prepared from methylthioisourea hydrobromide and decylamine; after recrystallization (EtOH) and drying over P_2O_5 it had mp 64.5–66 °C. The picrate had mp 149–150 °C (lit.[24] 149–151 °C).

Kinetics. Reactions were followed spectrophotometrically at 265 nm, using a Gilford spectrophotometer with water jacketed cells at 25.0 °C. This wavelength gave the maximum absorbance changes during reaction, but because the absorbances of the substrate and p-nitrobenzoate ion are similar, the absorbance changes during reactions are small, ca. 0.08 absorbance units for 5×10^{-5} M substrate, and the 0.1 absorbance scale of the instrument was used. Runs were done in duplicate or triplicate and rate constants agreed within ±10%. The first-order rate constants, k_ψ, are in s^{-1} at 25.0 °C in water. The surfactants prevented use of the standard hydroxamic acid method of following the hydrolysis.[2-4]

Products. The products of hydrolysis and aminolysis of p-nitrobenzoyl phosphate were examined. The formation of O-octyl p-nitrobenzohydroxamate in the reaction of p-nitrobenzoyl phosphate (4×10^{-5} M) with 1.4×10^{-2} M 1-octyloxyamine in 0.02 M CTABr at pH 4.5 (0.02 M acetate buffer) was shown spectrophotometrically. The absorbance decreases at 268 nm and increase at 345 nm when the pH is increased to 12.5 (Figure 1) are typical of hydroxamate esters[25] including the p-nitrobenzoate, and the increase in absorbance at 345 nm corresponds to 90% conversion of p-nitrobenzoyl phosphate into hydroxamate ester. The hydroxamate ester and p-nitrobenzoic acid and their anions absorb at ca. 270 nm so this spectral region was not used for calculation of the product composition.

Reaction of p-nitrobenzoyl phosphate (1.5×10^{-4} M) with 4×10^{-3} M dodecylamine in 2×10^{-2} M CTABr and 0.001 M NaOH gave a mixture of p-nitrobenzoic acid and N-dodecyl p-nitrobenzamide, based on spectral and chromatographic evidence. After complete reaction the uv absorption was measured and the pH was then brought to 2. The absorbance maximum shifted from 270 to 262 nm as expected from the spectra of p-nitrobenzoic acid and its anion.[22b,26] The increase in absorbance was that expected for a concentration of p-nitrobenzoic acid of ca. 6.5×10^{-5} M. A sample of the original reaction mixture was then neutralized ($HClO_4$) and after addition of MeOH and $NaClO_4$ was extracted several times with hexane. The dried hexane layer had λ_{max} 255 nm, characteristic of N-dodecyl-p-nitrobenzamide,[26] and the absorbance corresponded to an amide concentration of ca. 9×10^{-5} M in the original reaction mixture. Thin layer chromatography, silica gel in $CHCl_3$–petroleum ether (bp 65–110 °C), 1:1, gave a spot, R_f 0.65, coincident with that of authentic amide.

Results and Discussion

Reactions in the Absence of Surfactant. The reactions were followed at 25.0 °C in three regions of pH: at pH 2 (dilute

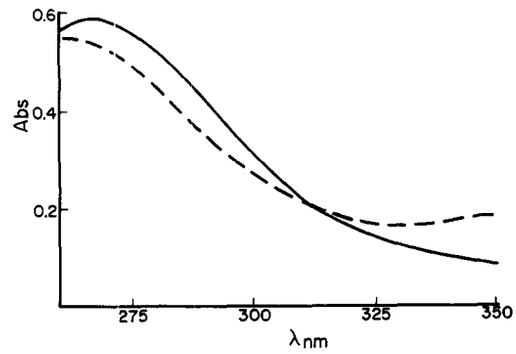


Figure 1. Uv spectra of the products of reaction of *p*-nitrobenzoyl phosphate monoanion with 1-octyloxyamine at pH 4.5 (solid line), and after pH increase to 12.5 (broken line).

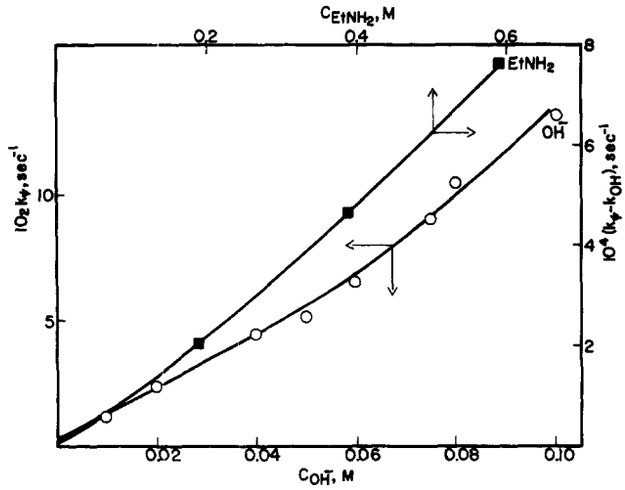


Figure 2. Reaction of *p*-nitrobenzoyl phosphate dianion with OH^- and $EtNH_2$ at 25.0.

Table I. Salt Effect upon Reactions of the Dianionic Substrate

Salt	$10^5 k_\psi$, s^{-1} [a]	Salt	$10^4 k_\psi$, s^{-1} [b]
	3.89		5.17
0.02 M $Me_3NCH_2CH_2OHCl$	4.57	0.08 M Me_4NCl	5.96
0.05 M $Me_3NCH_2CH_2OHCl$	4.62	0.016 M Me_4NCl	6.42
0.10 M $Me_3NCH_2CH_2OHCl$	4.70		

[a] At pH 8 in 1.25×10^{-2} M borate buffer. [b] In 0.05 M NaOH.

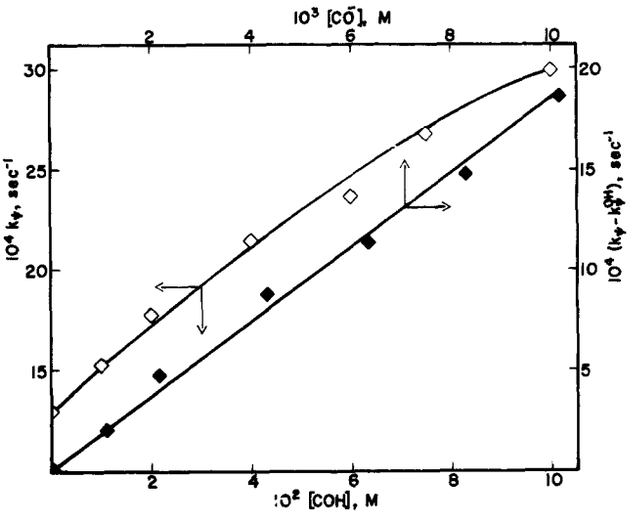


Figure 3. Reaction of *p*-nitrobenzoyl phosphate dianion with choline chloride at 25.0 °C, ◇; ◆, for reaction of zwitterion.

HCl) where the monoanion (III) is the bulk species, at pH 8.0 (1.25×10^{-2} M borate buffer) where the dianion (IV) is the bulk species, and in dilute alkali where the major reaction is attack of hydroxide ion upon the dianion.[2-4] The first-order rate constants in the absence of surfactant are, for the monoanion 3.80×10^{-5} s^{-1} and for the dianion 3.89×10^{-5} s^{-1}. Di Sabato and Jencks found the corresponding values to be 1.35×10^{-4} and 4.67×10^{-4} s^{-1} at 39 °C.[4] As is typical of these reactions of organic phosphates the activation energy is higher for hydrolysis of the dianion.[4,27]

Hydroxide ion attacks the carbonyl group, and the second-order rate constant (Figure 2) increases slightly with increasing hydroxide ion (initial value 9×10^{-3} M^{-1} s^{-1}), probably because there is a small positive salt effect as is found with Me_4NCl (Table I, cf. ref 28a).

Added amines attack the carbonyl group,[2,4] and our results for reaction of the dianion with ethylamine are in Figure 2. The concentrations of free amine and hydroxide ion were calculated from the total amine concentration and the pH of the solution (for $EtNH_2$ $pK_a = 10.64$). The second-order rate constants drift up slightly with increasing amine concentration, but the initial value of 10^{-3} M^{-1} s^{-1} is almost one-tenth that for reaction of OH^-. The upward drift in the second-order rate constants for reaction of amines has been ascribed to a general base catalysis,[4] although in some systems the rate varies linearly with amine concentration.[2] In many of these reactions it is necessary to separate the contributions of several independent reactions using dissociation constants and even when ionic strength is held constant, specific salt effects may complicate calculations of the individual rate constants.[28]

At pH 8.0 choline chloride has a small positive salt effect on hydrolysis of *p*-nitrobenzoyl phosphate dianion (Table I), but it is a very effective reagent at higher pH where the cholinate zwitterion is present ($pK_a = 13.9$ for choline[29]). The rate data are in Figure 3, where COH and CO^- denote choline and its zwitterion, respectively. The corrected first-order rate constants $k_\psi - k_\psi^{OH}$ (where k_ψ^{OH} is the first-order rate constant in the absence of choline) vary linearly with concentration of cholinate zwitterion and the second-order rate constant, $k_2 = 1.87 \times 10^{-2}$ M^{-1} s^{-1}, is larger than for reaction with hydroxide ion, as is found for reactions of triaryl phosphates,[12] triarylmethyl carbocations, and dihalonitrobenzenes.[30] The second-order rate constants for reactions in water are summarized in Table II.

Reactions of Mono- and Dianion (III and IV) in the Presence of Cationic Micelles. Hydrolysis of *p*-nitrobenzoyl phosphate monoanion at pH 2 ($k_\psi = 3.8 \times 10^{-5}$ s^{-1}) is slightly catalyzed by micelles of CTABr with $k_\psi = 5.36 \times 10^{-5}$ s^{-1} in both 0.025 and 0.05 M CTABr at 25.0 °C, although these micelles do not catalyze the hydrolysis of *p*-nitrophenyl phosphate monoanion.[9] Micellar effects should be small for reactions in which the transition state requires both proton transfer to the leaving aryloxy or carboxyl moiety and phosphorus–oxygen scission.

The spontaneous hydrolysis of the dianion is catalyzed by cationic micelles (Figure 4), as are the spontaneous hydrolyses of 2,4- and 2,6-dinitrophenyl phosphate dianions.[9] The values of k_ψ for hydrolysis of *p*-nitrobenzoyl phosphate dianion increase to plateaux values with increasing surfactant concentration as is typical of micellar catalyzed unimolecular reactions,[9,10,17,18] in contrast to the rate maxima which are gen-

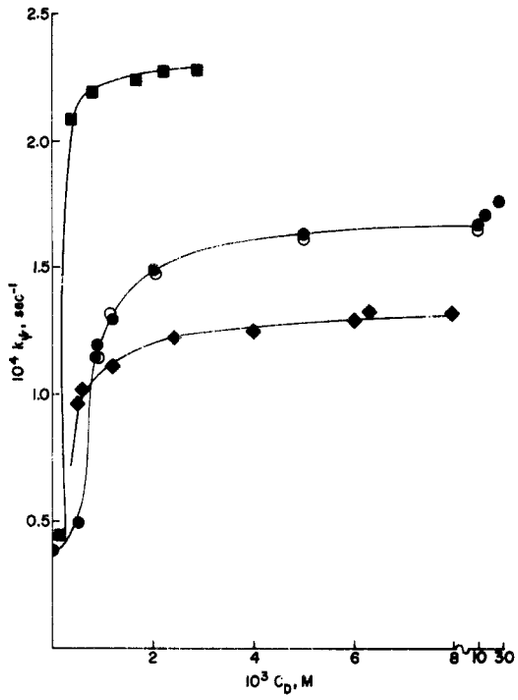
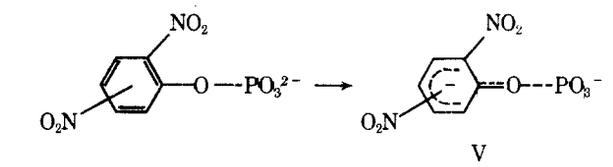


Figure 4. Micellar effects upon the spontaneous hydrolysis of p-nitrobenzoyl phosphate dianion at 25.0 °C. ●, CTABr; ■, I; ♦, II. The open points (○) are calculated values, eq 1.

erally found for micellar catalyzed bimolecular reactions.[6-8] These rate maxima and their significance are discussed in ref 6–8 and 31.

The micellar catalyses of several spontaneous hydrolyses and decarboxylations are compared in Table III. The rate enhancements for hydrolyses of the dinitrophenyl phosphate dianions are greater than for that of p-nitrobenzoyl phosphate dianion, although these reactions are formally very similar. Reduced solvation of the phosphate moiety in the substrate should increase the reaction rate,[4,27] and incorporation into a cationic micelle should both reduce this solvation and provide beneficial interactions between the cationic head groups of the micelle and the organic residue in the transition states V and VI.



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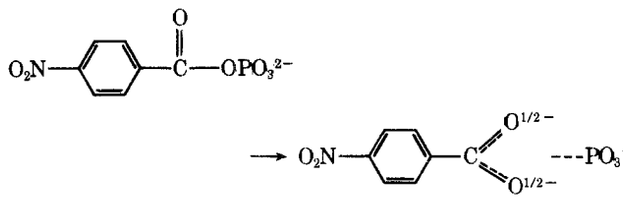


VI

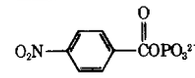
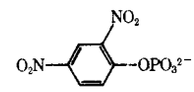
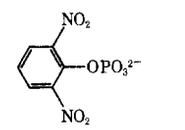
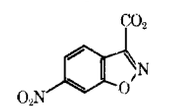
Aromatic compounds interact with both micellized and nonmicellized quaternary ammonium ions,[32,33] but the interactions should be stronger with a forming dinitrophenoxide ion with its delocalized charge than with a carboxylate ion with its localized charge. The micellar catalyses of decarboxylations of activated carboxylate anions are very much larger than those for hydrolysis of these dianionic organic phosphates (Table III) because of the strong interaction of the cationic head group of the surfactant with the carbanion-like transition state.[17] There is a similar pattern in the micellar catalyses of

Table II. Second-Order Rate Constants for Nucleophilic Attack upon the Dianion[a]

Nucleophile	Water	CTABr
OH^-	9×10^{-3}	77×10^{-3} [b]
$Me_3N^+CH_2CH_2O^-$	18.7×10^{-3}	
$EtNH_2$	10^{-3}	
$C_{12}H_{25}NH_2$		30×10^{-3} [c]

[a] Values of k_2, M^{-1} s^{-1} at 25.0 °C. [b] In 0.005 M CTABr and 0.01 M NaOH. [c] In 0.01 M CTABr.

Table III. Micellar Effects upon Spontaneous Reactions of Phosphate Dianions and Carboxylate Monoanions[a]

	Surfactant		
Substrate	CTABr	$(n\text{-}C_{16}H_{33}\text{-}N^+Me_2)_2\text{-}(CH_2)_6{\cdot}2Br^-$	$C_{16}H_{33}N^+\text{-}Me_2CH_2\text{-}CH_2OHBr^-$
	5	6	3.5
	21[b]		27[c]
	24[b]		
	95	400	90
$PhCH(CN)CO_2^-$ [d]	660		

[a] Values of k_{rel} compared with rate constant in the absence of surfactant. [b] Reference 9. [c] Reference 20. [d] Reference 17.

bimolecular reactions of phosphate and carboxylic esters and activated aryl halides.[6-8,11,30b]

The relation between rate constant and surfactant concentration for unimolecular micellar catalyzed and micellar inhibited reactions can be treated using a simple distribution model:[6-8,34]

$$S + D_n \overset{K}{\rightleftharpoons} SD_n$$
$$\downarrow k_w \qquad\qquad k_m \uparrow$$
$$\text{products}$$

where S is the substrate, D_n is the micelle of the surfactant (detergent) D, and k_w and k_m are the rate constants in the aqueous and micellar phases.

This scheme gives

$$k_\psi = [k_w + k_m K(C_D - \text{cmc})/N]/[1 + K(C_D - \text{cmc})/N] \quad (1)$$

where C_D is the surfactant concentration, cmc is the critical micelle concentration, and N is the aggregation number of the micelle.

Equation 1 can be rearranged to[11]

$$(k_\psi - k_w)/(k_m - k_\psi) = K(C_D - \text{cmc})/N \quad (2)$$

For the spontaneous reaction of the dianion in CTABr a plot of $(k_\psi - k_w)/(k_m - k_\psi)$ against C_D is linear (Figure 5), and the extrapolated value of cmc of 5×10^{-4} M is slightly lower than the literature value of 9×10^{-4} M for CTABr[35] probably because of substrate induced micellization.[11,36] The value of K/N

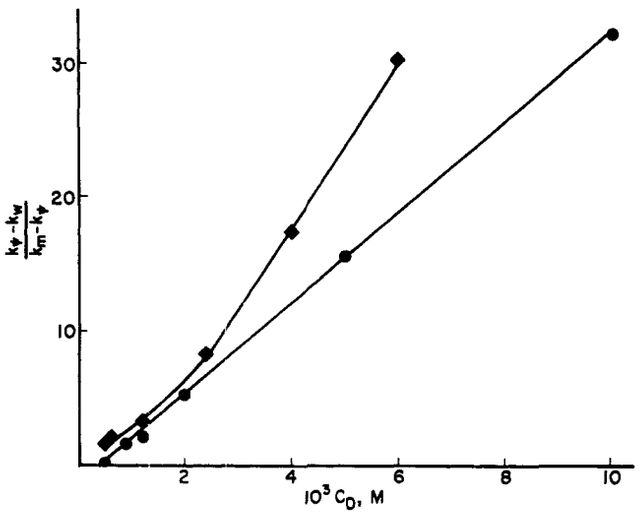


Figure 5. Estimation of association constants between *p*-nitrobenzoyl phosphate dianion and cationic micelles: ●, CTABr; ♦, hydroxyethyl surfactant (II).

Table IV. Salt Effects upon Reaction of the Dianion in CTABr[a]

Salt	C_{salt}, M	0.05	0.10	0.15
NaCl		1.26	1.08	0.97
NaBr		0.91	0.68	0.61

[a] Values of $10^4 k_\psi$ at 25.0 °C in 0.01 M CTABr at pH 8.0, in the absence of added salt $10^4 k_\psi = 1.7\ s^{-1}$.

is 3.4×10^3 and if N is ca. 60, and is unaffected by the substrate, K is ca. 2×10^5 and is similar to those of 1.1×10^5 and 3.9×10^4 for 2,4- and 2,6-dinitrophenyl phosphate dianions.[9] The values of k_ψ calculated using k_w, k_m, and K/N fit the experimental data (Figure 4).

Although we observe a plateau value of k_ψ for reaction in the presence of the hydroxyethyl surfactant (Figure 4), there is curvature in plots of $(k_\psi - k_w)/(k_m - k_\psi)$ against concentration of this surfactant (Figure 5). The intercept is close to zero surfactant concentration, suggesting that there is specific interaction between the dianionic substrate and the hydroxy group of II which should be a good hydrogen bonding donor.

We could not apply eq 1 and 2 to catalysis by the dicationic surfactant (I) because the rate reaches its plateau value at surfactant concentrations very close to the cmc (Figure 4) suggesting that the micelles bind the substrate very strongly.[11b] This surfactant is also a better catalyst than CTABr for spontaneous decarboxylation (Table III).

Added electrolytes typically reduce micellar catalysis by competing for the micelle with an ionic substrate,[6-8,37] and, so far as we know, unimolecular decarboxylations of carboxylate ions are the only exceptions to this generalization.[17] Added salts decrease the catalysis by CTABr of the spontaneous hydrolysis of *p*-nitrobenzoyl phosphate dianion (Table IV), and these salt effects follow the general pattern, with inhibition increasing with increasing hydrophobicity of the counterion to the surfactant.

Micellar Effects upon Reactions at High pH. Micelles of CTABr and the dicationic surfactant (I) speed the reaction of *p*-nitrobenzoyl phosphate dianion with hydroxide ion (Figure 6), as is general for deacylation.[6-8] The rate enhancements are small, even with micelles of I, probably because each anionic reagent hinders incorporation of the other into the Stern layer of the micelle. There is a problem in the

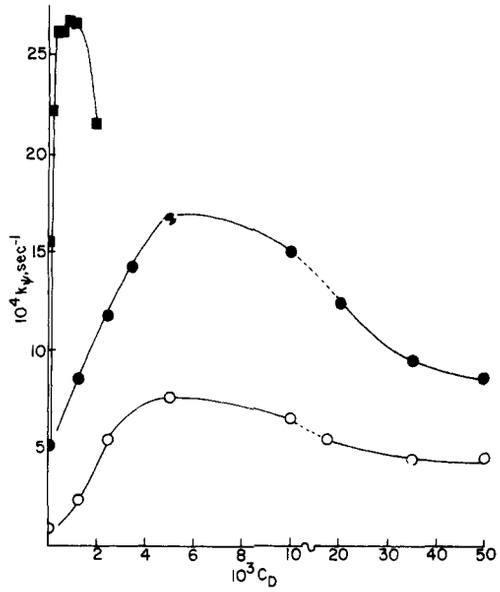


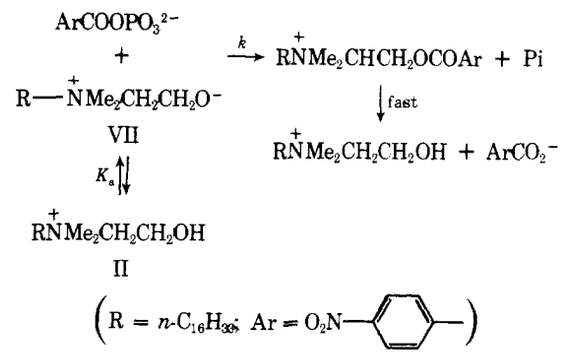
Figure 6. Effects of nonfunctional micelles on the reaction of *p*-nitrobenzoyl phosphate dianion at 25.0 °C: ○, 0.01 M OH^- in CTABr; ●, 0.05 M OH^- in CTABr; ■, 0.05 M OH^- in I.

distribution of ionic reagents between water and the micelle,[8,31,38] so that rate maxima are found in plots of k_ψ against surfactant concentration, and in CTABr the reaction is less than first order with respect to hydroxide ion.

These results for deacylation are similar to those for decomposition of *p*-nitrophenyl diphenyl phosphate and ethyl *p*-nitrophenyl phosphate monoanion, where nucleophilic attack was on the phosphoryl group.[12]

Attack by the alkoxide moiety in VII upon the acyl phosphate is shown in Scheme I, and the relation of rate to pH was analyzed, following the approach used for dephosphorylation.[12]

Scheme I



In Scheme I k is the first-order rate constant for reaction of VII with the substrate in the micelle. The kinetic form was treated making certain simplifying assumptions,[12] to give

$$k_m = \frac{kC_{OH^-}(K_a/K_w)}{1 + C_{OH^-}(K_a/K_w)} \quad (3)$$

where k_m is the observed first-order rate constant when all the substrate is incorporated into the micelle. Some of the assumptions, for example, that ionization of the hydroxyl group of II does not materially decrease the hydroxide ion concentrations, are easily satisfied but others are less certain. For example, the value of K_w for water may not be applicable on the micellar surface, and we do not know the distribution of hydroxide ion between aqueous and micellar phases. Therefore the values of k and K_a, calculated using eq 3, are appar-

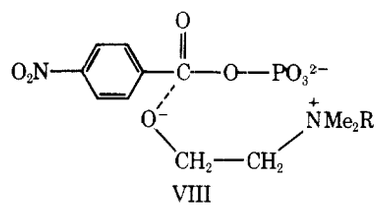
ent[12] but the value of K_a should be the same for reactions of different substrates in micellized II except for salt effects by the reagents, and we can test the relation between k_m and hydroxide ion concentration (eq 3) by using it for different reactions.

Equation 3 can be rewritten as

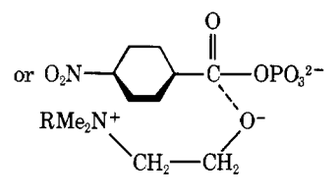
$$1/k_m = 1/k + K_w/kK_aC_{OH^-} \quad (4)$$

and a plot of k_m vs. $1/C_{OH^-}$ gives $k = 0.036\ s^{-1}$ and $pK_a = 12.1$ (this estimate is based on $K_w = 10^{-14}$). The value of pK_a agrees with that of 12.4 from reactions of di- and triaryl phosphates in the presence of micellized II,[12] and of 12.3 from reactions of 2,4-dinitrohalobenzenes.[30] These values of K_a and k lead to calculated rate constants which agree with the experimental values (Figure 7).

Catalysis by micelles of a functional surfactant is akin to the so-called "intramolecular catalysis" whose effectiveness is often measured by comparing the first-order rate constant for the intramolecular reaction with the second-order rate constant for the corresponding intermolecular reaction.[39] For reaction of hydroxide ion with p-nitrobenzoyl phosphate dianion $k_2 = 9 \times 10^{-3}\ M^{-1}\ s^{-1}$, so that our k value of $0.036\ s^{-1}$ corresponds to an effective hydroxide ion concentration of ca. 4 M. For the intermolecular reaction with cholinate zwitterion $k_2 = 1.9 \times 10^{-2}\ M^{-1}\ s^{-1}$, so that the k value corresponds to the hypothetical reaction rate in 2 M cholinate zwitterion suggesting that in both intermolecular and micellar reactions the quaternary ammonium ion center assists reaction by bringing together the substrate and the cholinate zwitterion or VII as in VIII or IX by interacting with anionic or aromatic



VIII



IX

residues in the transition state.[17,30b,32,33] Similar results were obtained in the reactions of the cholinate zwitterion with p-nitrophenyldiphenyl phosphate[12] and with carbocations and 2,4-dinitrohalobenzenes,[30] although in these systems the rate enhancements in micelles of II over the intermolecular reactions of OH^- and the cholinate zwitterion were much larger than those found here; e.g., for reactions in micelles of II the effective hydroxide ion concentrations were for p-nitrophenyldiphenyl phosphate, 8 M;[12] for 2,4-dinitrochlorobenzene, 410 M; and for 2,4-dinitrofluorobenzene, 170 M.[30b] These observations suggest that in the transition states for both deacylation and spontaneous hydrolysis the p-nitrobenzoyl moiety interacts less effectively with the cationic head groups than does an aryloxy or carbanion-like moiety,[12,17,30b] because negative charge is extensively delocalized into the aryl group in aromatic nucleophilic substitution, is less delocalized when a p-nitrophenoxide ion leaves a phosphoryl group, and is not delocalized into an aryl group in nucleophilic attack upon p-nitrobenzoyl phosphate.

Attack of II upon p-nitrobenzoyl phosphate dianion generates the p-nitrobenzoate but this compound, like other choline derived esters,[40] is very reactive in dilute alkali and undetectable under our reaction conditions.[41] (In 5×10^{-3} M II and 0.02 M NaOH $k_\psi = 12.5\ s^{-1}$ at 25.0 °C for the decomposition of the p-nitrobenzoate of II.[41]) However, an ether can be detected in the corresponding reactions of 2,4-dinitrohalobenzenes,[30b] and "burst" experiments have shown that acetylation of the hydroxyethyl moiety is the first step in the saponification of p-nitrophenyl acetate in micelles of a hydroxyethyl derived surfactant.[16,42]

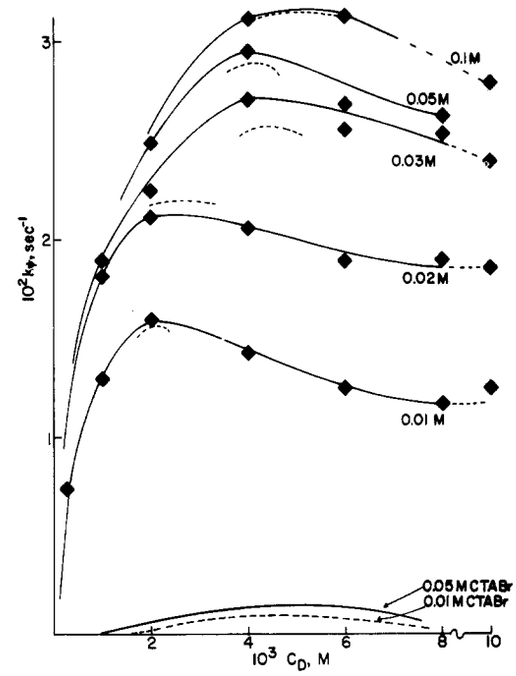


Figure 7. Reaction of p-nitrobenzoyl phosphate dianion with micelles of the hydroxyethyl surfactant (II), and CTABr at the indicated hydroxide ion molarities. The broken lines for II are calculated using eq 3.

All the evidence shows that micelles of hydroxyethyl derived surfactants related to II react as nucleophilic alkoxide ions, and proton loss is an equilibrium step and not concerted with making of the new bond.[12c] However, the magnitude of the micellar catalysis increases as the negative charge in the transition state is delocalized into an aryl group where it interacts favorably with the cationic head groups of the micelle.

Micellar Effects upon the Apparent pK_a of p-Nitrobenzoyl Phosphate. Added amines deacylate phosphates (ref 2, 4, and Figure 2), and, in the absence of surfactants, the various reactions can be separated using the dissociation constants of the amines and phosphates. The problem is more complicated for reactions in the presence of micelles which alter dissociation constants,[6-8,33,43] and complicate the use of buffers and the electrochemical determination of dissociation constants. We could not determine the dissociation constants of p-nitrobenzoyl phosphate spectrophotometrically, and therefore we used kinetic methods.

The hydrolysis of p-nitrobenzoyl phosphate was followed over a pH range in 0.01 M CTABr, where the substrate should be wholly in the micelles (Figure 4). At low pH the monoanion is the main reactant, and at high pH it is the dianion whose spontaneous hydrolysis is catalyzed by CTABr, and the midpoint value of k_ψ (Table V) corresponds to an apparent $pK_a = 4$ for the second dissociation in micelles of CTABr. (It is an apparent dissociation constant because we do not know the ionic distribution between water and the micelles.) In water at 39 °C $pK_a = 4.3$,[4] and a cationic micelle should decrease pK_a.[6-8,33,43]

Micellar Effects upon Amine Reactions. In order to examine attack of amine upon the monoanion in a micelle we

Table V. pH Dependence of the Hydrolysis of *p*-Nitrobenzoyl Phosphate[a]

pH	$10^4 k_\psi$, s^{-1}	pH	$10^4 k_\psi$, s^{-1}
1.0	0.54	4.0	1.21
2.0	0.54	4.5	1.51
2.5	0.60	5.0	1.70
3.5	0.81	8.0	1.76

[a] At 25.0 °C in 0.01 M CTABr; pH 1–2 in dilute HCl; pH 2.5–5 in 10^{-2} M acetate buffer; pH 8 in 1.25×10^{-2} M borate buffer.

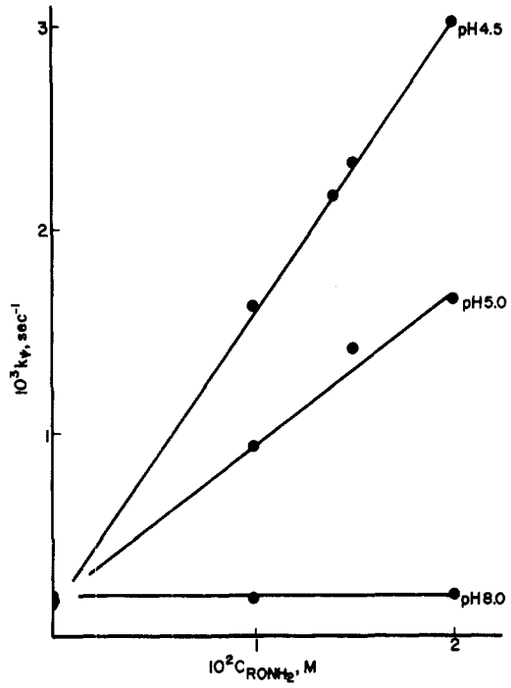


Figure 8. Reaction of 1-octyloxyamine with *p*-nitrobenzoyl phosphate monoanion in CTABr at 25.0 °C in 0.02 M CTABr. Buffers: pH 4.5 and 5.0 0.02 M acetate; pH 8.0 0.125 M borate.

needed an amine which is not extensively protonated at pH where the substrate is monoanionic, but we could not use aromatic amines which interfere with the spectrophotometric determination of reaction rate. Alkoxyamines are suitable reagents (for *n*-alkoxyamines pK_a = 4.6[44]), and we used octyloxyamine, which should be readily incorporated into micelles of CTABr. Alkoxyamines are α-effect nucleophiles, and they are often more nucleophilic than predicted by their basicity.[45]

The reaction was carried out at pH 4.5 in 0.02 M CTABr and 1.4×10^{-2} M octyloxyamine, where at least 90% of the product was hydroxamate ester (Experimental Section), and the first-order rate constant, $k_\psi = 2.17 \times 10^{-3}$ s^{-1}. This rate constant is approximately 14 times greater than that of hydrolysis under these conditions, $k_\psi = 1.55 \times 10^{-4}$ s^{-1}, in agreement with the product composition.

The first-order rate constants for reaction with octyloxyamine in CTABr are in Figure 8. The decreasing slopes of plots of k_ψ against oxyamine concentration with increasing pH show that nucleophilic attack upon *p*-nitrobenzoyl phosphate dianion is relatively unimportant. Under these conditions

$$k_\psi[S_T] = k'[S] + k''[S^{2-}] + k_N[S^-][RONH_2] \quad (5)$$

where S_T is stoichiometric substrate, k', k'' are first-order rate constants with respect to substrate mono- and dianion, respectively, and k_N is the second-order rate constant for nucleophilic attack.

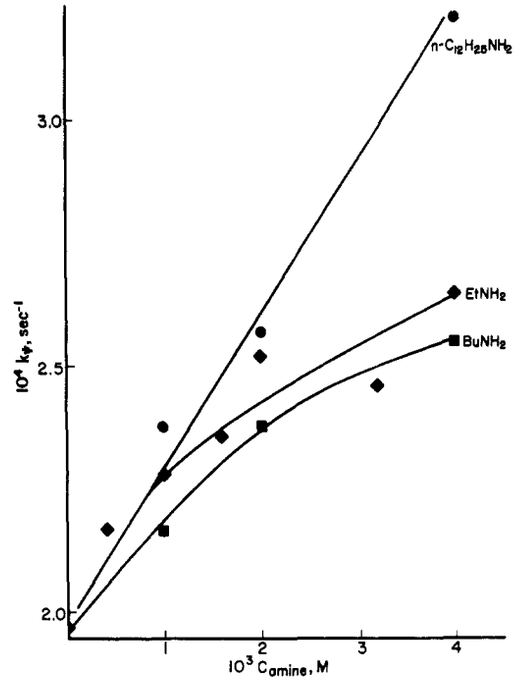


Figure 9. Micellar effects upon the reactions of *n*-alkylamines with *p*-nitrobenzoyl phosphate dianion at 25.0 °C in 0.02 M CTABr and 10^{-3} M NaOH.

Equation 5 can be simplified to

$$(k_\psi - k_0)[S_T] = k_N[S^-][RONH_2] \quad (6)$$

where k_0 is the first-order rate constant in the absence of alkoxyamine.

If K_N and K_s are respectively the ionization constants for octyloxyamine and the substrate *in the micelle* we can write

$$k_N = \frac{(k_\psi - k_0)([H^+] + K_N)([H^+] + K_s)}{K_N[H^+][N_T]} \quad (7)$$

The values of k_N and K_N in eq 7 can be estimated from the values of $k_\psi - k_0$ and K_s at pH 4.5 and 5 provided that k_N is independent of pH. Substituting the appropriate values from Figure 8 into eq 7 and simplifying gives

$$(K_N - 2.27 \times 10^{-5})(K_s - 2.27 \times 10^{-5}) = 1.77 \times 10^{-9} \quad (8)$$

The form of equation 8 is reasonable because both K_N and K_s must be greater or less than 2.27×10^{-5}, and we estimated pK_s = 4.0 in CTABr ($K_s = 10^{-4}$). Provided that we can use this value of K_s for comicelles of CTABr and octyloxyamine we calculate $K_N = 4.6 \times 10^{-5}$, i.e., pK_N = 4.34 (in water pK_N = 4.6[44]), and k_N = 10.1 M^{-1} s^{-1}. In this as in other reactions functional micelles or comicelles containing hydroxylamine moieties are very effective reagents at both carbonyl and phosphoryl centers.[14a,46] As a test of the assumption that there is no attack on the dianion and using eq 5, we calculate the following values of k_ψ at pH 8.0 in 0.02 M CTABr: with 0.014 M $C_8H_{17}ONH_2$, $10^3 k_\psi = 0.19$ s^{-1} (obsd 0.183) and with 0.0186 M $C_6H_{17}ONH_2$ 0.194 s^{-1} (obsd 0.198). Micelles of CTABr markedly catalyze the reaction of octyloxyamine so that at pH 4.5 and 5 it overwhelms the spontaneous hydrolyses of the mono- and dianions.

Although octyloxyamine does not attack the dianion even in CTABr, we can observe such a reaction by using more nucleophilic amines (Figure 9). In most micellar catalyzed reactions, first-order rate constants do not increase linearly with increasing reagent concentration[6-8,11,31,38] in part because the reagent is distributed between the micelles and bulk solvent.

Table VI. Effect of Decylguanidinium Bromide on Reactions of the Dianion[a]

pH	10^3 [$C_{10}H_{21}NHC(NH_2)_2$ Br], M	10^3 [CTABr], M	k_{rel}
8.0	4	2	0.96
8.0	4	4	0.98
10.6	15	40	0.86
12[b]	5	5	1.31
12[b]	7.5	7.5	1.57
12[b]	10.0	10.0	1.87
12[b]	10.4	10.4	2.05

[a] Values of k_{rel} to rate constant in the absence of decylguanidinium bromide at 25.0 °C. [b] 0.01 M NaOH.

But k_ψ increases linearly with amine concentration for reactions of dodecylamine with p-nitrobenzoyl phosphate dianion (and octyloxyamine with the monoanion), probably because of strong interactions between the cationic micelles and these hydrophobic nucleophiles. In low concentration ethyl-, butyl-, and dodecylamine have similar reactivities in CTABr solutions.

The second-order rate constant for reaction of dodecylamine with the dianion in CTABr is 3×10^{-2} M^{-1} s^{-1}, as compared with that of 10^{-3} M^{-1} s^{-1} for reaction of ethylamine in water. Dodecylamine could not be used in water, but it should have a similar reactivity to ethylamine, and this 30-fold rate enhancement of amine attack by micellized CTABr is considerably larger than that for attack of hydroxide ion (Table II and Figure 6). This difference could be due to the greater micellar incorporation of dodecylamine as compared with hydroxide ion, and the absence of electrolyte effects. In water hydroxide ion is considerably more reactive than ethylamine toward the dianion (Figure 2).

Effects of Alkylguanidinium Ions. Guanidinium moieties modify the biological properties of organic phosphates,[24] and we hoped that guanidinium salts would affect micellar reactions of p-nitrobenzoyl phosphate by hydrogen bonding to the phosphate group,[47] and assisting nucleophilic attack at carbonyl or phosphoryl groups. Such assistance would be similar to that of alkaline earth cations which catalyze neutral and basic hydrolysis probably by coordinating with the phosphate group.[2,4,22a] Guanidinium ion should also hinder spontaneous dephosphorylation. Relatively low concentrations of guanidinium halides were used because they could have a negative salt effect and disrupt the micelles by perturbing water structure. In CTABr decylguanidinium bromide slightly hinders spontaneous hydrolysis of p-nitrobenzoylphosphate dianion, but it assists attack of hydroxide ion (Table VI). The guanidinium salts generally inhibited the reactions with octyloxyamine and functional micelles of II (Table VII), by the usual salt effect or by disrupting the micelles. Decylguanidinium bromide should comicellize and deactivate octyloxyamine or the zwitterion (VII) by hydrogen bonding which would offset any rate assistance by hydrogen bonding to p-nitrobenzoyl phosphate.

Relation between Micellar Catalysis and Substrate Structure. Micelles assist bimolecular reactions by bringing reactants together into a small volume element and in a medium in which they can react, and it is difficult to separate the "concentration" and "medium" effects.[6-8,31] But for unimolecular reactions, only the second effect is important once the substrate is brought into the micelles, and as we noted earlier the catalysis is greatest when a localized charge in the initial state is delocalized in the transition state.[17] The quaternary ammonium ion in a cationic micelle can be regarded as a very soft acid which interacts best with a soft base,[48] e.g., better with a delocalized carbanion than with a carboxylate ion, and these principles should also apply to micellar catalyzed bimolecular reactions. It is difficult to compare data obtained under different conditions, but it appears that micellar catalysis is greater for reactions in which anionic attack generates transition states with a highly delocalized charge, as compared with those having their charge localized on oxygen atoms. For example, micellar catalysis appears to be smaller for reactions in which small anions attack acyl or phosphoryl centers than for those in which attack is on an aromatic moiety,[6-8,38,50] even under conditions in which reaction occurs wholly in the micelles.

Table VII. Effect of Guanidinium Salts on Reactions of Mono- and Dianionic Substrate[a]

Salt	Reagent: 0.02 M $C_8H_{17}ONH_2$[b]	Reagent: 0.008 M $C_{16}H_{33}N^+Me_2CH_2CH_2O$-HBr$^-$ [c]
0.02 M $(NH_2)_3CCl$	0.95	
0.04 M $(NH_2)_3CCl$		0.66 (0.81)
0.08 M $(NH_2)_3CCl$	0.90	
0.02 M MeNHC-$(NH_2)_2Cl$	1.04	
0.04 M MeNHC-$(NH_2)_2Cl$		0.55 (0.80)
0.08 M MeNHC-$(NH_2)_2Cl$	0.64	
0.04 M $C_{10}H_{21}NHC$-$(NH_2)_2Br$		1.04
0.1 M $C_{10}H_{21}NHC$-$(NH_2)_2Br$	0.45	

[a] Values of k_{rel} compared with rate constant in the absence of the guanidinium salt. [b] pH 4.5 and 0.02 M CTABr. [c] At pH 10.6; the values in parentheses are at pH 8.3.

Registry No.—I, 15590-96-2; II, 20317-32-2; IV, 60646-46-0; CTABr, 57-09-0.

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Reaction of Saturated (5α- and 5β-) 19-Hydroxy Steroids with Mixed Phosphorus and Halogen Containing Reagents[1a]

Enzo Santaniello[1b] and Eliahu Caspi*

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

William L. Duax* and Charles M. Weeks

Medical Foundation of Buffalo, Buffalo, New York 14203

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Attempts to convert saturated (5α- and 5β-) 19-hydroxylated steroids to 19-halogenated analogues with the use of mixed phosphorus and halogen containing reagents are described. The 19-halogenated analogues were not obtained, but certain transformations in the 5α series and rearrangements in the 5β series were noted and are discussed.

Previously, we have described the unsuccessful attempts to prepare saturated (5α- and 5β-) 10β-methyl sterols from 19-hydroxylated analogues via the hydrogenolysis of the corresponding sulfonate esters.[2a] In a search for an alternative approach, we considered the possibility of converting the 19 alcohol to a 19 halide (e.g., iodide) which, in turn, could be hydrogenolyzed to the 10β methyl. This approach suggested itself by the observations on the efficient conversion of numerous alcohols to halides with the use of mixed phosphorus and halogen containing reagents.[2b,3-9]

The attractiveness of the method was further enhanced by the observation that even alcohols prone to rearrangements gave unrearranged halides.[2b,8-10] For example, (1*S*)-neopentyl-*1-d* alcohol, on treatment with $(C_6H_5)_3P$–CCl_4, was transformed to presumably optically pure (1*R*)-neopentyl-*1-d* chloride.[11] In most instances, when the reaction is not assisted by a neighboring group, inversion of configuration takes place.[6,11] Retention of configuration in cases involving neighboring group participation was reported.[3,7] We have tested one of the procedures and obtained 17α-iodoestra-1,3,5(10)-trien-3-ol and 5α-cholestane 3α-iodide by treatment of estradiol and 5α-cholestan-3β-ol with $(C_6H_5O)_3P$–CH_3I, respectively.[12]

The preparation of the required 19-hydroxy-5α-androstane-3,17-bis(ethylene dioxide) (**1**) was previously described.[2a] Treatment of a dimethylformamide solution of **1a** with $(C_6H_5)_3P$ and bromine for 16 h at room temperature in the air resulted in the 19 formate **1b**. Formate ester formation under similar reaction conditions was previously observed.[13] Only starting material was recovered when the above mixture was refluxed (48 h) under nitrogen. Similarly, starting material was recovered when **1a** was refluxed (48 h) under nitrogen with $(C_6H_5)P_3$ in CCl_4.

The reaction of **1a** with triphenyl phosphite–methyl iodide [$(C_6H_5O)_3P$–CH_3I] (MTPI) gave an iodide, but did not proceed in the desired manner. When **1a** was stirred at room temperature with MTPI in formamide for 3 h under nitrogen, 3α-(2-iodo)ethoxy-3β,19-oxido-5α-androstan-17-ethylene dioxide (**2**) was obtained (60% yield). The mass spectrum of **2** showed peaks at *m/e* 502 (M^+), 348 (M − 154), and 99. The