Kinetics of Hydrolysis of Procaine in Aqueous and Micellar Media

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ABSTRACT: The kinetics of alkaline hydrolysis of procaine under the pseudo–first-order condition ($[OH^-] \gg [procaine]$) has been carried out. N,N-Diethylaminoethanol and *p*-aminobenzoate anion were obtained as the hydrolysis product. The rate of hydrolysis was found to be linearly dependent upon [NaOH]. The addition of cationic cetyltrimethylammonium bromide (CTAB), dodecyltrimethylammonium bromide (DDTAB) and tetradecyltrimethylammonium bromide, and anionic sodium dodecyl sulfate (SDS) micelles inhibited the rate of hydrolysis. The maximum inhibitive effect on the reaction rate was observed for SDS micelles, whereas among the cationic surfactants, CTAB inhibited most. The variation in the rate of hydrolysis of procaine in the micellar media is attributed to the orientation of a reactive molecule to the surfactant and the binding constant of procaine with micelles. The rate of hydrolysis of procaine is negligible in DDTAB micelles. The observed results in the presence of cationic micelles were treated on the basis of the pseudophase ion exchange model. The results obtained in the presence of anionic micelles were treated by the pseudophase model, and the various kinetic parameters were determined. © 2012 Wiley Periodicals, Inc. Int J Chem Kinet 45: 1–9, 2013

INTRODUCTION

Procaine, the 2-diethylaminoethyl ester of 4-aminobenzoic acid (PABA), is a local anesthetic drug that causes reversible loss of pain sensation of skin and mucous membrane. Procaine is metabolized in the plasma through hydrolysis into PABA, which is then excreted by the kidneys into the urine. It is a vasodilator and is often coadministered with epinephrine for the purpose of vasoconstriction in which it helps to reduce bleeding and prevents the drug from reaching systemic circulation in a large amount [1–3]. Surfactants (also known as amphiphiles or detergents) are frequently used in industries and pharmaceuticals as an emulsifier, stabilizer, wetting agent, solubilizer, preservatives, etc. [4–6]. During pharmaceutical formulation, the studies on surfactant–drug interactions are very important in view of their stability and maintenance of biological efficacy. Surfactants usually have an ionic or polar head group and a long alkyl tail. At concentrations above a critical micellar concentration (cmc) in water, they form normal micelles having a nearly spherical structure with the head groups in contact with water and a hydrocarbon-like interior. The use of micelles and other association colloids, such as microemulsions and vesicles in water and organic solvents, has been fascinating to scientists owing to their modifying effect on reaction rates. In micellar media, most of the ionic or polar species exist in the Stern and Guoy–Chapman

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regions as counterions or coions. The micelles play a critical role in the localization and/or dispersion of charges on reactants and their activated states, and thus can easily influence reaction rates, equilibrium, and concentration, or depletion of reactants in the interfacial region. These effects depend on transfer of the substrate from water to micelles, the reaction mechanism, and properties of the interfacial region, that is, local charge, polarity, and water content. Therefore, the reaction media of surfactants are capable of both catalyzing and inhibiting the reaction rates, depending on the nature of interaction between the surfactant and reactants, micellar aggregation number, cmc values, the extent of incorporation of reactants as counterions or coions in micelles, etc. [7–12]. The studies on the hydrolysis of procaine in micellar media will be helpful in determining the extent of association of drug with micelles and, thereby, their stability in that environment. Therefore, kinetic experiments were performed in the presence of cationic cetyltrimethylammonium bromide (CTAB), dodecyltrimethylammonium bromide (DDTAB) and tetradecyltrimethylammonium bromide (TDTAB), and anionic sodium dodecyl sulfate (SDS) micelles for the alkaline hydrolysis of procaines to observe the role of surfactant on the stability of drugs in the micellar media. The observed results have been discussed with the help of the Poisson–Boltzman equation model and the pseudophase ion exchange (PIE) model [13–16]. The kinetic parameters were determined and are reported herewith.

EXPERIMENTAL

Materials

Procaine hydrochloride (99%; Sigma, St. Louis, MO), SDS (99%; BDH, Parkstone, Poole, UK), sodium bromide (99%; BDH), and CTAB (99%, Aldrich, Taufkirchen, Germany) were used without further purification. DDTAB and TDTAB were synthesized in the laboratory. DDTAB was synthesized by adding 1-bromododecane (0.1 mol) to trimethylamine (0.1 mol) dissolved in 100 mL isopropyl alcohol. The mixture was refluxed for 48 h. Isopropyl alcohol was removed by distillation, and the remaining solvent was evaporated by using a rotary evaporator. The dried product was recrystallized from absolute alcohol–dry ethyl ether. TDTAB was synthesized by using 1-bromotetradecane instead of 1-bromododecane and following the same procedure as for DDTAB. The sodium salt of toluene-4-sulfonate was used from BDH. Sodium hydroxide of AnalR grade was used during the experiments. Deionized double-distilled water (specific conductance: (1–2) $\times 10^{-6}$ Ω^{-1} cm^{-1}) was used as a solvent.

Kinetic Measurements

The kinetic experiments were performed spectrophotometrically using a Lambda 45 double-beam UV/vis spectrophotometer (Perkin Elmer, Shelton, CT) provided with multiple cell holders and thermostated by circulating water. The reactants (procaine and sodium hydroxide) were equilibrated at the desired temperature ($\pm 0.1^{\circ}$C) for $\sim$15 min in the water bath. The reaction was started by injecting calculated amount of procaine into the sodium hydroxide solution taken in a 3-mL quartz cuvette. All the kinetic runs were carried out under the pseudo–first-order reaction conditions in which [NaOH] was in high excess over [procaine]. The rate of reaction was measured by monitoring the decrease in absorbance at $\lambda_{max} = 286$ nm. The observed pseudo–first-order rate constant (k_1, s^{-1}) was obtained from slopes of plots ln A_t versus time. The kinetic experiments were performed till the reaction was almost completed. The values of correlation coefficients were quite satisfactory ($r^2 > 0.995$) for all rate constants determined. Critical micelle concentrations for the surfactants under the reaction conditions were determined using a Kruss type 10 tensiometer (Karl Kolb Scientific Technical Supplies, Dreieich, Germany).

RESULTS AND DISCUSSION

Hydrolysis of Procaine in Aqueous Medium

The repetitive scans of the mixture containing procaine (6.50×10^{-5} mol dm^{-3}) and NaOH (5.00×10^{-2} mol dm^{-3}) were recorded at constant intervals of time in the UV/vis region. The spectra are shown in Fig. 1, and a shift in maximum absorption was observed from 286 to 265 nm with the increase in reaction time. The absorbance decreased at 286 nm and increased at 265 nm with the progress of the hydrolysis of procaine. The spectra presented in Fig. 1 have two well-defined isobestic points within the interest range, indicating that the decrease in absorbance at 286 nm is due to hydrolysis of procaine and an increase in absorbance at 265 nm is attributed to formation of the *p*-nitrobenzoate anion as a hydrolysis product.

The pseudo–first-order rate constant determined at different concentrations of sodium hydroxide in the range 0.10–1.40 mol dm^{-3} at fixed [procaine] ($= 6.50 \times 10^{-5}$ mol dm^{-3}) at $25.0 \pm 0.1^{\circ}$C shows that the rate is linearly dependent upon [OH$^-$]. The rate of hydrolysis was decreased when an organic solvent

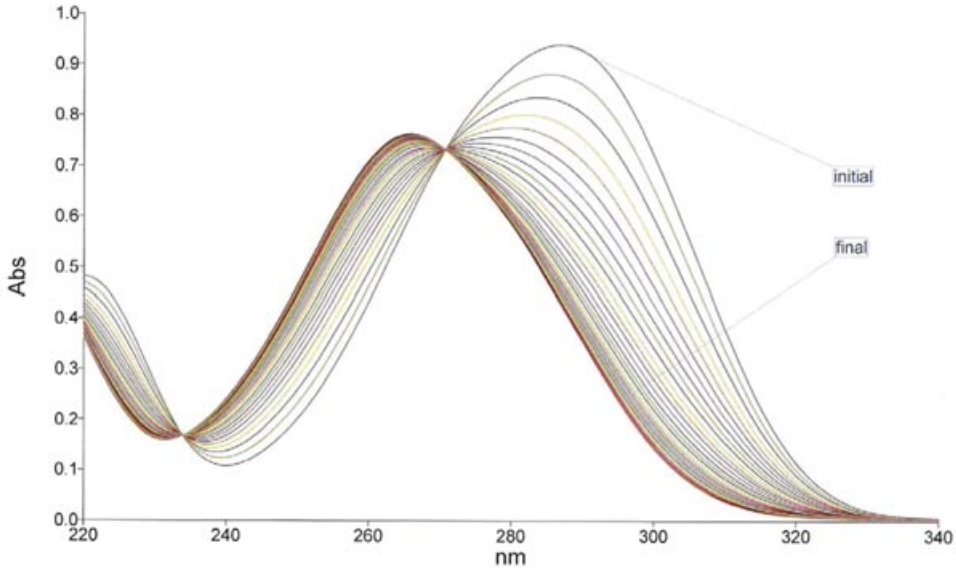


Figure 1 Repetitive scan for the hydrolysis of procaine (6.50×10^{-5} mol dm^{-3}) with 5.00×10^{-2} mol dm^{-3} NaOH at 25.0 $\pm$ 0.1°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(methanol, ethanol, and tetrahydrofuran) was added to the reaction mixture. The increase in proportion of the organic solvent decreased the reaction rate.

During the alkaline hydrolysis of procaine, the reaction starts with the attack of nucleophile OH^- to the carbonyl carbon group of procaine to form a tetrahedral intermediate (see Scheme 1), which, in turn, finally gives *N*,*N*-diethylaminoethanol and *p*-aminobenzoate anion [17–19].

The rate constant for the reaction followed the relationship

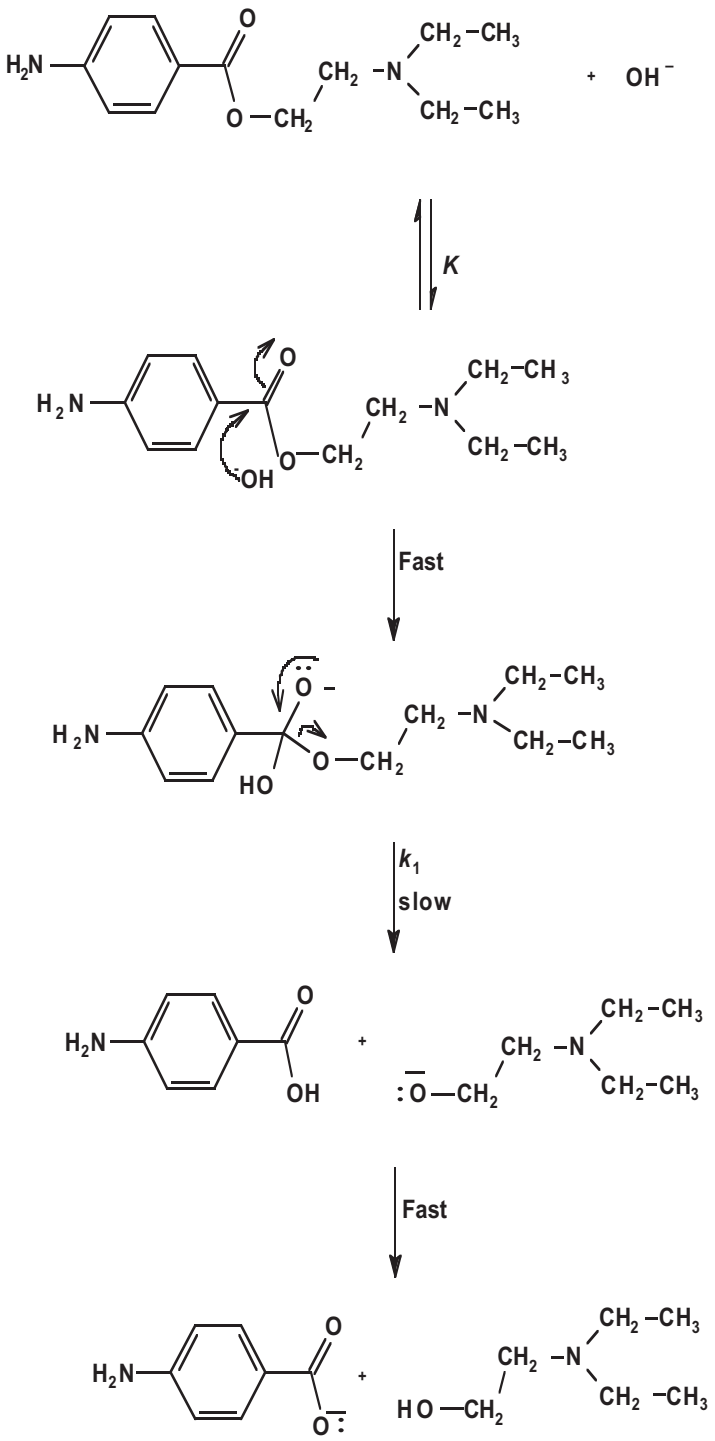
$$k_1 = k_2[\mathrm{NaOH}]^a \quad (1)$$

where k_1 and k_2 are the pseudo–first-order rate and second-order rate constants, respectively. The bimolecular rate constant, k_2, could not be determined directly as the disappearance of the hydroxide ion with time could not be accurately measured due to being in large excess over procaine. So, it has been conveniently determined after obtaining the pseudo-unimolecular rate constant k_1. The slope of the plot of log k_1 versus log [NaOH] (Fig. 2) gave the values of a (= 0.947), and its intercept gave the values of the second-order rate constant, k_2 (= 3.82×10^{-3} mol^{-1} dm^3 s^{-1}).

The addition of the organic solvent, namely, methanol, ethanol, and tetrahydrofuran, to the reactants solution decreased the rate of reaction. The inhibitive effect on the rate of hydrolysis by the added organic solvent is associated with the lowering of the polarity of the solvent on increasing its fraction (Fig. 3). According to the Hugges–Ingold rules [20], an increase in solvent polarity results in increased reaction rates for the reaction in which the charge density is higher in the activated complex than the initial reactant molecules. The higher polarity of the solvent stabilizes the charged intermediate and, therefore, increases the reaction rate by its solvation. Thus, the addition of the organic solvent lowers the polarity and decreases the stability of the transition state and, therefore, the rate of reaction is decreased on increasing the proportion of organic solvents.

Hydrolysis of Procaine in Surfactant Media

The addition of CTAB, DTAB, TDTAB, and SDS micelles to the reactants inhibited the rate of hydrolysis of procaine. The inhibitive effect on the rate of hydrolysis of procaine by SDS is presented in Fig. 4. The inhibitive effect of micellar solutions was observed in the order: SDS > CTAB > TDTAB > DDTAB. The lowering of the overall rate of the reaction in the presence of cationic and anionic micelles is indicative of the presence of a strong interaction between procaine and micelles. According to the pseudophase model, the reaction proceeds at different rates in the aqueous and micellar phases. The rate of the reaction depends on the distribution of procaine in aqueous and micellar regions and on its orientation on the micellar surface. The model proposed by Romsted [15,16] has been used to predict the distribution of procaine in the Stern region of micelles. The mechanism of hydrolysis of procaine occurring in the presence of micelles is presented in Scheme 2 with the different values of the first-order rate constants k'_m and k'_w in micellar and aqueous media, respectively.



Scheme 1

In this scheme, D_n presents the micellized surfactant ($D_n = [D] - cmc$, where D is the total surfactant concentration) and K_s is the binding constant for procaine to the micelle. S_m and S_w are the concentrations of procaine distributed in micellar and aqueous media. K_s is given by

$$K_s = \frac{[S_m]}{[S_w][D_n]} \tag{2}$$

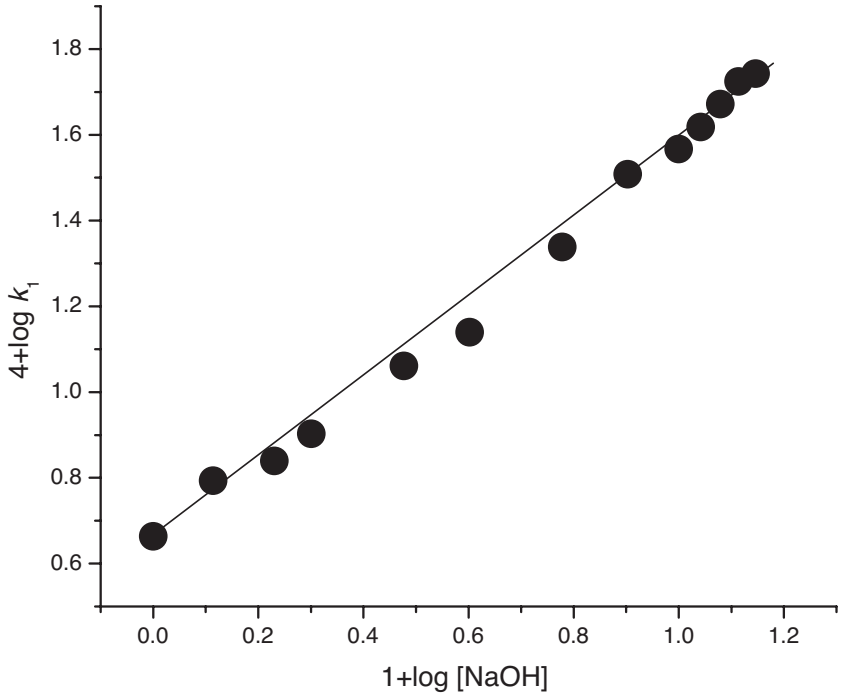


Figure 2 Logarithm plot of $4 + \log k_1$ versus $1 + \log$ [NaOH] for the hydrolysis of procaine in aqueous medium. Reaction conditions: [procaine] $= 6.50 \times 10^{-5}$mol dm^{-3}, temperature $= 25.0 \pm 0.1$°C.

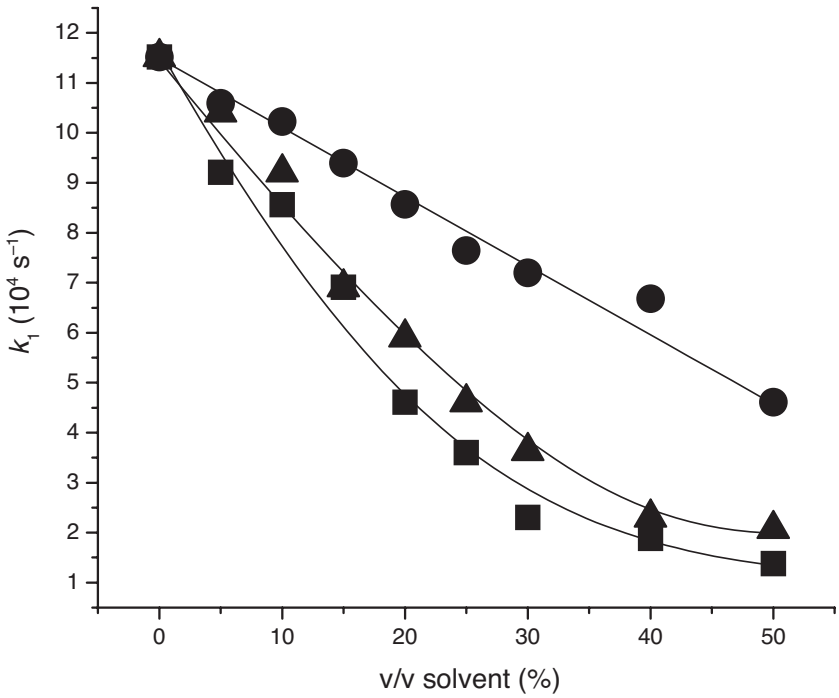


Figure 3 Variation of observed rate constant, k_1 versus % v/v solvent; methanol (●), ethanol (▲), and tetrahydrofuran (■) for the hydrolysis of procaine. Reaction conditions: [procaine] $= 6.50 \times 10^{-5}$mol dm^{-3}, [NaOH] $= 3.00 \times 10^{-1}$ mol dm^{-3}, and temperature $= 25.0 \pm 0.1$°C.

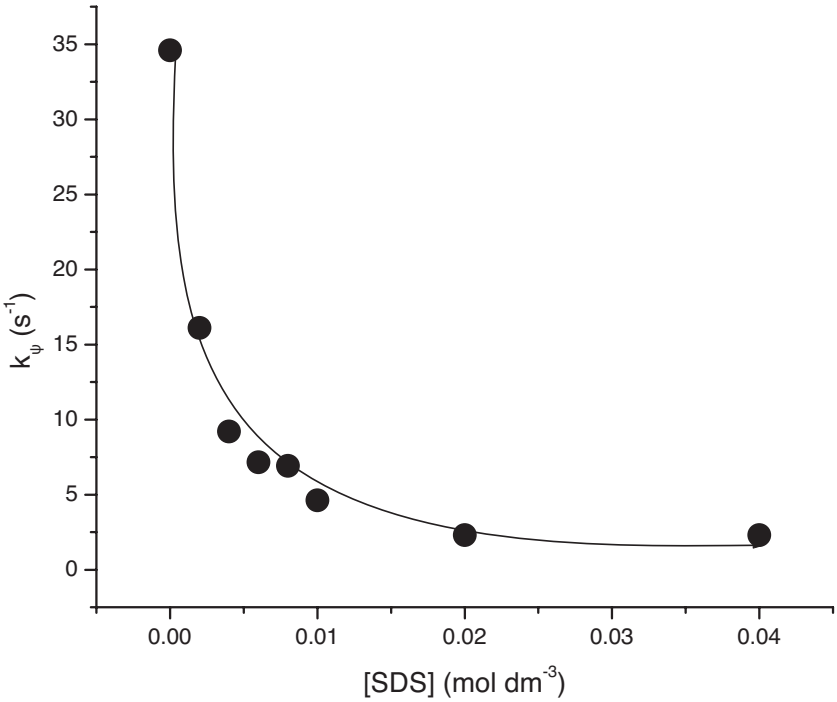
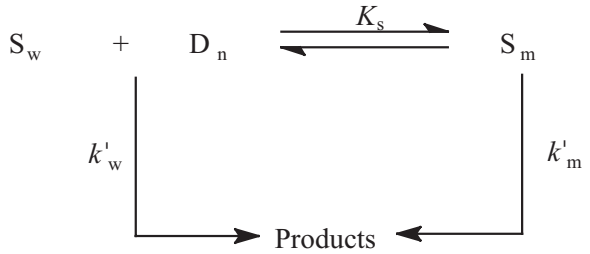


Figure 4 Plot of k_Ψ versus [SDS] for the hydrolysis of procaine in micellar medium. Reaction conditions: [procaine] = 6.50 $\times$ 10^{-5}mol dm^{-3}, [NaOH] = 3.00 $\times$ 10^{-1} mol dm^{-3}, and temperature = 40.0 $\pm$ 0.1°C.



Scheme 2

The overall rate can be expressed as

$$v = k_\Psi[S_T] = k\,[S_T]\,[OH_T^-] = k'_w[S_w]\,[OH_w^-] + k'_m[S_m]\,[OH_m^-] \quad (3)$$

where

$$[S_T] = [S_w] + [S_m] \quad (4)$$

$$[OH_T^-] = [OH_w^-] + [OH_m^-] \quad (5)$$

and

$$k_\Psi = \frac{k'_w + k'_m K_s[D_n]}{1 + K_s[D_n]} \quad (6)$$

The hydrolysis of procaine occurring in the micellar media of CTAB, DTAB, and TDTAB can be explained on the basis of the PIE model [21–23] in which Br^- ions are exchanged by OH^- ions from the micellar surface as its counterions. These OH^- ions bound to the micellar surface in the Stern region are reactive and participate in the hydrolysis of procaine. The exchange of Br_m^- and OH_w^- ions occurring at the micellar surface can be presented by the following equation:

$$OH_m^- + Br_w^- \overset{K_{OH}^B}{\rightleftharpoons} OH_w^- + Br_m^- \quad (7)$$

The equilibrium constant for the ion exchange process is given by

$$K_{OH}^{Br} = \frac{[OH_w^-][Br_m^-]}{[OH_m^-][Br_w^-]} \quad (8)$$

in which OH_m^-, OH_w^-, Br_m^-, and Br_w^- are the ions participating in the equilibrium around micellar surfaces as surfactant counterions; the subscript "w" represents the ions in aqueous medium and "m" the micellar medium.

The fraction of the micellar head group neutralized by OH_m^- and Br_m^- may be defined in terms of β and is given by

$$\beta = m_{OH} + m_{Br} \tag{9}$$

where m_{OH} and m_{Br} are the neutralized fractions of the micellar head groups with reactive (OH^-) and nonreactive (Br^-) ions:

$$m_{OH} = \frac{[OH_m^-]}{[D_n]} \tag{10}$$

$$m_{Br} = \frac{[Br_m^-]}{[D_n]} \tag{11}$$

Thus, on considering the equilibrium constant and reactive OH^- ions concentrations involved during the ion exchange process at the micellar head group, Eq. (6) can be written as

$$k_\psi = \frac{k_w[OH_T^-] + (k_m K_s - k_w)m_{OH}[D_n]}{1 + K_s[D_n]} \tag{12}$$

where

$$[OH_T^-] = [OH_w^-] + [OH_m^-] \tag{13}$$

Similarly,

$$[Br_T^-] = [Br_w^-] + [Br_m^-] \tag{14}$$

The following quadratic gave the value of m_{OH} at constant values of $[OH_T^-]$ and β at varying concentrations of surfactant $[D_n]$:

$$m_{OH}^2 + m_{OH}\left[\frac{[OH_T^-] + K_{Br}^{OH}[Br_T^-]}{(K_{Br}^{OH} - 1)[D_n]} - \beta\right] - \frac{\beta[OH_T^-]}{(K_{Br}^{OH} - 1)[D_n]} = 0 \tag{15}$$

Thus, with the help of the PIE model, the k_Ψ–[CTAB] profile (Fig. 5) was used to obtain various kinetic parameters, viz., k_m, K_s, and K_{Br}^{OH} using a computer program. The values of these parameters were observed to be in the similar order, as reported by Rodenas and Vera [21,22] and are given in Table I.

The hydrolytic reaction of procaine occurring in anionic SDS micelles is treated quantitatively by using the pseudophase model. On rearranging Eq. (6), we obtained the following equation:

$$\frac{1}{k'_w - k_\Psi} = \frac{1}{k'_w - k'_m} + \frac{1}{(k'_w - k'_m)K_s[D_n]} \tag{16}$$

The plot of $1/(k'_w - k_\Psi)$ versus $1/[D_n]$ gave a straight line (Fig. 6) with intercept at $1/(k'_w - k'_m)$ and slope $= 1/(k'_w - k'_m)K_s$. The values of k'_m and K_s were calculated using the values of the slope and intercept obtained for the above plot. These values are given in Table I. The values of K_s were found in the order SDS > DDTAB > CTAB > TDTAB. Tomida et al. [18] reported that procaine is associated with the SDS in both protonated (at lower pH) and free base (at higher pH) forms, whereas it is associated with polyoxyethylene ether, CTAB, and *N*-dodecyl betaine (NDB) micelles as a free base. All the studied cationic (CTAB and NDB), anionic (sodium lauryl sulfate, SLS), and nonionic (polyoxyethylene lauryl ether, PLE) surfactants inhibited the hydrolysis of procaine. Their order of inhibition followed the sequence SLS > CTAB > PLE > NDB. The inhibitive effect by cationic micelles is contrary to the electrostatic theory for the base-catalyzed hydrolysis of ester [24]. Meakin et al. [25] described that the inhibitive effect of cationic micelles for the hydrolysis of ethyl *p*-aminobenzoate and *p*-aminophenyl acetate is due to the electron-releasing effect of the -NH_2 group. Eriksson and Gilberg [26] on the basis of NMR studies suggested that the hydrolysis of a simple aromatic ester depends on the orientation manner of solubilizate on the micellar surface. The observed inhibitive effect of CTAB on the hydrolysis of 2-diethylaminoethyl 4-nitrobenzoate (*p*-nitro substituent of the *p*-amino group of procaine) [18] shows that the substituent -NO_2 does not play a significant role during the hydrolysis. Therefore, these observations suggest that the manner of orientation of procaine molecules on the micellar surface plays an important role in their rate of hydrolysis. The site of reaction, that is, the ester group, is either strongly adsorbed to the micellar cationic head group of $DDTA^+$, CTA^+, and $TDTA^+$,

Table I Kinetic Parameters Obtained for the Alkaline Hydrolysis of Procaine in Micellar Media

[Surfactant]	β	K_{Br}^{OH}	k_m (10^4 s^{-1})	K_s
SDS	–	–	2.24	5722
CTAB	0.8	16	4.44 ± 0.09	2400
DDTAB	0.8	16	8.13 ± 0.16	2800
TDTAB	0.8	16	6.65 ± 0.36	2000

Reaction conditions: [NaOH] = 0.30 mol dm^{-3}, [procaine] = 6.50×10^{-5} mol dm^{-3}, $k_1 = 3.45 \times 10^{-3}$ s^{-1} (in the absence of surfactant at 40.0 ± 0.1 °C), and temperature = 40.0 ± 0.1°C.

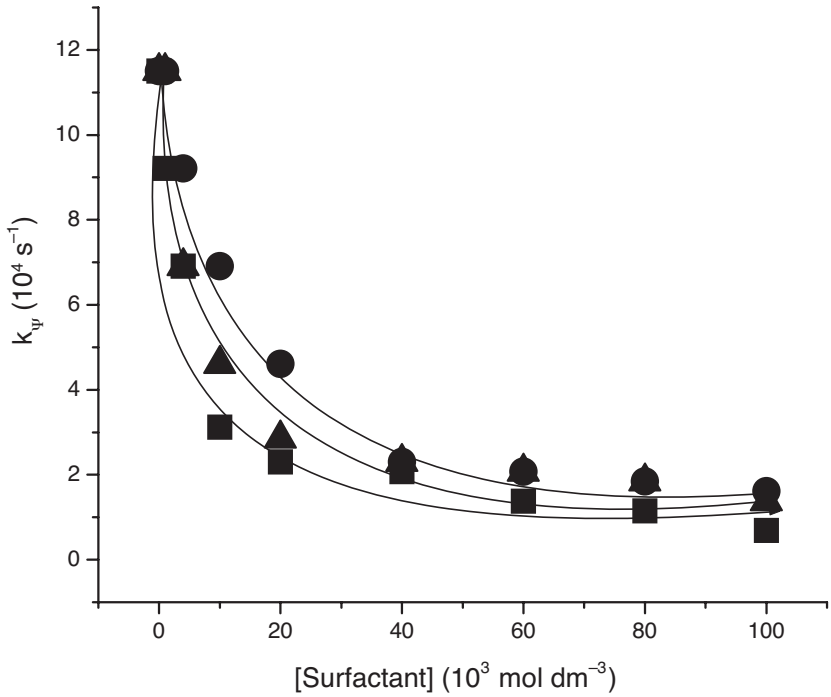


Figure 5 Plot of $k\Psi$ versus [surfactant] for the hydrolysis of procaine in micellar media of CTAB (■), TDTAB (▲), and DDTAB (●). Reaction conditions: [procaine] = 6.50×10^{-5}mol dm^{-3}, [NaOH] = 3.00×10^{-1} mol dm^{-3}, and temperature = 40.0 ± 0.1°C.

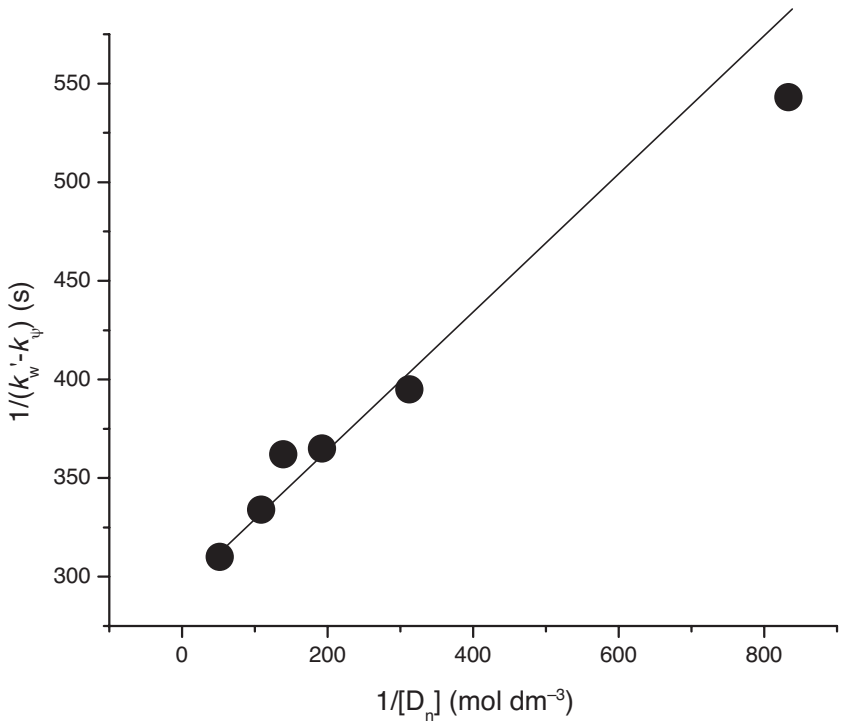


Figure 6 Plot of $1/(k'_w - k_\Psi)$ versus $1/[D_n]$ for the hydrolysis of procaine. Reaction conditions: [procaine] = 6.50×10^{-5}mol dm^{-3}, [NaOH] = 5.00×10^{-2} mol dm^{-3}, and temperature = 25.0 ± 0.1°C.

surface or solubilized inside the hydrophobic interior, and thereby decreases the rate of hydrolysis. The higher inhibitive effect of $DDTA^+$ may be due to better solubilization of the reactive ester group to the interior of micelle by possessing the longer hydrophobic chain. The lower inhibitive effect by $TDTA^+$ micelles may be attributed to its folding, resulting in weak binding of procaine to the micellar surface.

The inhibition by DS^- micelles is the result of the preferential binding of procaine onto the micellar surface/Stern region and expulsion of OH^- from the micellar region. The reactive part of procaine molecules binds to the hydrophobic hydrocarbon interior of the micelles, whereas negatively charged OH^-ions are repelled by the negatively charged micellar surface. Thus, the micelles of DS^- keep the reactive center of procaine and OH^-ions away from each other and slow the rate of hydrolysis. The order of binding constant (i.e., SDS > DDTAB > CTAB > TDTAB) for procaine with micelles is not in the same order for the rate of inhibition of the hydrolysis of procaine (i.e., SDS > CTAB > TDTAB > DDTAB). This may be due to the micelles of the different surfactants having different volume fractions in the micellar phase (at the same surfactant concentration). Among CTAB, TDTAB, and DDTAB surfactants, the binding constant is highest for DDTAB owing to its having a longer hydrocarbon chain; however, in TDTAB, the still longer hydrocarbon chain may result in folding to have less space for binding to procaine.

CONCLUSION

The alkaline hydrolysis of procaine yields *N*,*N*-diethylaminoethanol and *p*-aminobenzoate anion. The rate of hydrolysis under the pseudo–first-order conditions ($[OH^-] \gg$ [procaine]) has been found to be linearly dependent upon [NaOH]. The addition of cationic (CTAB, TDTAB, and DDTAB) and anionic (SDS) surfactants to the reaction mixture (procaine and sodium hydroxide) decreased the rate of hydrolysis. The maximum decrease in the rate constant was observed for SDS micelles. Among the cationic surfactants, CTAB inhibited the most. The orientation of reactive molecule to the surfactant, values of the binding constant, and volume fractions of micelles are attributed to the variation in the rate of hydrolysis of procaine in the micellar media. The hydrolytic rate becomes negligible in DDTAB micelles.

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