Hydrolytic cleavage of paraoxon and parathion by oximate and functionalized oximate ions: A comparative study

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Bimolecular reactions of O,O-diethyl-O-*p*-nitrophenylphosphate (paraoxon) and O,O-diethyl-O-*p*-nitrophenyl phosphorothioate (parathion) with oximate (pyridinealdoxime 2-PyOx⁻ and 4-PyOx⁻) and its functionalized oximate, 4-(hydroxyimino)methyl)-1-alkylpyridinium bromide ions (alkyl = $C_{10}H_{21}$ (4-C_{10}PyOx⁻); alkyl = $C_{12}H_{25}$ (4-C_{12}PyOx⁻)) have been investigated in aqueous and cationic micellar media of cetylpyridinium bromide, cetyltrimethyl-ammonium bromide and cetyltetradecyltrimethylammonium bromide at *p*H 9.5 and 27 °C. Under the micellized condition, a 1.2×10^3 fold and 9.0×10^6 fold rate enhancement over the aqueous reaction of paraoxon ($k_o = 7.5\times10^{-8}$ s^{-1}) and parathion ($k_o = 9.5\times10^{-11}$) is observed.

Over the past decade, a number of approaches have been used to address the problem of hydrolysis/detoxification of organophosphorus compounds which are extremely potent inhibitors of acetylcholinesterase enzyme[1-3]. Therefore, there is an immediate need to develop potential and safe methods for counteracting the effects of hazardous organophosphorus compounds[4-5]. Decomposition of pesticides with different types of α-nucleophiles[6], such as iodosobenzoate (IBA)[7], oximate[8]

and hydroxamate ions has been reported[9-11]. The α-nucleophile is known to describe the abnormally enhanced nucleophilicity exhibited by nucleophiles having one or more non-bonding electron pairs at the position adjacent to the nucleophilic center[12-14].

Recently, Ghosh *et al.*[15] examined the hydrolysis of PNPDPP and BDNPP by a functionalized oximate ion and documented a prominent effect towards the ester cleavage. An earlier study has reported the catalytic activity of functionalized micelles including functional IBA and 1-cetyl-3-(2-oximopropyl) imidazolium chloride[16]. The cleavage of organophosphorus compounds by an α-nucleophile in the presence of cationic micellar media is a frequently studied reaction[17-19]. It is well established that in many cases rate and pathway of all kinds of chemical reactions can be altered by performing the reaction in micellar media instead of pure bulk solvents. Rate of reaction accelerates or reduces depending on the size of the head group and space between two head groups as well as solubilization capacity at the interface region of micelles[20-25].

With a view to investigate the effects of functionalized oxime on the catalytic reactivity of pesticides, we have designed a micellar mediated platform to study the reaction of oximate ions for the hydrolysis of pesticides. Herein, we have examined the nucleophilic efficiency of oximate (2 and 4-pyridinealdoxime) and functionalized (4-hydroxyiminomethy-1-alkylpyridinium bromide) oximate ions towards the cleavage of phosphate (P=O) and thiophosphate bond (P=S) of pesticides, i.e, paraoxon and parathion in aqueous and cationic micellar media (Scheme 1).

Experimental

Paraoxon, parathion, cetyltrimethylammonium bromide (CTAB), cetylpyridinium bromide (CPB),
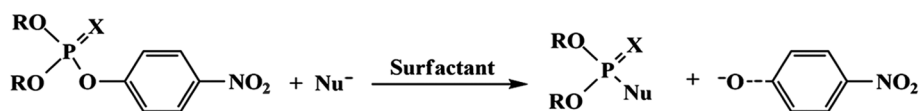
X = O (Paraoxon), X= S (Parathion), R = C_2H_5

Reaction of paraoxon and parathion with oximate and functionalized oximate ions

Scheme 1

tetradecyltrimethylammonium bromide (TTAB), 4-pyridinealdoxime (4-PyOx) and 2-pyridinealdoxime (2-PyOx) were procured from Sigma/Aldrich Chemicals Pvt. Ltd, Bangalore, (India). 4-Hydroxy-iminomethyl 1-alkyl pyridinium bromide (alkyl = C_nH_{2n+1} n = 10, 12) were prepared by quaternization of 4-pyridinealdoxime according to literature method[26]. Other chemicals used of AR/high purity grade and used without further purification. All the solutions were prepared in triply distilled water.

All reactions were performed at 27 °C with a Thermo Fisher Evolution 300 UV-visible spectrophotometer equipped for temperature control (Peltier). All the kinetic runs were followed under pseudo-first-order conditions in which the concentration of nucleophiles was at least 10 times higher than the initial concentration of substrates. The cuvettes were allowed to equilibrate thermally (27±0.1 °C) in the cell holder for 30 min. After temperature equilibrium, the stock solutions of substrates were added to each cuvettes and kinetic studies were performed. The initial concentration of substrates in the cuvettes was $5.0 \times 10^{-5} M$. The k_{obs} of nucleophilic reaction with substrate (paraoxon, parathion) was determined by monitoring the increase in absorption of p-nitrophenoxide anion at 400 nm. All the kinetic experiments were performed at an ionic strength of $0.1 M$ (with KCl). Borate buffer was employed. For all of the kinetic runs, the absorbance/time results fitted very well in the first-order rate equation.

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

The pseudo-first-order rate constants (k_{obs}) were obtained from linear plots of log $(A_\infty - A_t)$ versus time. Each experiment was repeated at least twice, and the observed rate constant was found to be reproducible within a precision of better than 3%.

Results and discussion

The effect of pH on the k_{obs} values for the cleavage of 5.0×10^{-5} M paraoxon and parathion by 4-hydroxyimminomethyl-1-alkyl pyridinium bromide (alkyl = C_nH_{2n+1}; n = 12) in aqueous and CTAB micellar media shown in Fig. 1. It is observed that the pH-dependent k_{obs} of the reaction increases with increasing pH in the range of 7–12. The rate of reaction shows drastic changes at the pH > pK_a of the functionalized oxime (pK_a = 8.65, 9.20)[15]. The ionized moiety of oxime (C=NHO⁻) plays an important role in the cleavage of phosphate esters, hence information about the favoured ionization site is important.

The nucleophile concentration dependent pseudo-first order rate constant was monitored spectrophotometrically at 400 nm. All kinetic terms are defined by Eq. (2) and k_o defined in Eq. (3) corresponds to the intercept in the k_{obs} versus [Nu⁻] plots and are found to be negligible. In this reaction we used an excess of nucleophile for the reaction of paraoxon and parathion at 27 °C and pH 9.5.

$$k_{obs} = k_o + k_{Nu}[Nu^-] \qquad \ldots(2)$$

$$k_o = k_{H_2O} + k_{OH^-}[OH^-] \qquad \ldots(3)$$

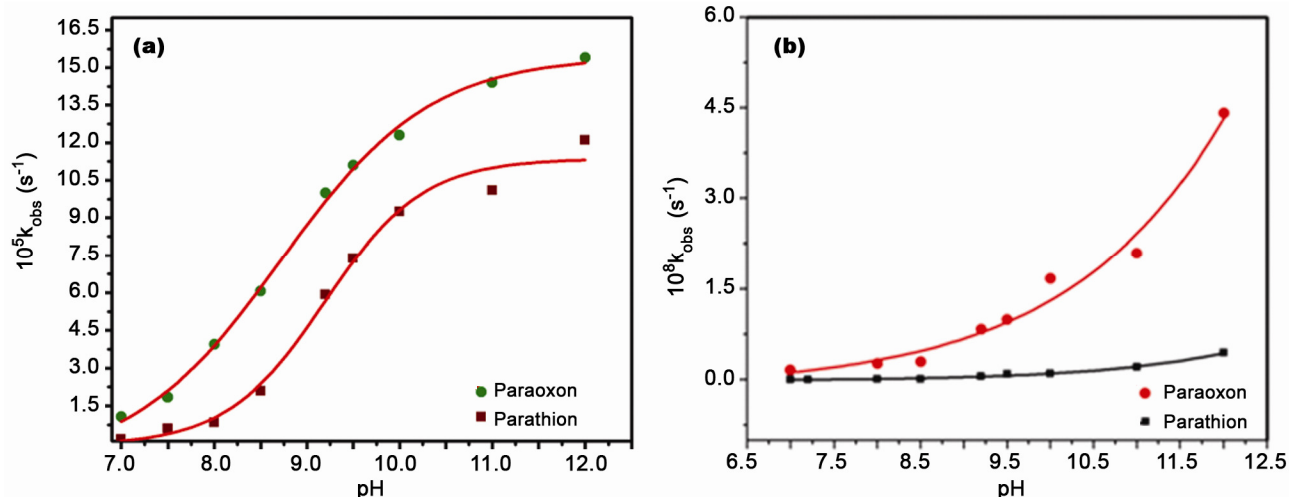The term k_{H_2O} represents aqueous hydrolysis and can be significante in the presence of very weak

Fig. 1 – Effect of pH on reaction between 4-C$_{12}$PyOx⁻, and, paraoxon (●) and parathion (■). (a) in micellar medium; (b) in aqueous media. React. cond. : Temp. = 27 °C, [Ester] = $5.0 \times 10^{-5} M$; [4-C$_{12}$PyOx⁻] = $5.0 \times 10^{-4} M$; [CTAB] = $0.5 \times 10^{-3} M$.

Table 1 – Effect of concentration of nucleophiles on the reaction with paraoxon and parathion.
[React. cond.: Temp: = 27 °C, [Ester] = $5.0 \times 10^{-5} M$, [CTAB] = $0.5 \times 10^{-3} M$, pH = 9.5 (Borate buffer)]

[Nu⁻] (mM)	$10^5 k_{obs}$ (s⁻¹)					
	Paraoxon			Parathion		
	4-PyOx⁻	4-C$_{10}$PyOx⁻	4-C$_{12}$PyOx⁻	4-PyOx⁻	4-C$_{10}$PyOx⁻	4-C$_{12}$PyOx⁻
0.3	1.22	2.34	3.34	0.23	0.25	0.29
0.5	1.69	5.55	6.46	0.26	0.30	0.32
0.8	2.34	8.00	9.32	0.28	0.35	0.37
1.0	5.21	11.1	15.3	0.35	0. 40	0.43

nucleophiles. At high pH the intercept is dominated by the k_{OH^-} term.

Table 1 summarizes the first-order-rate constant for the cleavage of paraoxon (P=O) and parathion (P=S) with oximate and functionalized oximate ions. The functionalized oximate ions, i.e., 4-C$_{12}$PyOx⁻ and 4-C$_{10}$PyOx⁻, show higher efficiency for the cleaving of phosphate ester than the non-functionalized oximate ions. The order of reactivity is: 4-C$_{12}$PyOx⁻ > 4-C$_{10}$PyOx⁻ > 4-PyOx⁻ towards the hydrolysis of phosphate ester. The k_{obs} values increases with increasing chain length due to the increase in the electrical surface potential of the micelle and also due to an increase in hydrophobicity of the palisade layer of micelle (Fig. 2). The hydrophobicity of functionalized oxime is governed by the number of alkyl groups[27]. Therefore, 4-C$_{12}$PyOx⁻ oximate ions are more reactive towards phosphate ester than 4-C$_{10}$PyOx⁻. The rate upgrading may be discussed on the basis of acid dissociation constant of functionalized oxime. The pK_a of the functionalized oximate, 4-C$_{12}$PyOx⁻ and 4-C$_{10}$PyOx⁻ ions are respectively 8.65 and 9.20 (ref. 15). This indicates that the ionization of functionalized oxime of dodecylalkyl chain length is 80% except in the case of decyl alkyl chain length which is only 50% ionized at pH 9.5. The larger active concentration of oximate ions leads to the higher reactivity. Under micellized conditions, the functionalized oximate ions, 4-C$_{12}$PyOx⁻, shows greater reactivity than the oximate ion 4-PyOx⁻. The nucleophilic efficiency of both oximate ions are lower towards the P=S center of parathion than P=O center of paraoxon which supports that the P=S bond possess lower electrophilicity as compared to P=O centers of paraoxon.

Figures 3 and 4 show the hydrolytic cleavage of paraoxon and parathion at pH 9.5 in cationic micellar media of CTAB, TTAB and CPB with 2-PyOx⁻, 4-PyOx⁻ and the functionalized oximate ions, 4-C$_{10}$PyOx⁻, 4-C$_{12}$PyOx⁻. Functionalized oxime shows more reactivity than the non functionalized
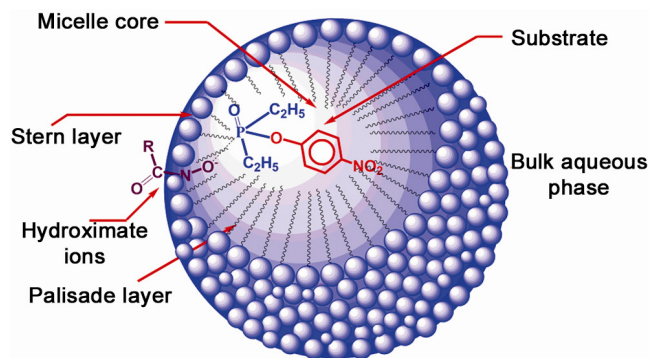

Fig. 2 – Schematic representation of orientation of substrate and nucleophiles in the micelle.

oximate ions in the presence of surfactants (Table 2). Rate surfactant profiles for the hydrolytic cleavage of paraoxon and parathion with cationic surfactants are shown in Figures 3 and 4. The rate constant of the reaction (k_{obs}) increases with increasing concentration of the surfactants, attains a maximum value, and then slightly decreases when the concentration of surfactant further increases from 3.0 to 8.0 mM (Figs 3 & 4). This indicates that surfactants enhance or moderate the reactivity of nucleophiles, depending on the charge of head group, chain length and counter ion of the surfactant. This trend supports a typical micellar-assisted bimolecular reaction. The electrostatic attraction of cationic head groups of the surfactants at the micellar surface to the nucleophilic anions, counterions leads to the increase of the local concentration of the nucleophile, whereas the incorporation of substrate in the micelle leads to higher local concentration of reactant[28]. Rate enhancement on the addition of surfactant would be expected to be more significant with pyridinium surfactant than with quaternary ammonium surfactants. This may be because of the electrostatic interaction between the cationic micelle and anionic oximate ions (2-PyOx⁻, 4-PyOx⁻, 4-C$_{12}$PyOx⁻ and 4-C$_{10}$PyOx⁻) at the palisade layer of micelles. Functionalized oximate ions are more hydrophobic
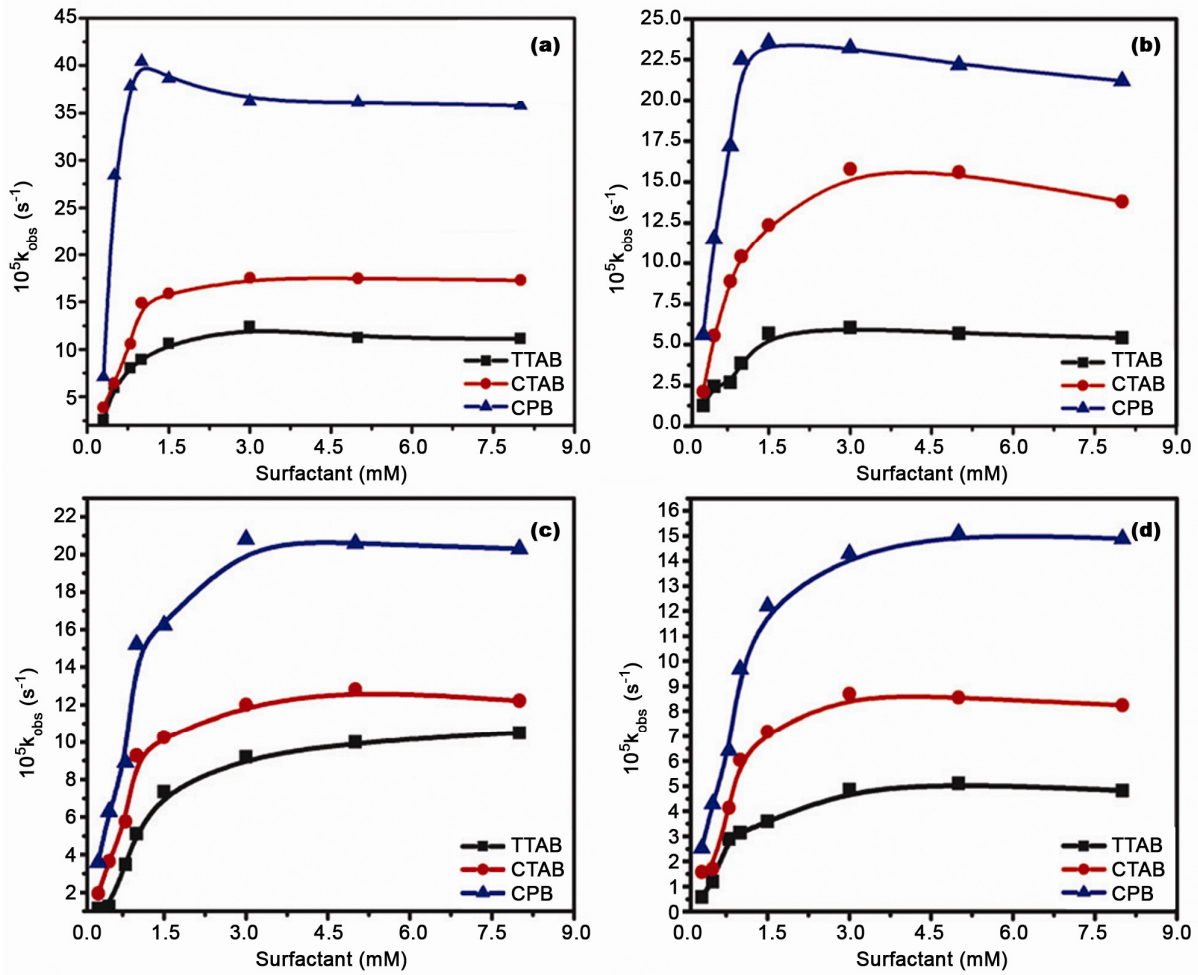
Fig. 3 – Plots of the kinetic rate data for the reaction of paraoxon with (a) 4-C_{12}PyOx⁻, (b) 4-C_{10}PyOx⁻, (c) 2-PyOx⁻, and, (d) 4-PyOx⁻ in borate buffer at pH 9.5 in cationic surfactant.
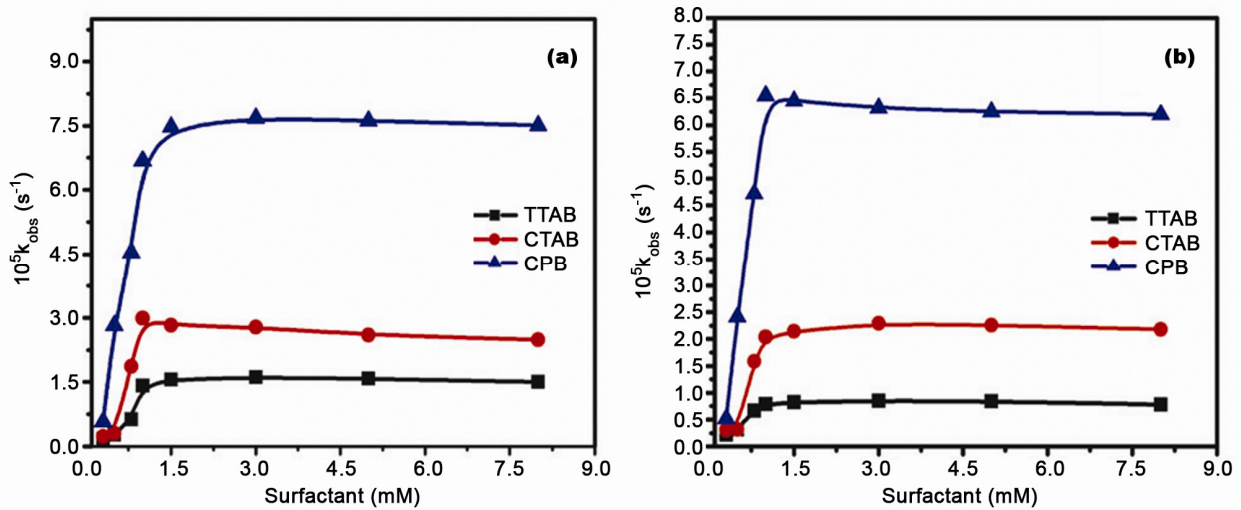

Fig. 4 – Plots of the kinetic rate data for the reaction of parathion with (a) 4-C_{12}PyOx⁻, and, (b) 4-C_{10}PyOx⁻ in borate buffer at pH 9.5 in cationic surfactant.

Table 2 – Kinetic rate data for the reaction of paraoxon with oximate and functionalized oximate ions in micellar media.
[React. cond.: Temp: = 27 °C, [Paraoxon] = $5.0 \times 10^{-5} M$, [Nu$^-$] = $5.0 \times 10^{-4} M$, pH 9.5 (Borate buffer)]

[Surf.] (mM)	$10^5 k_{obs}$ (s^{-1})											
	4-C$_{12}$PyOx$^-$			4-C$_{10}$PyOx$^-$			2-PyOx$^-$			4-PyOx$^-$		
	TTAB	CTAB	CPB	TTAB	CTAB	CPB	TTAB	CTAB	CPB	TTAB	CTAB	CPB
0.3	2.56	3.89	7.08	1.25	2.11	5.60	1.16	1.94	3.61	0.58	1.57	2.52
0.5	5.95	6.46	16.2	2.43	5.55	11.5	1.24	3.65	6.29	1.20	1.69	4.29
0.8	8.01	10.6	28.4	2.68	8.89	17.2	3.49	5.76	8.92	2.89	4.14	6.42
1.0	8.92	14.9	37.8	3.85	10.4	22.5	5.12	9.28	15.2	3.14	6.05	9.69
1.5	10.6	15.8	40.4	5.68	12.3	23.5	7.36	10.3	16.3	3.59	7.18	12.2
3.0	12.4	17.5	38.6	6.03	15.7	23.2	9.21	12.2	20.8	4.86	8.69	14.3
5.0	11.2	17.5	36.2	5.69	15.6	22.2	10.3	12.8	20.6	5.10	8.55	15.1
8.0	11.1	17.3	36.1	5.41	13.8	21.2	10.5	12.2	20.3	4.82	8.25	14.9

than non-functionalized oximate ions, therefore, the functionalized oximate ions shows better nucleophilicity, wherein cationic surfactants augment the efficiency of the nucleophiles towards the electrophilic center of P=O and P=S bond. This rate acceleration is mainly due to the hydrophobic and charge effects of cationic surfactant where the reactant concentration is bulk at the stern layer. In micellar media, reaction takes place at the stern layer. On adding the substrate to the reaction medium, the hydrophobic part of substrate (aromatic ring) is buried in the core of the micelle (Fig. 2). Paraoxon and parathion as substrate have two ethyl groups (diethyl) which are also slightly hydrophobic, and therefore, it moves towards the palisade layer. The monoanionic oximate ions (2-PyOx$^-$, 4-PyOx$^-$, 4-C$_{12}$PyOx$^-$ and 4-C$_{10}$PyOx$^-$) act as effective α-nucleophiles due to unshared electron pairs on oxygen and nitrogen atom. The nucleophilicity is not only governed by the basicity but also by the strength of interaction between nucleophile and the surfactant aggregate[29]. The nucleophilicty of oximate and functionalized oximate ions towards P=O and P=S bond was found to be in the order: 2-PyOx$^-$ < 4-PyOx$^-$ < 4-C$_{10}$PyOx$^-$ < 4-C$_{12}$PyOx$^-$. A marked increase in micellar effects was observed in the order: TTAB < CTAB < CPB. The trend of reactivity followed the order of variation of critical micelle concentrations (cmc), i.e., TTAB (cmc = 3.0 mM) < CTAB (cmc = 1.0 mM) < CPB (cmc = 0.7 mM)[30]. The reactivity of nucleophiles in micellar media depends on the type of head groups such as quaternary ammonium (CTAB, TTAB) and pyridinium group (CPB) of the surfactants. The molecular packing of organized self-assemblies depends on the structure of surfactant head groups such as quaternary ammonium (CTAB, TTAB) and pyridinium groups (CPB) and plays an important role

towards aggregation of surfactants[31-33]. An increase in the head group size leads to an increase in the interfacial region, and the space between the two groups is also enhanced[34]. During the self organization process of surfactants the large head groups provide additional space between two head groups and it permits the reactant to easily solubilize itself at the interfacial region. Due to the enhanced interfacial area, the concentration of nucleophile and substrate increases and shows higher activity. In comparison, we found that the rate enhancements of oximate ions with CPB are higher than with CTAB and TTAB for the cleavage of phosphate esters. It is clearly manifested that the increase in reactivity of 4-C$_{12}$PyOx$^-$ with CPB is 2.5 fold and 4.23 fold higher than with CTAB and TTAB respectively. Similarly reaction of 4-C$_{10}$PyOx$^-$ with CPB is 2.16 fold and 5.84 fold faster than with CTAB and TTAB. Likewise, 1.60 fold and 3.08 fold rate enhancement was observed in the reaction of 4-PyOx$^-$ with CPB as compared to with CTAB and TTAB for the hydrolysis of paraoxon. The reactivity of 4-C$_{12}$PyOx$^-$ toward parathion in CPB is 6.32 and 3.0-fold higher than in TTAB and CTAB, respectively. On the other hand, the reactions of 4-PyOx$^-$ and 2-PyOx in CPB showed 12.29 and 5.36 fold higher reactivity than in TTAB, whereas 10.81 and 3.63 fold increase was observed in CTAB. The difference of k_{obs} values of the reactions depend on the micellar structure, that is head group, hydrophobic tail length, and counter ion. Figures 3 and 4 show that the k_{obs} values increase with increasing alkyl chain lengths (R = 14 to R = 16) of surfactants, that is, with increasing aggregation number of micelle and increase the electrical surface potential, k_{obs} also increases with increasing hydrophobicity of micelle at palisade layer. The results indicate that the reactivity of oximate and

functionalized oximate ions with pyridinium head group of surfactants (CPB) is more effective than with quaternary ammonium head group for the cleavage of phosphate esters.

In this study, we found that the nucleophilicity of functionalized oximate ions towards P=O and P=S center of phosphate ester is higher than that of non-functionalized oximate ion. The $4\text{-}C_{12}PyOx^-$ ions show 3.82 fold higher reactivity than $4\text{-}PyOx^-$ for paraoxon and 1.15 fold higher reactivity for parathion. Cationic surfactants contribute to enhance the catalytic acitivity of oximate ions. The reactivity of nucleophile with pyridinium (CPB) surfactants is better than with quaternary ammonium surfactants (CTAB and TTAB) due to hydrophobicity, low cmc value and more space between two head groups. The large solubilizing effect of the reactant leads to increase in concentration of the reactant at the stern layer, where reactions take place. This study helps to elucidate the cleavage mechanism of phosphotriester bond and design of effective nucleophile.

Acknowledgement

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