Research Article

Journal of Physical Organic Chemistry

Received: 25 October 2007, Revised: 1 March 2008, Accepted: 4 March 2008, Published online in Wiley InterScience: 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1370

Comparative nucleophilic reactivities in carboxylate, phosphinate, and thiophosphate esters cleavage†

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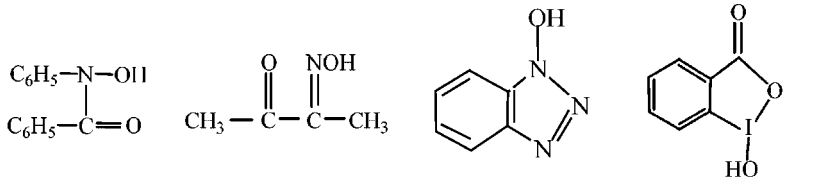
Nucleophilic substitution reaction of *p*-nitrophenyl acetate (PNPA), *p*-nitrophenyldiphenyl phosphinate, and pesticide parathion with different α-nucleophiles [I] have been studied at 27 °C in different pH in the presence of a novel cationic surfactant.



N-Phenylbenzo-hydroxamic acid | Butane 2,3 -dione-monoxime | Hydroxybenzotriazole | 2 -Iodosobenzoic acid

[I]

The kinetic study was performed spectrophotometrically under pseudo-first order conditions with the α-nucleophile in excess. The pK_a of nucleophiles have also been determined by kinetic method. In the presence of surfactant, the rate constant increased with increasing surfactant concentration up to a limiting value. This behavior has been analyzed in quantitative terms on the basis of pseudo-phase model of micellar catalysis. Finally the nucleophilic reactivity of hydroxamate ions has been compared with other α-nucleophiles, like oxime, hydroxybenzotriazole, and 2-iodosobenzoic acid (IBA). The order of cleavage of electrophilic centers, that is, C=O, P=O, and P=S have also been discussed. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: α-nucleophile; p*K*a; pseudo-phase model

INTRODUCTION

There is a growing need for fast detoxification and technological advancements to combat chemical and biological warfare agents. The α-effect has been reported in many different types of reactions in solutions.[1–4] Classical physical organic chemistry studies over the last 20 years have yielded some important clues about the nature of α- effect.[5–10] Although many attempts have been made to rationalize α-effects in terms of physicochemical factors (e.g., polarizability, hydrogen bonding, single electron transfer character, orbital splitting, and other), mechanistic details have not been sufficiently clear. α-nucleophiles are also characterized by anomalously high nucleophilic reactivity with respect to electron deficient centers of various origins, for example, carbon, sulfur, and phosphorus. This fact attracts interest from the viewpoints of utilization of organophosphorus ecotoxicants and search for effective and novel detoxicants.

Various strategies[11–28] have been studied to enhance the hydrolysis of phosphoester and carboxylate esters, and these include the employment of metal ions which act as Lewis acid catalysts, metallomicelles, enzymes, nanoparticles/biomimetic nanocatalyst, and reactive α-effect nucleophiles such as oximates, hydroximates, hydrazines, and hydroxylamine to name a few. It has also been recognized that cationic micelles serve to enhance the rate of hydrolysis of such compounds via micellar catalysis.[11–16] Moss and others[17–21] have studied extensively the catalytic cleavage of carboxylate and phosphate esters by a series of *o*-iodosobenzoic acid. Similarly Bhattacharya *et al*. introduced tetrazole,[22] hydroxybenzotriazole,[23] and their suitably designed derivatives as powerful ester cleaving reagents. Recently Buncel *et al*. studied the reactivities of fenitrothion with a series of oximate α-nucleophiles with pK_a values ranging from 7.7 to 11.8.[12] Recently, biomimetic nanocatalyst, magnetic nanoparticles, and functionalized polymer nanofibre membrane have also been used for detoxification.[26–28]

Changing the electrophilic center from a carbonyl to a sulfonyl or phosphonyl group would exert significant effect on their

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† *Presented in part at 12th Asian Chemical Congress, Kuala Lumpur, Malaysia, 23–25 August 2007.*

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electrophilicity. However systematic studies on changing such electrophilic centers have been lacking. Only scattered information on the reactivity of carbonyl, sulfonyl, and phosphonyl esters of similar structures is available.[29–31]

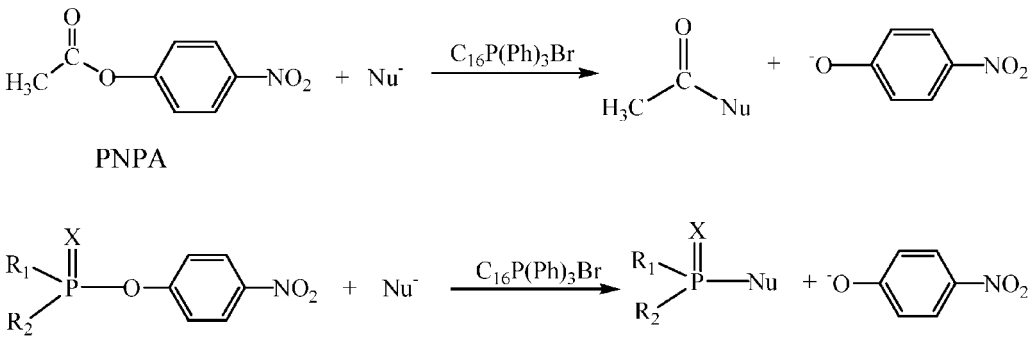
In the past few years, our laboratory has aimed at demonstrating the role of hydroxamate ions (α-nucleophiles) for the degradation of carboxylic and neurotoxic phosphate esters.[32–35] In the present work comparative nucleophilic reactivities in carboxylate, phosphate and thiophosphate esters cleavage have been studied. The nucleophilic substitution reaction of *p*-nitrophenyl acetate (PNPA), *p*-nitrophenyl diphenyl phosphinate (PNPDP) and *p*-nitrophenyl diethyl phosphorothioate (parathion) with different α-effect nucleophiles (I), that is, *N*-phenylbenzohydroxamic acid (PBHA), oximate (butane-2,3-dione monoxime), 1-hydroxybenzotriazole, and 2-iodosobenzoic acid (IBA) have been investigated in the absence and presence of cationic surfactant cetyltriphenylphosphonium bromide ($C_{16}PPh_3Br$)(II).

RESULTS AND DISCUSSION

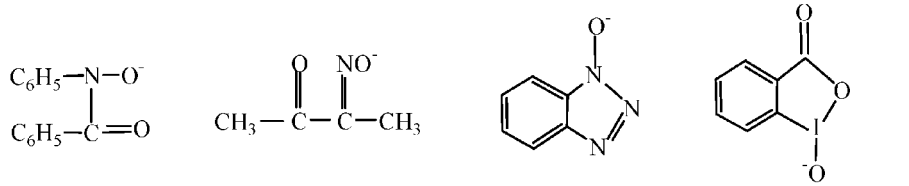
pH-dependent reaction

Pseudo-first order rate constants for the reaction of PNPDP with a series of α-nucleophiles, that is, IBA, 2,3-Butanedione monoxime (oxime), and PBHA have been determined over a pH range 6.5–11.1 at 27 °C. The apparent pK_a of these α-nucleophiles were determined from the rate constant *versus* pH plots for the cleavage reactions.

The rate data (data not shown) indicate that the rate of reaction increases with increasing pH values. Plot of log k_{obs} *versus* pH (Fig. 1) gave a discontinuity at definite pH value for IBA, oxime, and PBHA. These break points were taken as apparent pK_a values for these nucleophiles (IBA = 7.45, oxime = 9.0, PBHA = 8.9). These values are in close agreement with literature values.[30–35]

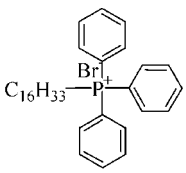


Nu^- =



N-Phenylbenzo-hydroxamate (PBHA) | Butane 2,3-dione -monoximate (Oxime) | Hydroxybenzotriazole (HOBT) | 2 -Iodosobenzoate (IBA)

(I)



Cetyltriphenylphosphonium bromide ($C_{16}PPh_3Br$)

(II)

Scheme 1.

Effect of cationic surfactant

Cationic surfactants are known to accelerate the hydrolysis of carboxylic and phosphate esters. The ability of micellized surfactants to control rates of moderately slower reactions is well established.[30–36] Acceleration of organic reactions in micelle solution is determined mainly by two factors that is concentration of the reactants in the micelle pseudophase and considerable increase in the rate of reaction. Cationic micelles bring reactants closer by hydrophobically binding of substrate and coulombically attracting the negatively charged nucleophile. The effects of $C_{16}PPh_3Br$ on the hydrolysis of PNPA, PNPDP, and

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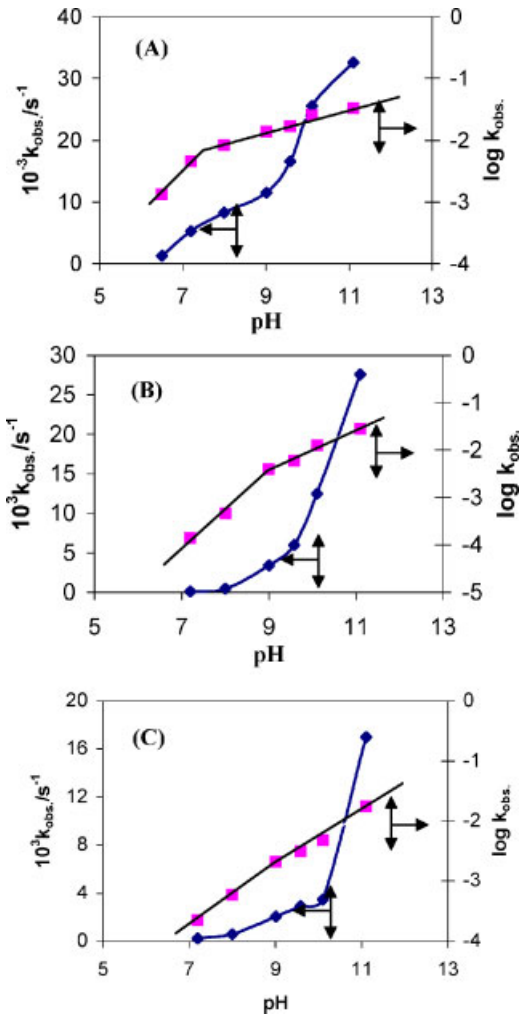

Figure 1. Plots of observed rate constant *versus* pH and log of observed rate constant *versus* pH for the hydrolysis of *p*-nitrophenyl diphenyl phosphinate by IBA (A), oxime (B), and PBHA (C) at 27 °C. This figure is available in colour online at www.interscience.wiley.com/journal/poc

parathion are shown in Table 1. It has been shown that observed first order rate constants increase sharply with increase in the concentrations of the surfactants. The rate-surfactant concentration profiles obtained with various surfactants/catalysts are characteristic of micelle catalyzed reaction.[36] The reactivity of these α-nucleophiles, that is, IBA, oxime, PBHA, and HOBT have been observed to be more significant for the hydrolysis of PNPA. Figure 2 shows that under comparable conditions, the k_{obs} values for hydrolysis of PNPA by PBHA was found to be greater than IBA which in turn was more reactive than oxime and HOBT. It is illustrated in Table 1 that the observed first order rate constant reactivity for the hydrolysis of PNPA, PNPDP, and parathion increases with surfactant concentration. The nucleophilic reactivity of micelle depends upon the binding of substrate and interaction with anionic nucleophiles. In case of phosphinate, on comparison with other α-nucleophiles, IBA was found to be the most reactive and HOBT the least reactive. In case of parathion, irrespective of concentration of surfactants, IBA shows the maximum rate as compared to oxime, PBHA, and HOBT. PBHA and oxime exhibited comparable reactivity. The reactivity order for all the nucleophiles was IBA > PBHA > oxime > HOBT. In case

Table 1. Summary of kinetic rate data for the reaction of PNPA, PNPDP, and parathion in micellar media

$[C_{16}PPh_3Br]$ (mM)	$10^3k_{obs}/s^{-1}$												
	PNPA				PNPDP				Parathion				
	IBA	Oxime	PBHA	HOBT	IBA	Oxime	PBHA	HOBT	IBA	Oxime	PBHA	HOBT
0	2.45	2.21	5.69	0.60	8.30	0.46	0.58	0.91	0.26	0.18	0.29	0.09
0.1	3.80	3.71	9.21	0.88	15.5	5.10	5.30	1.23	0.42	0.21	0.38	0.12
0.3	8.50	10.6	14.7	1.2	20.0	11.2	6.01	1.30	0.53	0.24	0.49	0.20
0.6	14.5	19.0	19.0	1.75	*a*	18.9	9.29	1.46	0.64	0.26	0.60	0.41
0.9	18.0	20.0	24.5	2.6	*a*	20.0	11.0	2.01	0.8	0.38	0.8	0.47
1.2	24.5	22.0	28.0	2.80	*a*	22.3	12.6	2.38	1.07	0.46	0.98	0.52
1.6	26.0	28.0	32.0	4.0	*a*	28.6	13.3	3.01	1.01	0.52	0.97	0.58
2.0	29.1	30.0	35.5	4.90	*a*	32.0	13.0	3.94	1.09	0.55	1.01	0.63
2.5	29.6	35.0	39.8	5.01	*a*	35.3	12.7	4.02	1.11	0.64	1.07	0.67
3.0	30.0	38.9	42.7	5.21	*a*	37.7	11.4	4.21	1.12	0.68	1.11	0.68
3.6	30.1	41.2	46.3	5.40	*a*	40.1	9.12	4.78	1.12	0.72	1.16	0.69

[Substrate] = 1.0×10^{-4} M, [Nu] = 1 mM, μ = 0.1 M KCl, pH = 8.0, a = very fast reaction.

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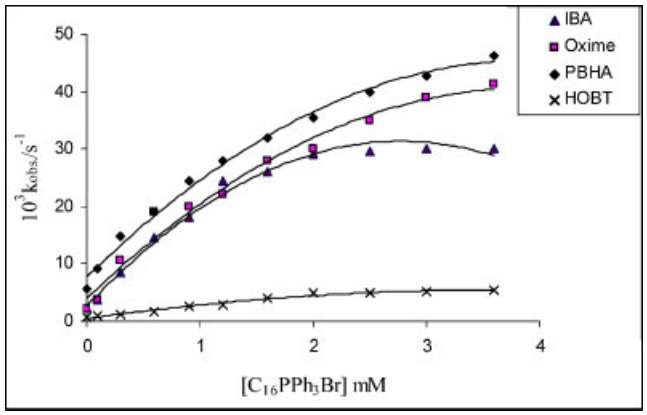


Figure 2. Rate surfactant plots of k_{obs} (rate constant) *versus* [surfactant] for the nucleophilic reaction of PNPA with different α-nucleophiles [I]. This figure is available in colour online at www.interscience.wiley.com/journal/poc

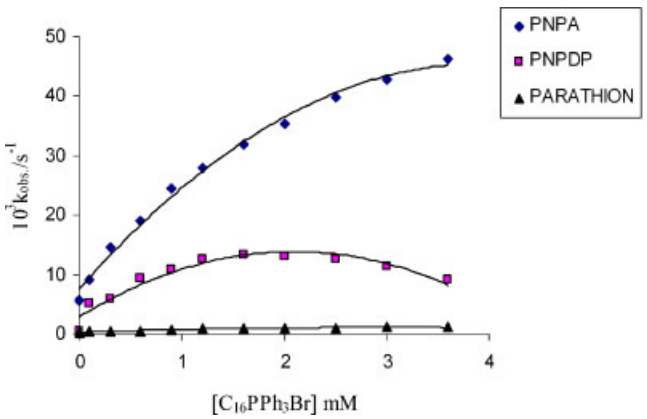
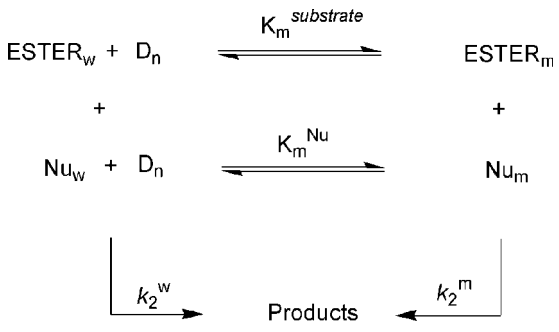


Figure 3. Rate surfactant plots of k_{obs} (rate constant) *versus* [surfactant] for the reaction of PNPA, PNPDP, and parathion using PBHA. This figure is available in colour online at www.interscience.wiley.com/journal/poc

of all the substrates studied, IBA showed the highest reactivity among all the nucleophiles. PBHA was the next most reactive relative to other nucleophiles.

An attempt has been made to compare the reactivity of different α-nucleophiles in carboxylate, phosphate, and thiophosphate esters in the presence of $C_{16}PPh_3Br$. As shown in Table 1 and Fig. 3, the reactivity of PNPA, PNPDP, and parathion toward these α-nucleophiles is PNPA (C═O) > PNPDP (P═O) > parathion (P═S). The nucleophilic reactivity of these α-nucleophiles toward P═S center is less than P═O center



Scheme 2.

Table 2. Kinetic parameters obtained by applying pseudophase model for the nucleophilic reaction of PNPA, PNPDP, and parathion with different α-nucleophiles [I] in the presence of cetyltriphenylphosphonium bromide micelles

	PNPA				PNPDP				Parathion			
	IBA	Oxime	PBHA	HOBT	Oxime	PBHA	HOBT	IBA	Oxime	PBHA	HOBT
k_2^w ($M^{-1}s^{-1}$)	2.45	2.21	5.69	0.60	0.46	0.58	0.91	0.26	0.18	0.29	0.09
$K_m^{substrate}$ (M^{-1})	300	300	300	300	900	900	900	500	500	500	500
K_m^{Nu} (M^{-1})	190	28	49	32	25	35	32	126	27	46	29
k_2^m ($M^{-1}s^{-1}$)	7.25×10^{-2}	4.29×10^{-1}	2.79×10^{-1}	5.01×10^{-2}	2.89×10^{-1}	8.03×10^{-2}	2.32×10^{-2}	2.70×10^{-3}	5.03×10^{-3}	5.91×10^{-3}	5.89×10^{-3}

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due to strong pπ–dπ interaction in P═O than in P═S center. Electrophilicity of central atom in P═O and P═S esters reduce in same order due to pπ–dπ bonding, which hinders the attack of α-nucleophile in the rate determining step. On the contrary, the non-existence of pπ–dπ bonding manifested to highest reactivity of C═O ester.

Quantitative treatment of rate data: pseudophase model

The pseudophase model treats water and micelles as distinct reaction regions and rationalizes a great deal of data quantitatively.[37–41] The interfacial ion exchange and the binding constant of the substrate are the key factors at the origin of micellar catalysis since it is now recognized that accelerations in surfactant solutions arise not because of an increase in the micellar rate constants, k_m, as compared to those in water, k_w, but because of large reagent concentrations in the small interfacial volume in which the reaction occurs. A quantitative interpretation of the experimental behavior observed can be carried out by means of formalism of the micellar pseudophase. The influence of cationic micelles on the k_{obs} values for the nucleophilic bimolecular reactions of PNPA, PNPDP, and parathion with α-nucleophiles can be described as illustrated in Scheme 2.

In Scheme 2, subscripts w and m indicate aqueous and micellar pseudophases, respectively, and D_n represents the micellized surfactant, that is, $[D_n] = [D_T]$-cmc, where $[D_T]$ is the stoichiometric surfactant concentration and cmc the critical micellar concentration, obtained under the experimental conditions as the minimum surfactant concentration required to observe any kinetic effect.

Scheme 2 considers the distribution of PNPA, PNPDP, and parathion between the aqueous and micellar pseudophases, K_m^{PNPA}, K_m^{PNPDP}, and $K_m^{Parathion}$. The association constants of PNPA, PNPDP, and parathion have been obtained from fitting the reaction data with the values of $K_m^{PNPA} = 300\,M^{-1}$, $K_m^{PNPDP} = 900\,M^{-1}$, and $K_m^{Parathion} = 500\,M^{-1}$ in $C_{16}PPh_3Br$ micelles. The distribution of the nucleophiles, Nu, between both pseudophases is considered through the distribution constant K_m^{Nu}. The different reactivities in the aqueous and micellar pseudophases have been taken into account through the corresponding-second order rate constants: k_2^w and k_2^m. The values of k_2^w have been obtained by studying the reaction in the absence of the surfactant.

The concentration of nucleophile in the micellar pseudophase has been defined as the local, molar concentration within the micelle pseudo phase. $\overline{V}$ is the molar volume in $dm^3\,mol^{-1}$ of the reaction region and $[D_n]$ denotes the micellar fractional volume in which the reaction occurs. We assume $\overline{V}$ equal to the partial molar volume of the interfacial reaction region in the micellar pseudophase, determined by Bunton[42] as $0.14\,dm^3\,mol^{-1}$. Micellar binding of substrates, PNPA, PNPDPP, and parathion and nucleophile is governed by hydrophobic interactions and the equilibrium constants K_m^{PNPA}, K_m^{PNPDP}, and K_m^{Nu} are expressed by referring these concentrations to the total volume of the micelle. The observed rate constant, k_{obs}, based on Scheme 2 and on the above considerations, is given by the following:

$$k_{obs} = \frac{k_2^w + \frac{k_2^m}{\overline{V}} K_m^{Nu} K_m^{Substrate} [D_n]}{\left(1 + K_m^{Nu}[D_n]\right)\left(1 + K_m^{Substrate}[D_n]\right)} [Nu] \qquad (1)$$

Second order rate constants at the micellar interface and association constants of the hydroxamate, oximate, hydroxybenzoate, and 2-iodosobenzoate ions to the cationic micelles were obtained by fitting Eqn 1 to the experimental data that are listed in Table 2. Figure 4 shows the simulated rate-surfactant profiles for the reaction of PNPA, PNPDP, and parathion with different α-nucleophiles [I] in the presence of $C_{16}PPh_3Br$ micelles.

EXPERIMENTAL

Materials

PNPA was purchased from s.d.fine and was used as received. PNPDP, parathion, and PBHA were prepared by literature method

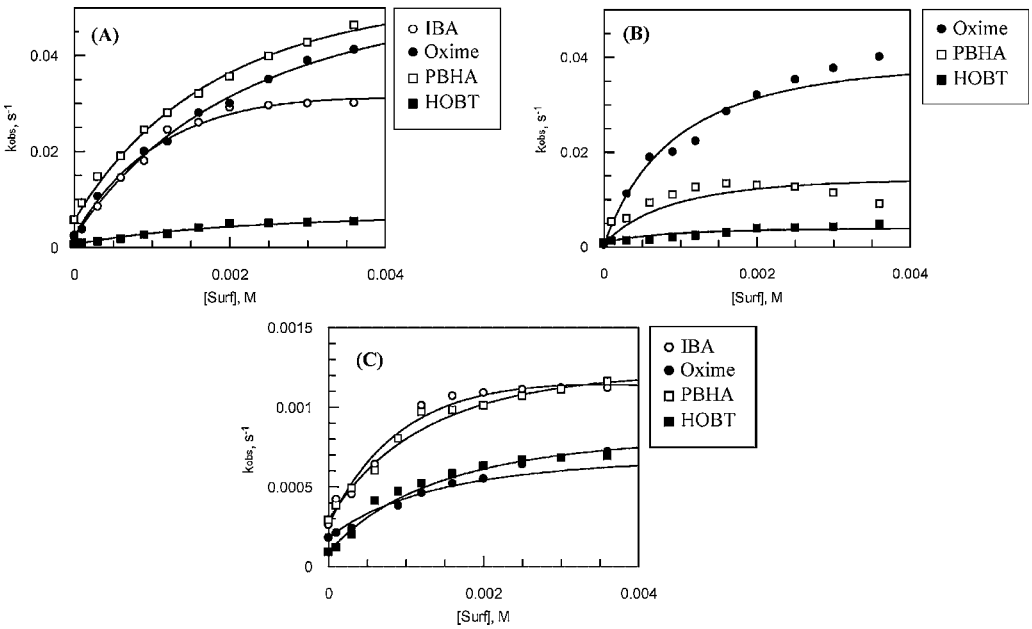

Figure 4. Simulated rate-surfactant profiles for the reaction of PNPA (A), PNPDP (B), and parathion (C) with different α-nucleophiles [I] in the presence of cetyltriphenylphosphonium bromide micelles (lines are predicted values with model)

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at the Vertox laboratory of Defence Research Development Establishment, Gwalior. $C_{16}PPh_3Br$ surfactant was obtained from Prof. R. M. Palepu, St. Francis Xavier University, Antigonish, Canada. Oxime, IBA, and HOBT were purchased from Sigma.

Methods

All of the reactions were followed at 27 ± 0.2 °C with a Varian Cary-50 spectrophotometer and Systronics (Type-104) spectrophotometer. Substrate stock solution of 0.0015 M was prepared with triply distilled water. The rate of nucleophilic reaction was determined by following the increase in absorption of *p*-nitrophenoxide anion (400 nm). All of the kinetic experiments were performed at an ionic strength of 0.1 M (with KCl). Phosphate buffer was employed to control the pH of the media. The pH of the reaction medium was measured using Systronics (Type-335) pH-meter. All reactions were conducted under pseudo-first order conditions.

CONCLUSIONS

The hydrolysis was studied with PNPDP with IBA, oxime, and PBHA to obtain the pK_a values, which was found to be approximately 7.45, 9.0, and 8.9, respectively. The effects of $C_{16}PPh_3Br$ on the hydrolysis of PNPA, PNPDP, and parathion have been studied and the observed first order rate constants increases sharply with increase in the concentrations of the surfactant upto a limiting value. PBHA was found to be the most reactive, and HOBT the least reactive for the hydrolysis of PNPA. The order of cleavage by α-nucleophiles of different electrophilic center is in the order of $C{=}O > P{=}O > P{=}S$.

Acknowledgements

The authors are grateful for the financial support from Defence Research Development Organization, Government of India, New Delhi (Grant No. ERIP/ER/0303406/M/01). The authors are also grateful to Dr P. R. Dafonte, University of Santiago de Compostela, Spain for applying Pseudo-phase model.

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