# Nucleophilic Attack of Salicylhydroxamate Ion at C═O and P═O Centers in Cationic Micellar Media

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The reaction between the salicylhydroxamate anion ($SHA^-$) and *p*-nitrophenyl benzoate (PNPB), tris(3-nitrophenyl)phosphate (TRIS), and bis(2,4-dinitrophenyl)phosphate (BDNPP) have been examined kinetically. The α-nucleophile, $SHA^-$, incorporated into cetyltrimethylammonium bromide (CTAB) micelles accelerates dephosphorylation of tris(3-nitrophenyl)phosphate (TRIS) over the pH range 6.7−11.4. With a 1.0 mM of SHA in CTAB, the nucleophilicity of SHA followed the order of reactivity, PNPB (C═O, carboxylate ester) > TRIS (P═O, triester) > BDNPP (P═O, diester), and monoanionic $SHA^-$ and dianionic $SA^{2-}$ are the reactive species. The critical micelle concentration, cmc, of cetyltrimethylammonium bromide (CTAB) decreases and the fractional ionization constant, α, increases with increasing the concentration of $SHA^-$. Addition of 1 and 10 mM SHA under the reaction conditions (pH 9.2, borate buffer) led to saturation of the micellar surface and provided qualitative information for the micellar incorporation of hydroxamate ion. Plots of the pseudo-first-order rate constant, $k_{obs}$, log $k_{obs}$, fraction of hydroxamic acid ionized, $\alpha_{SHA^-}$ and $\alpha_{SA^{2-}}$, vs pH showed bifunctional nucleophilicity of hydroxamic acid under micellar condition. Plotting $k_{obs}$ vs $[SHA]_T$ gave a straight line with intercept $k_0$. This indicates that hydroxamate ions are very strong nucleophiles for nucleophilic attack at the C and P center. The pseudo-first-order rate constant−surfactant profiles show micelle-assisted bimolecular reactions involving interfacial ion exchange between bulk aqueous media and micellar pseudophase.

## Introduction

Esterolytic reactions of carboxylate, phosphate, thiophosphate, and sulfonate have recently received intensive attention due to the importance in chemical and biological processes.[1−5] The phosphotriester-based Paraoxon and Parathion are used as pesticides and are most frequently responsible for the poisoning of agricultural field workers.[6] Due to their potential toxicity, considerable attention has been directed toward detection and methods of facilitating the hydrolysis or decomposition of organophosphates.[7−10] Nucleophile-aided hydrolysis is the most preferred reaction to detoxify them.[11−15] In this regard, nucleophiles such as peroxides,[11] hypochlorites,[12] oximates,[13] *o*-iodosylcarboxylate,[14] and hydroxamate[15] have been investigated alone or in concert with surfactants. Considerable research efforts have been focused on the nucleophilic reagents such as monoperoxyphthalates,[16] 4-*N*,*N*-dialkylaminopyridines,[17] and metallomicelles.[18] Recently, ester cleavage properties and significant turnover catalysis of synthetic hydroxybenzotriazoles[19] and 5-alkyl-1*H*-tetrazoles[20] have been reported.

Hydroxamate ions are α-effect nucleophiles, i.e., their reactivity is higher than that predicted by the Bronsted relationship between nucleophilicity and basicity.[21] They are effective deacylating and dephosphorylating agents, and reactivities of amphiphilic hydroxamate ions are increased by comicellization with surfactant in water. It is interesting to note that hydroxylamine is the parent compound for the three typical classes of the oxygen-containing α-nucleophiles: oximate and hydroxamic acid.[22] Investigation of the α-effect of hydroxamic acids in micellar media is of paramount importance, as compared to those in homogeneous aqueous solvents, since it is currently claimed that solvation/desolvation phenomena are the source of the enhanced reactivity of the α-nucleophiles.[23]

Reactivities of hydroxamate ions are increased by incorporation in functional polymers or by comicellization with inert surfactants in water.[24] As expected on the basis of pseudophase treatments of micellar rate effects,[25] high local concentrations of hydroxamate ions in the interfacial micellar region are largely responsible for these rate increases.[24b] Considering that (i) cationic micelles of cetyltrimethylammonium bromide, CTAB, accelerate the spontaneous hydrolysis of BDNPP up to 30-fold and high pH accelerates the reaction by concentrating nucleophiles,[25b,26] e.g., $OH^-$, and (ii) cationic micelles accelerate the reaction of hydroxamates and phosphate triesters.[27]

We studied micellar effects on reactions of the *p*-nitrophenyl benzoate (PNPB), tris(3-nitropheny)phosphate (TRIS), and bis(2,4-dinitrophenyl)phosphate (BDNPP) with salicylhydroxamic acid (SHA) in cetyltrimethylammonium bromide micellar media (Chart 1). In view of micellar incorporation of $SHA^-$, we reported the critical micelle concentration, cmc, and fractional ionization constant, α, in the presence of hydroxamic acid under buffered condition.

## Experimental Section

**Materials.** Salicylhydroxamic acid, *p*-nitrophenyl benzoate, and cetyltrimethylammonium bromide were obtained from

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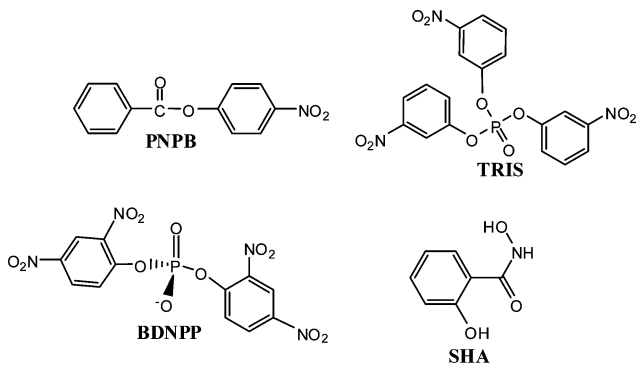
**CHART 1**




Sigma/Aldrich. Samples of tris(3-nitrophenyl)phosphate (TRIS) and bis(2,4-dinitrophenyl)phosphate (BDNPP) were synthesized in the Department of Chemistry, Federal University of Santa Catarina, Florianopolis-SC, Brazil.

**Kinetics.** All reactions were followed at 27 °C with a SL 159 Elico UV−visible spectrophotometer. The rate of nucleophilic reaction with esters was determined by following the increase in the absorption of *p*-nitrophenoxide and 3-nitrophenoxide anion (400 nm). All kinetic experiments were performed at an ionic strength of 0.1 M (with KCl). Borate buffer was employed. All reactions were conducted under pseudo-first-order conditions. For all of the kinetic runs, the absorbance/time results fit very well to the first-order rate equation

$$\ln(A_\infty - A_t) = \ln(A_\infty - A_0) - kt \qquad (1)$$

The pseudo-first-order rate constants can be determined by least-squares fits (Figure 1). Each experiment was repeated at least twice, and the observed rate constant was found to be reproducible within a precision of about 3% or better. The spectrum exhibits an increase in absorbance at 400 nm with the formation of *p*-nitrophenoxide and 3-nitrophenoxide ions during the course of reaction. The p$K_a$ values of hydroxamic acids were determined by pH metrically and spectrophotmetric titration using a Systronics (Type-335) pH meter.

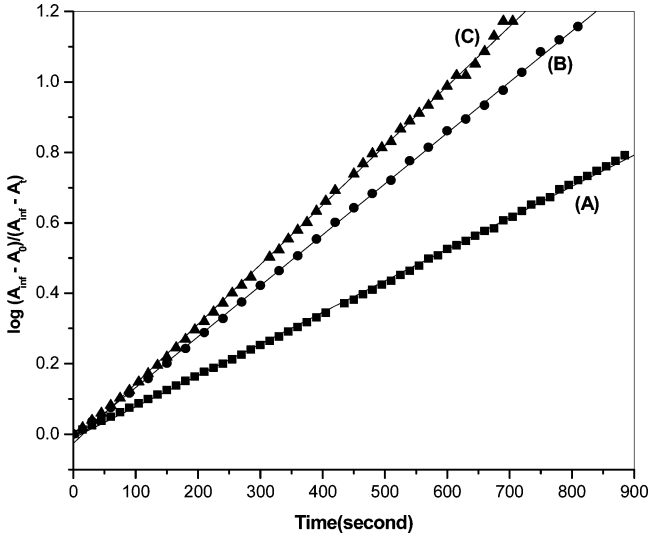



**Figure 1.** Kinetic plots of $\log(A_{inf} - A_0)/(A_{inf} - A_t)$ vs time for production of nitrophenolate from reaction of SHA with (A) TRIS, [TRIS] = $1.0 \times 10^{-4}$ M, [SHA] = $1.0 \times 10^{-3}$, [CTAB] = $2.0 \times 10^{-3}$ M, pH = 10.0, borate buffer, (B) PNPB, [PNPB] = $1.0 \times 10^{-4}$ M, [SHA] = $1.0 \times 10^{-3}$ M, [CTAB] = $3.7 \times 10^{-3}$ M, pH = 9.2, borate buffer, and (C) BDNPP, [BDNPP] = $1.0 \times 10^{-4}$ M, [SHA] = $1.0 \times 10^{-3}$ M, [CTAB] = $5.4 \times 10^{-3}$ M, pH = 9.2, borate buffer.

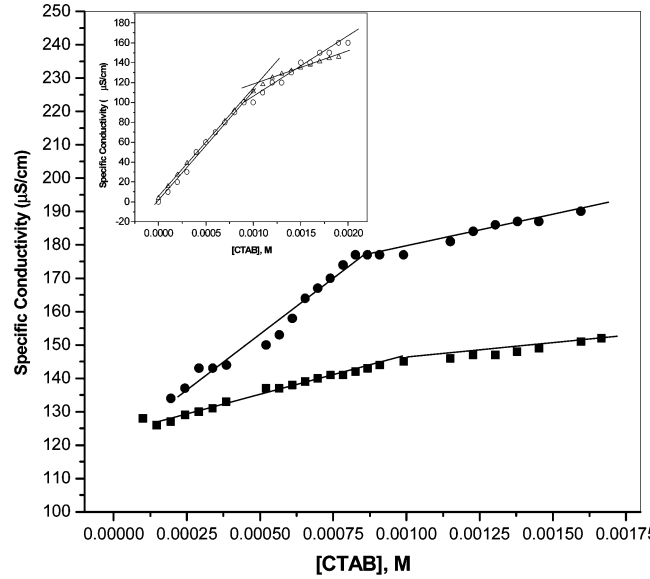



**Figure 2.** Specific conductance as a function of [CTAB] in the presence of [SHA] = (■) 0.001 and (●) 0.01 M at pH 9.2. (Inset) Plots of specific conductance versus [CTAB] in the absence (Δ) and presence (○) of buffer (pH 9.2).

**TABLE 1: Critical Micelle Concentrations and α at Different [SHA] in CTAB/HA Mixtures**

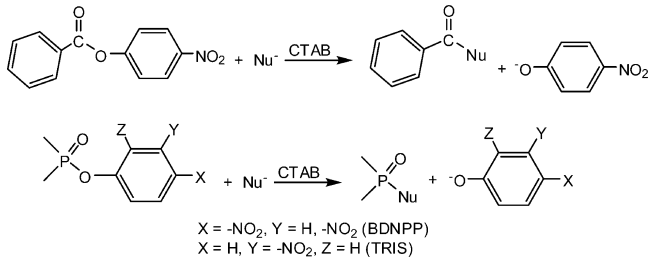
| [SHA] (mM) | α | $10^3$ cmc, M |
|---|---|---|
| 0 | 0.28 | 1.10 |
| 0 (pH 9.2) | 0.49 | 0.90 |
| 1.0 | 0.40 | 0.97 |
| 10.0 | 0.47 | 0.87 |

**Conductance Measurements.** Conductance measurements were carried out using a Systronics (Type-306) conductimeter. Values of the cmc were determined in the usual manner from plots of specific conductance against surfactant concentration. Solutions were buffered by borate buffer, pH 9.2.

## Results and Discussion

**Micelle Formation and Fractional Ionization.** Critical micelle concentrations, cmc, and fractional micellar ionizations, α, for the micelles of CTAB in the presence of buffer and SHA (buffered at pH 9.2) were estimated from plots of conductance against [surfactant], Figure 2. Breaks in these plots give cmc values that change little with increasing concentration of SHA, but approximate values of α, from the ratio of slopes,[28] increase with increasing [SHA], indicating that addition of salicylhydroxamate ion effectively neutralizes the cationic micelles, decreasing the micellar surface potential and affinity for counteranions. This effect is very sensitive to [SHA] (Table 1). The cmc of CTAB in water is $1.1 \times 10^{-3}$ M, but for a mixture of CTAB and SHA, the cmc decreases to $0.97 \times 10^{-3}$ M in the presence of $1.0 \times 10^{-3}$ M SHA and $0.87 \times 10^{-3}$ M in the presence of $10.0 \times 10^{-3}$ M SHA. The fractional micellar ionizations, α, sharply increase from 0.28 to 0.47, i.e., SHA significantly increases the fractional micellar charge of CTAB depending on SHA concentration. The fractional ionization constants in the presence of buffer and SHA are comparable, indicating the competitive efficiency to bind cationic micellar surface. However, the catalytic efficiency of SHA is much higher than the $HO^-$ ion (buffer alone).

**SCHEME 1: Nucleophilic Reaction of Salicyhydroxamate Ions ($Nu^-$) with Esters**




**Kinetic Studies in Cationic Micelles.** Pseudo-first-order rate constants for the reactions of PNPB, TRIS, and BDNPP with salicylhydroxamate ion (Scheme 1) have been determined at 27 °C in 4% (v/v) MeCN micellar media ($2.0 \times 10^{-3}$ M CTAB) with the nucleophiles in large excess over the substrate. The pH-dependent rate constant increases with increasing pH in the range pH 6.7−11.0. The kinetic curves plotted in Figure 3 illustrate variation of the absorption of 4-nitrophenoxide (PNPB) and 3-nitrophenoxide ion (TRIS) with time at different pH for the reaction of SHA with esters in the presence of 5.4 mM CTAB. The curves correspond to accumulation of 4-nitrophenoxide and 3-nitrophenoxide ions in the system as a result of substrate dissociation. The rate of reaction shows drastic change at the pH where the 50% hydroxamic acid deprotonated, i.e., p$K_a$, of salicylhydroxamic acid. The p$K_{a1}$ of salicylhydroxamic acid was determined pH metrically. The plot of log $k_{obs}$ vs pH (Figure 4) gave a break at 9.45, which is taken as p$K_{a2}$ for the SHA. The rate−pH profile for the reaction of TRIS with salicylhydroxamate ion in cationic micellar solution is typical of a pH-dependent nucleophilic reaction. Hydroxamic acids have been suggested to behave as either NH or OH acids depending on solvents.[29] Numerous studies indicate that hydroxamic acids are OH, rather than NH, acids in $H_2O$.[29a] It is known that the anion of hydroxamic acid (N−$O^-$) acts as a reactive species in the hydrolysis of esters. Consequently, the p$K_a$ for conversion of the N−OH to the N−$O^-$ form plays an important role for cleavage of phosphate esters. A pH−rate constant profile for the nucleophilic cleavage of 0.1 mM TRIS by 1.0 mM salicylhydroxamate ion in CTAB micellar media (2.0 mM) gave the apparent p$K_a$ value for the salicylhydroxamic acid. Typically, the pseudo-first-order rate constants for reaction of TRIS were determined at different pH values between 6.7 and 11.0. In Figure 4, we present a representative pH−rate constant profile for cleavage of 0.1 mM TRIS by 1.0 mM salicylhydroxamic acid in micellar CTAB (2.0 mM) at 27 °C.

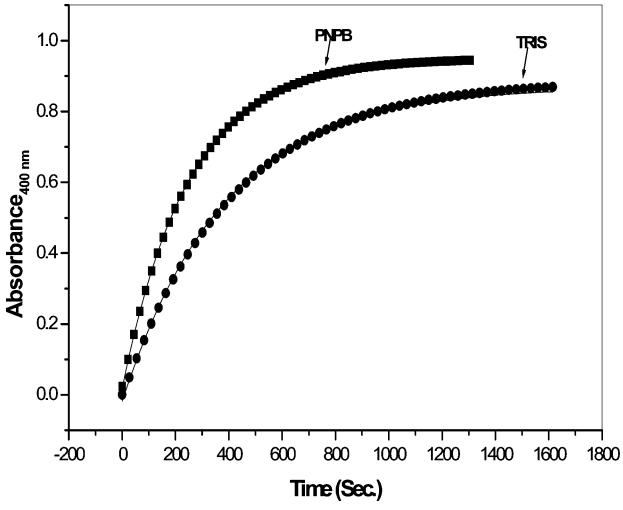



**Figure 3.** Time-dependent increase of absorbance at 400 nm upon hydrolysis of PNPB (at pH 9.2) and TRIS (at pH 10) by salicylhydroxamate ion in the presence of CTAB. Conditions: 27 °C, [SHA] = $1.0 \times 10^{-3}$ M, [CTAB] = $5.4 \times 10^{-3}$ M. Substrate concentrations: [PNPB] = $1.0 \times 10^{-4}$ M, [TRIS] = $1.0 \times 10^{-4}$ M.

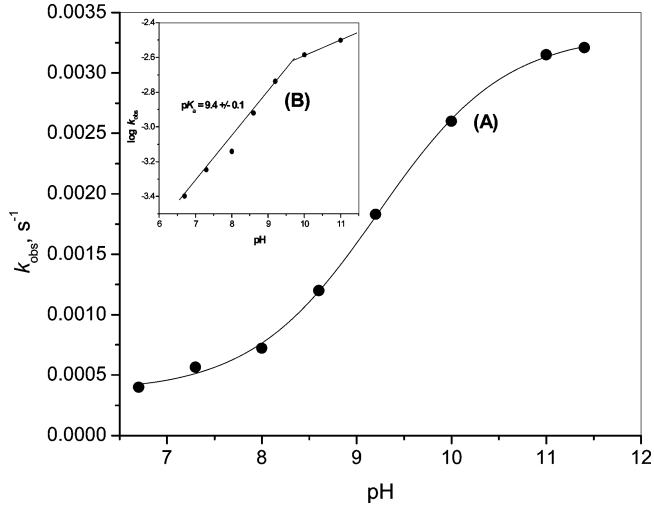



**Figure 4.** Plot of first-order rate constants vs pH for the reaction of TRIS with salicylhydroxamate ion in CTAB ($2.0 \times 10^{-3}$ M). (Inset (B)): Plot of log $k_{obs}$ vs pH under identical condition.

**TABLE 2: Nucleophile-Dependent Pseudo-First-Order Rate Constant for the Reaction of BNPB and TRIS**

| | $k_{obs} \times 10^{-3}$, $s^{-1}$ | |
|---|---|---|
| [SHA], mM | PNPB | TRIS |
| 0.0 | 0.50 | 0.62 |
| 0.5 | 1.26 | 0.77 |
| 1.0 | 1.75 | 0.87 |
| 1.5 | 2.70 | 1.03 |
| 2.0 | 3.58 | 1.14 |
| 2.5 | | 1.25 |

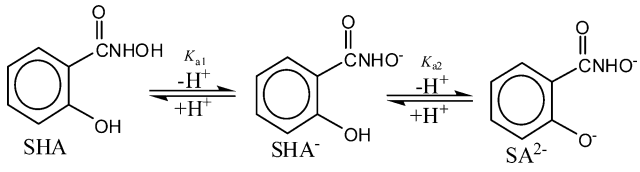
The nucleophile concentration-dependent first-order rate constant was determined for reaction of PNPB and TRIS with salicylhydroxamic acids in excess. Table 2 summarizes the data for reaction of PNPB and TRIS with different concentrations of salicylhydroxamate ion at pH 9.12. Kinetic data show additional support for the hypothesis that hydroxamic acid is acting as a nucleophilic catalyst for reaction of PNPB and TRIS. Equation 2 describes the reaction of PNPB and TRIS with nucleophile, and $k_0$ defined in eq 3 corresponds to the intercept in the $k_{obs}$ vs [$Nu^-$] plot (Figure 6)

$$k_{obs} = k_0 + k_{Nu-}[Nu^-] \quad (2)$$

$$k_0 = k_{H_2O} + k_{OH-}[OH^-] \quad (3)$$

The $k_{H_2O}$ term may assume some significance for very weak nucleophiles and at very low $OH^-$ concentrations. At high pH, the intercept is dominated by the $k_{OH^-}$ term. Plotting $k_{obs}$ vs [$Nu^-$] gave a straight line (Figure 6) with intercept $k^0$. This indicates that competition with other nucleophiles, i.e., $OH^-$ and $H_2O$, is not expected, hydroxamate ions are very strong

**SCHEME 2: pH-Dependent Ionization of Salicylhydroxamic Acid**




nucleophiles for the nucleophilic attack at the C and P centers of PNPB and TRIS, and $k_{obs}$ is simply given by $k_{obs} = k_{Nu}[Nu^-]$.

It is assumed that catalysis by nucleophile is dependent upon the ionization state of the hydroxamic acid. Equation 4 may be written to describe the actual value of $k_{obs}$. In this equation, $k_{HA}$ is second-order rate constant, $[SHA]_T$ is the analytical concentration of hydroxamic acid, and $\alpha_{HA-}$ is the fraction of $[SHA]_T$ ionized.

$$k_{obs}^{HA} = k_{obs}^{0} + k_{HA-}[HA]_T\alpha_{HA-} \quad (4)$$

The salicylhydroxamic acid, containing two proton-active sites, may give two types of reactive forms $SHA^-$ and $SA^{2-}$ (Scheme 2)

$$k_{obs} = k_{obs}^{0} + k_{SHA-}[SHA]_T\alpha_{SHA-} + k_{SA^{2-}}[SHA]_T\alpha_{SA^{2-}} \quad (5)$$

Since $\alpha_{HA^-}$ is equal to $K_{a1}/K_{a1} + [H^+]$ and $\alpha_{SA^{2-}}$ is equal to $K_{a2}/K_{a2} + [H^+]$, where $K_{a1}$ and $K_{a2}$ are the kinetically apparent dissociation constants of salicylhydroxamic acid, this equation is applicable to the condition of catalyst in excess. Plotting $k^{HA}_{obs}$ versus $[HA]_T$ (Figure 6) should give a straight line with slope $= k_{HA}\alpha_{HA}$ and intercept $= k^0_{obs}$.

Figure 5 represents the plots of $k_{obs}$ and fraction of SHA ionized ($\alpha_{SHA^-}$ and $\alpha_{SA^{2-}}$) vs pH for reaction of TRIS with salicylhydroxamic acid. It is evident from plots that monoanionic, $SHA^-$, is the reactive species below the pH 9.0, and dianionic form becomes significant after pH 9.5. This behavior

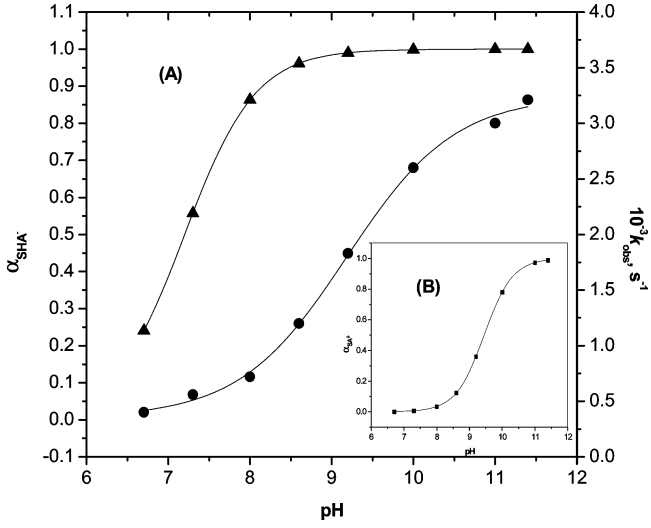



**Figure 5.** Plots of $k_{obs}$, $\alpha_{HA-}$ (A), and $\alpha_{SA^{2-}}$ vs pH for the reaction of TRIS with salicylhydroxamic acid. Condition: $[TRIS] = 1.0 \times 10^{-3}$ M, $[SHA]_T = 1.0 \times 10^{-3}$ M, $[KCl] = 0.1$ M, $[CTAB] = 2.0 \times 10^{-3}$ M.

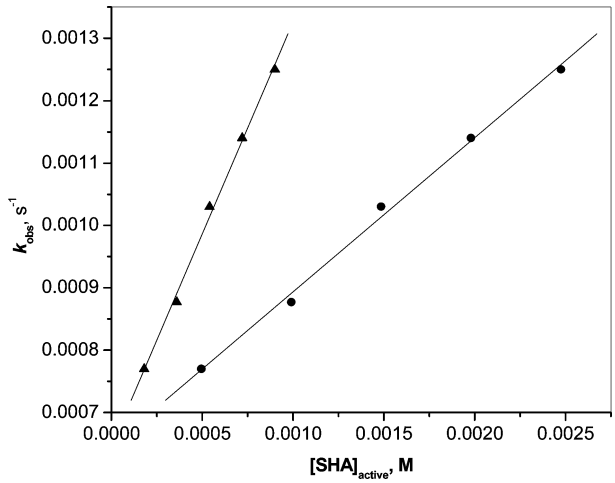
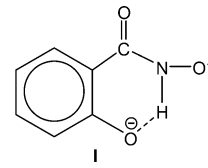



**Figure 6.** Plots of $k_{obs}$ vs $[SHA^-]$ (●) and $[SA^{2-}]$ (▲) for the reaction of TRIS at pH 9.2 (0.01 M borate buffer).

can be explained by the hypothesis that a complex of type **I** with intramolecular hydrogen bonding exists in micellar solution.



**I**

The degree of proton transfer in this complex is not obvious, and so either (a) the complex of type I may act as a true nucleophilic reagent or (b) nucleophilic attack on the substrate with participation of such a complex is subjected to general base catalysis relative to the phenoxide ion. In the first case, proton transfer in I is accomplished in the initial state of the reaction. In the second case, in the initial state of the reaction only partial transfer in I occurs, while the final transfer occurs only in the transition state of the reaction. These two mechanisms are indistinguishable kinetically. Additional support for the fact that the dianionic form is the reactive species comes from the linear dependence of $k_{obs}$ on $[SHA^-]$ and $[SA^{2-}]$, the active concentration of hydroxamate mono- and dianionic species (Figure 6). The second-order rate constant of the monoanionic hydroxamate ion ($SHA^-$) $k_{SHA^-}$ is 0.2427 $M^{-1}$ $s^{-1}$ and dianionic species ($SA^{2-}$), $k_{SA^{2-}}$, is 0.6795 $M^{-1}$ $s^{-1}$ for the reaction of TRIS. This behavior supports the fact that (1) the nucleophilicity of hydroxamate ions in the dianionic form ($SA^{2-}$) is intrinsically greater than that of the monoanionic hydroxamate ion ($SHA^-$) or (2) the phenolate anion in $SA^{2-}$ is directly involved in the reaction besides the hydroxamate anion.

The micelle-bound salicylhydroxamate ion shows large catalytic activity for the decarboxylation and dephosphorylation reactions. The rate constant for reaction of BDNPP with hydroxide ion at pH 9.15, in the absence of $SHA^-$, is ca. $4 \times 10^{-7}$ $s^{-1}$. The rate constant of spontaneous water reaction of BDNPP is ca. $1.90 \times 10^{-7}$ $s^{-1}$ (reported).[30] At the rate maxima (Figure 7), $k_{obs}$ for the reaction of BDNPP with micellar-bound salicylhydroxamate ion is ca. $3.2 \times 10^{-4}$ $s^{-1}$, that is, there is up to 800-fold catalysis over the reaction of hydroxide ion and 1684-fold rate enhancement over the spontaneous water reaction.

In the previous paper, we studied the comparative catalytic reactivity of acetohydroxamate ion ($AHA^-$), benzohydroxamate ($BHA^-$), and salicylhydroxamate for cleavage of paraoxon in

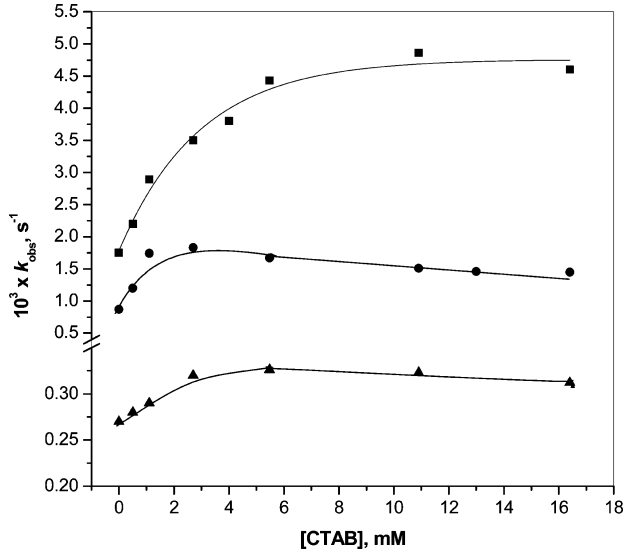



**Figure 7.** Observed rate constant for the hydrolysis of PNPB (■), TRIS (●), and BDNPP (▲) as a function of [CTAB], pH = 9.2 at 27 °C in borate buffer 0.01 M. (The lines are drawn to guide the eye.)

**SCHEME 3: Nucleophilic Attack of Hydroxamate Ion at the P Center of Paraoxon**

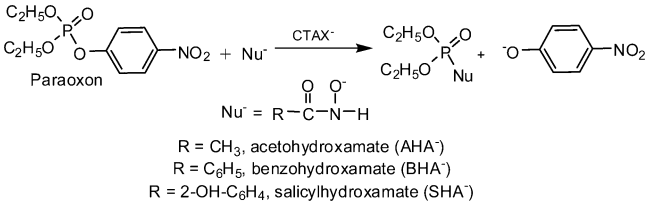



**TABLE 3: Effect of Concentration of CTAB on the Hydrolysis Reaction of Carboxylate and Phosphate Ester by Salicylhydroxamate Ion at 27 °C**

| | $k_{obs} \times 10^{-3}$, $s^{-1}$ | | |
|---|---|---|---|
| [CTAB], mM | PNPB | TRIS | BDNPP |
| 0.0 | 1.75 | 0.87 | 0.27 |
| 0.50 | 2.20 | 1.20 | 0.28 |
| 1.10 | 2.89 | 1.74 | 0.29 |
| 2.70 | 3.25 | 1.83 | 0.32 |
| 4.00 | 3.80 | | |
| 5.48 | 4.43 | 1.67 | 0.31 |
| 10.9 | 4.86 | 1.51 | 0.32 |
| 13.0 | | 1.46 | |
| 16.4 | 4.60 | 1.45 | 0.31 |

$CTA^+$ micellar media (Scheme 3).[15a] It is observed that $SHA^-$ ion showed remarkable enhanced catalytic efficiency in identical conditions: [paraoxon] = $1.0 \times 10^{-4}$ M, [HA] = $1.0 \times 10^{-3}$ M, [KCl] = 0.1 M, [CTAB] = $3.6 \times 10^{-3}$ M, pH 11.0, borate buffer, 30 °C. Therefore, it is expected that the catalytic efficiency of the SHA is further enhanced in micellar microenvironments compared to BHA and AHA and due to the active participation of dianionic species, $SA^{2-}$.

**Dependence of $k_{obs}$ on [CTAB].** The hydrolytic property of SHA was assessed from the rate constants versus CTAB profile for cleavage of esters PNPB, TRIS, and BDNPP (Table 3 and Figure 7). Rate constants go through a maximum with increasing [CTAB] at fixed [SHA], which is typical of micellar-assisted bimolecular reactions. These rate maxima are observed because of "dilution effects" brought about by increasing concentrations of surfactant. Initially, an increase in the surfactant concentration generates more cationic micelles and increases the initial rate. As the number of micelles becomes large, virtually all the substrate gets associated to the micellar phase. Further addition of surfactant proliferates the number of micelles which simply take up the nucleophilic anions into the "Stern layer", thereby deactivating them, since substrate in one micelle cannot react with nucleophile in another.

The rate−surfactant concentration profiles obtained with various surfactants/catalysts are characteristic of the micelle-catalyzed reaction. The variation of rate constants below the critical micelle concentration (cmc) is difficult to quantify due to reactant-induced micellization and interaction with nonmicellized surfactants. The fractional ionic dissociation, α, of micelle is often little affected by the nature or concentration of the counterion. In other words, the micellar surface appears to be saturated with counterions and the fractional coverage $\beta = 1 - \alpha$ is constant. If $\beta$ is constant, the rate of reaction should increase as substrate is taken up by the micelles, but once the substrate is fully bound, the rate should be independent of added surfactant or counterion (Table 1). According to Buncel et al.,[31] the electrostatic attraction of the cationic head groups of the surfactants at the micelle surface to the nucleophilic anion counterions leads to augmentation of the local concentration of the nucleophile, whereas incorporation of the substrate in the micelle leads to a higher local concentration of the substrate. This enhanced concentration of the reactants accounts for the higher rate of reaction. Implicit in this explanation is the requirement that the reactive site of the esters be situated in close proximity to the nucleophile, that is, at the micelle−water interface, the Stern layer. Subsequent addition of the cationic surfactant after cmc caused a decrease in the reaction rate possibly due to the decrease in the catalyst/reagent concentration in the micellar pseudophase. The excess of unreactive counterions ($X^-$) competes with hydroxamate ions for available sites in the Stern layer.

**Kinetic Studies with Excess Substrates.** A point of interest was whether the catalyst was consumed as the reaction proceeded or regenerated and indeed a true catalyst. To examine the true catalytic efficiency of salicylhydroxamate ion, kinetic runs were carried out in the presence of excess substrate. At pH 8.5, [SHA] = $1.0 \times 10^{-4}$, [CTAB] = $3.5 \times 10^{-3}$ M, and 5-fold excess ($5.0 \times 10^{-4}$ M) of PNPB over salicylhydroxamate concentration, we observed a nearly quantitative monoexponential release of *p*-nitrophenoxide ion with no indication of burst kinetics. In another experiment, kinetic run was performed at pH 9.5, [SHA] = $1.0 \times 10^{-4}$, [CTAB] = $3.5 \times 10^{-3}$ M, and 10-fold ($1.0 \times 10^{-3}$ M) of BDNPP over salicylhydroxamate concentration. Under these conditions, the release of *p*-nitrophenoxide ion also followed pseudo-first-order kinetics and yielded a consistent $k_{obs}$ value. The reaction was also carried out in the presence of a 1:1 molar ratio of substrate and catalyst. The monoexponential time course (Figure 8) reveals the rapid acylation and phosphorylation of salicylhydroxamate ion. Since we did not observe "burst"-type kinetics, there is no accumulation of *O*-acyl or *O*-phosphoryl species in the reaction media. The hydroxide ion attack on to the *O*-acylated or *O*-phosphorylated species at the micellar surface must be fast, and it cleaves the intermediate species rapidly to furnish hydrolyzed products, concurrently regenerating salicylhydroxamate ion in the reaction media to be available to react with a fresh substrate molecules (Scheme 4). There is no direct experimental evidence for the complete regeneration of hydroxamic acids. Other α-nucleophiles such as *O*-iodosylcarboxylates,[32] oximate,[13a] hydroperoxide,[11b] and hydroxybenzotriazoles[19] rapidly cleaved phosphate esters with turnover in micelle.

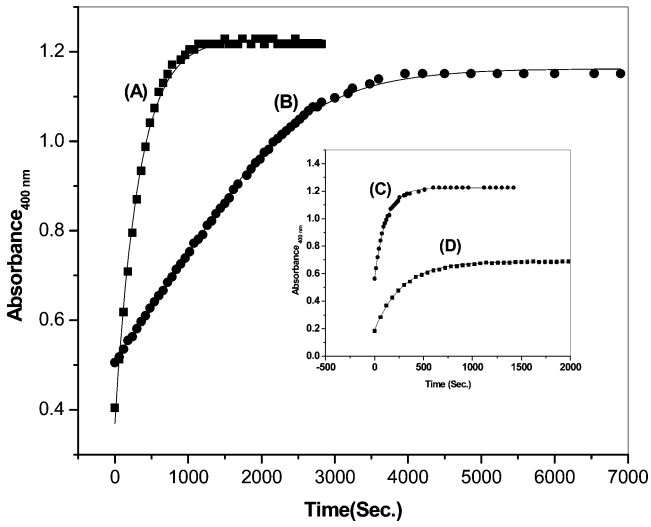
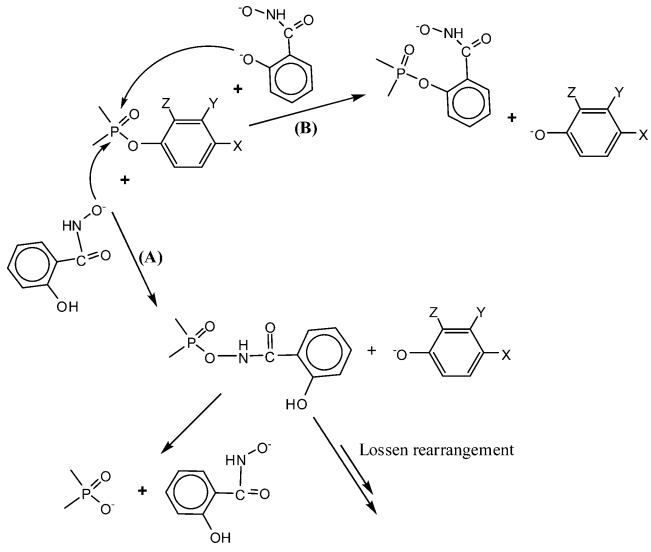



**Figure 8.** Time-dependent release of *p*-nitrophenoxide upon hydrolysis of BDNPP and PNPB by SHA/CTAB in the presence of excess substrates over SHA in micellar media ([CTAB] = $3.5 \times 10^{-3}$ M). Conditions: (A) [BDNPP] = $1.0 \times 10^{-3}$ M, [SHA] = $1.0 \times 10^{-3}$ M, [KCl] = 0.1 M, pH 9.5. (B) [BDNPP] = $1.0 \times 10^{-3}$ M, [SHA] = $1.0 \times 10^{-4}$ M, [KCl] = 0.1 M, pH 9.5. (C) [PNPB] = $1.0 \times 10^{-3}$ M, [SHA] = $1.0 \times 10^{-3}$ M, [KCl] = 0.1 M, pH 8.5. (D) [PNPB] = $1.0 \times 10^{-3}$ M, [SHA] = $1.0 \times 10^{-4}$ M, [KCl] = 0.1 M, pH 8.5.

**SCHEME 4: Proposed Mechanism for the Nucleophilic Attack of Salicylhydroxamate at the P═O Center of Phosphate Esters**




Bhattacharya et al.[19] documented turnover catalysis for the cleavage of *p*-nitrophenyl hexanoate (PNPH) and *p*-nitrophenyl diphenyl phosphate (PNPDPP) by hydrobenzotriazoles (N−O$^-$ nucleophile). The hydroxybenzotriazoles are rapidly acylated or phosphorylated by PNPH or PNPDPP at pH 8.2 in micellar condition. The resulting products do not, however, retain the acyl or phosphoryl groups. In fact, the acylated and phosphorylated hydroxybenzotriazoles rapidly deacylate in a second and even faster step, regenerating the parent hydroxybenzotriazoles. A considerable body of evidence now exists for the formation of acylated or phosphorylated monoperoxyphthalate in catalytic esterolytic reactions in micellar media.[33] On the basis of the combined use of $^1$H and $^{31}$P NMR spectrometry and synthesis of intermediate, it has been suggested that monoperoxyphthalates are efficient deacylating and dephosphorylating agents. Mechanistic evidence is provided that the OH$^-$-mediated scission of the diphenylphosphorylated or acylated monoperoxyphthale intermediate provides a way for turnover and completion of the catalytic cycle.

The kinetic results reveal that salicylhydroxamate attacks nucleophilically to the P═O center via phenolate and hydroxamate functional groups (Scheme 4). Faruk et al.[34] reported detailed mechanism of reaction of benzohyroxamate[34] and laurylhydroxamate[24c] ion with bis(2,4-dinitrophenyl)phosphate. NMR spectroscopy and ES-MS study allow monitoring of the most important species with time for the reaction of BDNPP. Results obtained from the detection of products, 2,4-dinitrophenoxide ion (DNP), more reactive dianionic 2,4-dinitrophenyl phosphate monoester (DNPP), and aromatic-substituted product by ESI-MS indicated nucleophilic attack of BHA$^-$ on the aromatic ring and on phosphorus of BDNPP. Reaction products from the reaction of LHA$^-$ and BDNPP, identified by EI-MS and NMR spectra data, clearly indicated formation of *O*-phosphorylated intermediate which breaks down by a Lossen-type rearrangement to give phenyl isocyanate, which reacts with benzohydroxamic acid, yielding *O*-phenylcarbamyl benzohydroxamate. Hydroxamic acid and hydroxylamine are α-effect *O*-nucleophiles, and the charge on the oxido atom (N−O$^-$) of the conjugate bases is responsible for the hydrolytic cleavage of carboxylate and phosphate esters.

The reaction of ternary copolymer containing *N*-phenylacrylohydroxamate, 1-vinyl-2-methylimidazole, and acrylamide moieties (PHA-MIm-AAm) with excess of *p*-nitrophenyl acetate (PNPA) showed typical burst kinetics with the initial rapid liberation of *p*-nitrophenol due to actylation of the hydroxamate present and the subsequent slower release due to regeneration of the hydroxamate group through decomposition of the acyl intermediate.[35] *O*-Acetyl hydroxamates (*N*-acetoxy benzamides) are important candidates for classical Lossen rearrangements. Generally, the *N*-acetoxy amides are prepared by the acylation of hydroxamic acids.[36] Furthermore, the product analysis performed with the HPLC method has revealed that only the *O*-acylated product is produced in 100% yield from the reaction of PNPA with benzohydroxamate (BHA$^-$).[37]

## Conclusion

The study was undertaken with a view to develop a hydroxamate function based "hydrolyzing nucleophile" in micellar medium to detoxify the toxic phosphorus esters. For this purpose, PNPB, TRIS, and BDNPP were selected as substrate. To achieve this target, the SHA and surfactant (CTAB) was selected for kinetic study and "SHA-CTAB" was formulated as a potential esterolytically detoxifying system against nerve agents. Catalysis by SHA is dependent upon the ionization state. The salicylhydroxamic acid contains two proton-active sites and gives two types of reactive forms SHA$^-$ and SA$^{2-}$. The multifunctional nucleophilicity of salicylhydroxamate fulfills the requirement of the reactive nucleophile for the esterolytic cleavage of the carboxylate and phosphate esters.

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**Supporting Information Available:** pH-dependent pseudo-first-order rate constant for the reaction of TRIS; calculated values of $\alpha_{SHA^-}$ and $\alpha_{SA^{2-}}$ of salicylhydroxamic acid at different pH; kinetic plots of $k_{obs}$ vs concentration of SHA for the reaction

of (A) PNPB and (B) TRIS. This material is available free of charge via the Internet at http://pubs.acs.org.

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