

Effect of colloidal self-assemblies on the basic hydrolysis of 2-(4-bromophenoxy)quinoxaline

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ABSTRACT: In the presence of cationic surfactants ($C_{16}H_{33}NR_3Cl$; $R = Me, n-Pr, n-Bu$), the shape of rate versus surfactant concentration profiles for the basic hydrolysis of 2-(4-bromophenoxy)quinoxaline depends on substrate concentration. At low substrate concentration there is a single rate maximum and with a 10-fold substrate concentration increase a double rate maximum is observed. The first rate maximum is ascribed to reaction occurring in premicellar aggregates and the second to reaction in micelles. At low substrate concentration the effect of surfactant head group size was examined. Second-order rate constants in the micellar pseudophase increase with increasing head group size. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: 2-(4-bromophenoxy)quinoxaline; hydrolysis; colloidal self-assemblies; micellar systems; cationic surfactants; kinetics

INTRODUCTION

The effect of premicellar assemblies and surfactant head group size upon reaction rates is currently of interest.^{1–5} In this work we are concerned with the role of associative colloids on nucleophilic heteroaromatic substitution reactions. To this end, we investigated the basic hydrolysis of 2-(4-bromophenoxy)quinoxaline (**1**) in the presence of cationic surfactants with different head group size and over a wide range of surfactant concentrations over and below the surfactant critical micelle concentration (cmc).

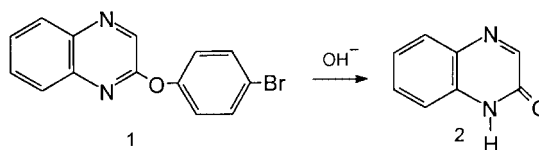
Micellar effects upon reaction rates and equilibria are generally described by using the pseudophase model.^{6–8} According to the model, micelles create a distinct reaction medium, a pseudophase, where reactions occur. Typically micelles accelerate bimolecular reaction of counter-ions and inhibit those of co-ions. Below the cmc surfactants are present as monomers and above the cmc as fully formed micelles. Previously, we examined the effect of micellar systems on the nucleophilic heteroaromatic substitution of some quinoxaline derivatives,^{3,9–12} and rate increases below the surfactant cmc were observed. In this work, we hoped to gain further insight into the structure of association colloids that affect the

basic hydrolysis of **1** and of the nature of the interactions between the substrate and the surfactant's head group. Reaction of **1** with OH^- was also followed in solutions of non-micellizing tri-*n*-octylalkylammonium ions. Substrate **1** is highly hydrophobic, binds strongly to micelles and its reaction can be easily followed by ultraviolet spectroscopy. Surfactants were hexadecyltrialkylammonium chlorides [$C_{16}H_{33}NR_3Cl$; $R = Me$ (CTACl), *n*-Pr, (CTPACl), *n*-Bu (CTBACl)]. The non-micellizing ammonium salt was tri-*n*-octylammonium mesylate (TOAMS).

RESULTS AND DISCUSSION

Reaction in water

Compound **1** hydrolyzes to form 2-quinaxolone (**2**) at 25.0°C (Scheme 1). The basic hydrolysis was studied following the appearance of product **2** at 362 nm. The second-order rate constant value is $9.1 \times 10^{-2} \text{ l mol}^{-1} \text{ s}^{-1}$.



Scheme 1

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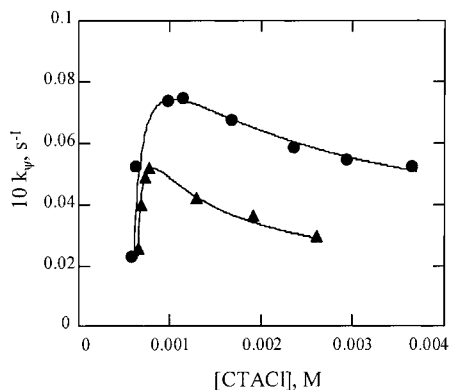
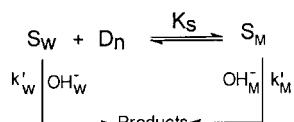


Figure 1. Basic hydrolysis of **1** in CTACl. (\blacktriangle) With 0.002 M NaOH; (\bullet) with 0.02 M NaOH. [Substrate] = 8.0×10^{-6} M



Scheme 2

Reaction in micelles

Figures 1–3 show the observed rate versus surfactant concentration profiles for the alkaline hydrolysis of **1** at low substrate concentration (8.0×10^{-6} M) and in the presence of CTACl, CTPACl and CTBACl.

Rate versus concentration profiles show a single rate maximum, a common feature of micelle-modified bimolecular reactions. After the initial catalytic acceleration at low surfactant concentration, the rate constant values tend to decrease as the surfactant concentration increases owing to dilution of the reagents in the micellar pseudophase.

The results for the hydrolysis of **1** in cationic micelles at low substrate concentration can be described in terms of Scheme 2, where S is the substrate, D_n is the micellized

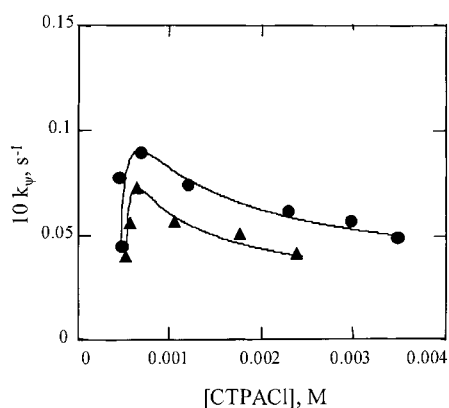


Figure 2. Basic hydrolysis of **1** in CTPACl. (\blacktriangle) With 0.002 M NaOH; (\bullet) with 0.02 M NaOH. [Substrate] = 8.0×10^{-6} M

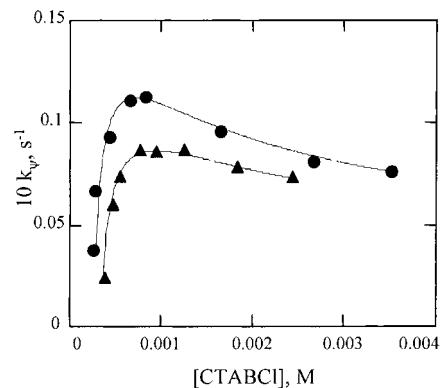


Figure 3. Basic hydrolysis of **1** in CTBACl. (\blacktriangle) With 0.002 M NaOH; (\bullet) with 0.02 M NaOH. [Substrate] = 8.0×10^{-6} M

surfactant, i.e. $[D_n] = [D] - \text{cmc}$ (the cmc is taken as the concentration of the monomeric surfactant), K_S is the substrate binding constant and k'_W and k'_M are first-order rate constants in the aqueous and micellar pseudophase, respectively. The first-order rate constant is given by⁶

$$k_\Psi = \frac{k'_M K_S [\text{OH}_M^-]}{1 + K_S [D_n]} \quad (1)$$

First-order rate constants can be written as second-order rate constants, k_W and k_M , with the concentration of OH^- in the micellar pseudophase written as a mole fraction:

$$k'_W = k_W [\text{OH}_W^-] \quad (2)$$

$$k'_M = k_M m_M^{\text{OH}} = k_M [\text{OH}_M^{\text{OH}}] / [D_n] \quad (3)$$

$[\text{OH}_W^-]$ is a molarity in terms of total solution volume. In order to quantify the micellar effect under these specific reaction conditions, we applied a mass action model proposed by Bunton and co-workers.¹³ Micellar binding of OH^- and Cl^- is assumed to follow the equations,¹³

$$K'_{\text{OH}} = [\text{OH}_M^-] / \{([\text{OH}_W^-]([D_n] - [\text{OH}_M^-] - [\text{Cl}_M^-]))\} \quad (4)$$

$$K'_{\text{Cl}} = [\text{Cl}_M^-] / \{([\text{Cl}_W^-]([D_n] - [\text{OH}_M^-] - [\text{Cl}_M^-]))\} \quad (5)$$

Table 1 shows the estimated rate constants in the micellar pseudophase and the values of the parameters that best fit the experimental results for hydrolysis of **1** in cationic micelles and at low substrate concentration. Solid lines in Figs 1–3 represent the values of k_Ψ calculated with these parameters by Eqns ((1)–(5)). The fit of theory and experiment is reasonably good. k_M and K_S were treated as adjustable parameters although the fitting is relatively insensitive to K_S values. k_W and k_M are second-order rate constants, the units of k_W are $\text{l mol}^{-1} \text{s}^{-1}$ following the usual convention, but concentration of the nucleophile in the micelles is written as a mole ratio, so that dimensions of k_M are s^{-1} [Eqn. (3)]. This

Table 1. Parameters that best fit the kinetic results for substrate **1** in micelles^a

Surfactant	$10^2 [\text{OH}^-_{\text{T}}]$ (M)	K'_{Cl} (l mol^{-1})	10^4cmc (M)	k_{M} (s^{-1})	$10 k_2^{\text{m}}$ ($\text{l mol}^{-1} \text{s}^{-1}$)
CTACl	0.2	115	7	0.84	1.2
CTACl	2.0	115	7	0.84	1.2
CTPACl	0.2	60	5	1.2	1.7
CTPACl	2.0	60	5	1.2	1.7
CTBACl	0.2	48	4	2.9	4.1
CTBACl	2.0	48	4	2.9	4.1

^a At 25.0 °C and with $K_{\text{S}} = 9000 \text{ l mol}^{-1}$, $k_{\text{W}} = 9.1 \times 10^{-2} \text{ l mol}^{-1} \text{ s}^{-1}$, $K'_{\text{OH}} = 55, 25$ and 12 l mol^{-1} for CTA^+ , CTPA^+ and CTBA^+ , respectively.^{5d} $[\text{Substrate}] = 8.0 \times 10^{-6} \text{ M}$.

concentration can be written as molarity with molar volume V_{M} , and the second-order rate constant, k_{M} , $\text{l mol}^{-1} \text{ s}^{-1}$, is given by^{7b}

$$k_2^{\text{m}} = k_{\text{M}} V_{\text{M}} \quad (6)$$

Estimates of V_{M} range from 0.14 to 0.371,^{7,8} and in this report the lower limit was selected. The second-order rate constant in the micellar pseudophase increases as the surfactant head group size increases (Table 1). Several factors may alter reaction rates when using surfactants with bulky head groups. The observed micellar rate increase with increase in head group size might be due to the disruption of hydroxide ion hydration in the more hydrophobic interfacial region. The local concentration of water in the interfacial region decreases as the head group bulk increases, increasing OH^- nucleophilicity in this region. Another possible factor is interfacial polarity changes with head group size. Interfacial region polarity is known to decrease with bulky head groups. There is evidence that micelles favor reactions in which there is extensive charge dispersion in the transition state, and that the discrimination increases with increasing bulk of the surfactant head group.^{5c,14}

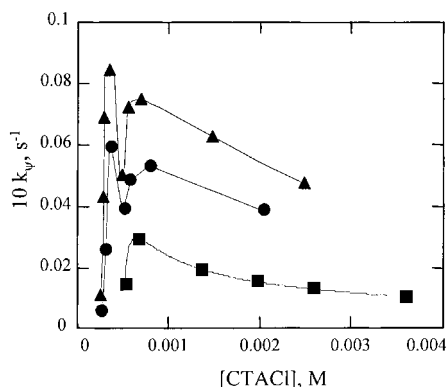


Figure 4. Basic hydrolysis of **1** in CTACl. (■) With 0.002 M NaOH; (▲) with 0.02 M NaOH; (●) with $[\text{NaCl}] = 0.025 \text{ M}$ and $[\text{NaOH}] = 0.02 \text{ M}$. $[\text{Substrate}] = 8.0 \times 10^{-5} \text{ M}$

Reaction in colloidal self-assemblies

Figures 4–6 show the rate versus concentration profiles for the alkaline hydrolysis of **1** with a 10-fold increase in substrate concentration, $8.0 \times 10^{-5} \text{ M}$, and in the presence of CTACl, CTPACl and CTBACl, respectively. The profiles show four distinctive characteristics: (a) double rate maxima, (b) rate increases below the cmc, (c) the first rate maximum is higher than the second rate maximum and (d) double rate maxima disappear with added salt. One possible explanation for the observed characteristics is that substrate hydrophobicity induces micellization and, consequently, there are rate effects below the surfactant cmc; however, this rationalization does not explain the observed double rate maxima. Another possibility is that at very low surfactant concentration, surfactants self-aggregate forming associative complexes, which bind the substrate and speed the reaction rate. These pre-micellar aggregates disappear as micelles form and take up the substrate, hence the first rate maximum is ascribed to reaction in pre-micelles. As the surfactant concentration increases, the rate maximum disappears as micelles form and dissolve the pre-micellar complexes. The presence of double rate maxima has been observed previously for other micellar-catalyzed reactions.^{2,3} Rate versus concentration profiles for the

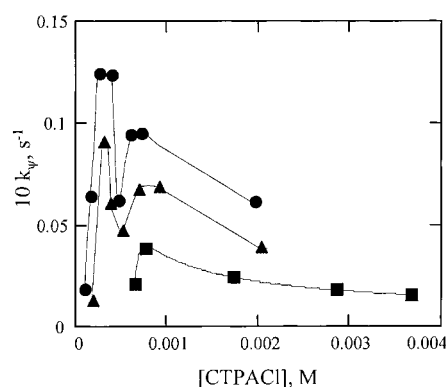


Figure 5. Basic hydrolysis of **1** in CTPACl. (▲) With 0.002 M NaOH; (●) with 0.02 M NaOH; (■) with $[\text{NaCl}] = 0.025 \text{ M}$ and $[\text{NaOH}] = 0.02 \text{ M}$. $[\text{Substrate}] = 8.0 \times 10^{-5} \text{ M}$

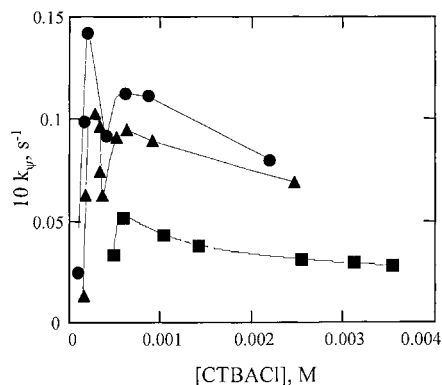


Figure 6. Basic hydrolysis of **1** in CTBACl. (▲) With 0.002 M NaOH; (●) with 0.02 M NaOH; (■) with [NaCl] = 0.025 M and [NaOH] = 0.02 M. [Substrate] = 8.0×10^{-5} M

alkaline hydrolysis of 4-chlorophenoxy- and 2-fluorophenoxyquinoxaline show a double rate maximum at high substrate concentration.^{3,15} It is known that the pseudophase model fails near the cmc mainly because of the pseudophase assumptions.^{7b,8} One of those assumptions is that there are no interactions between the substrate and the monomeric surfactant, so that the concentration of micellized surfactant can be related to that of total surfactant in terms of the cmc.^{6,7b,8} The present and previous data^{3,15} support the idea that at very low surfactant concentrations the quaternary ammonium head group interacts with quinoxaline derivatives, probably by polarizing its π electron cloud.

Observed rate values for the basic hydrolysis of **1** are lower in the presence of fully formed micelles than in the presence of clustered surfactants. These clusters are more effective than micelles in promoting the reaction. In the presence of cationic surfactants, there should be a strong interaction between the cationic head group and the quinoxaline π electron cloud that induces the formation of hydrophobic tight ion pairs or associative complexes that attract further substrate molecules. Added salts suppress the double maxima by inducing micellization.

Some experiments were performed in the presence of the highly hydrophobic salt trioctylmethylammonium mesylate (TOAMs, Fig. 7) with 8.0×10^{-5} M substrate concentration and 0.02 M NaOH. The ammonium salt aggregates, forming supramolecular structures, but they do not form micelles. The physical properties of solutions of these ammonium salts do not change with aggregation. The tetralkylammonium salt accelerates the basic hydrolysis of **1** (Fig. 7). This result provides evidence for the existence of pre-micellar particles that are able to associate with the substrate and increase the reaction rate.

The results from the present study allow us to make some general remarks concerning future work on nucleophilic heteroaromatic substitution reactions assisted by both micelles and, more efficiently, by submicellar aggregates. For micellar catalyzed reactions

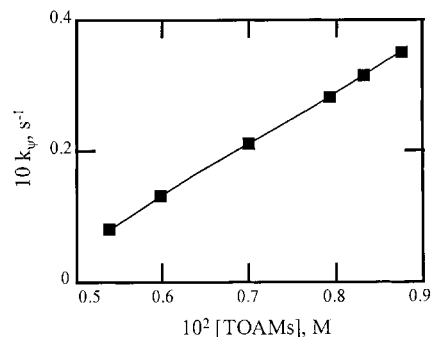


Figure 7. Basic hydrolysis of **1** in TOAMs, with 0.02 M NaOH. [Substrate] = 8.0×10^{-5} M

it is important to make a distinction between reactions favored by both micelles and submicellar aggregates. There are relatively few systems where this distinction could be made.^{2,3} Observation of rate extrema in the basic hydrolysis of quinoxaline derivative **1** allows us to distinguish between these possibilities. At surfactant concentrations close to the cmc, pre-micellar complexes are important in most surfactant-mediated reactions. However, double rate maxima are observed only with hydrophobic and polarizable substrates such as **1**, which interacts with hydrophobic ammonium ions.

In the present study, data analysis indicated that pre-micelles are much better catalysts than cationic micelles. In dilute surfactant solutions, substrate **1** induces the formation of submicellar clusters and alters their catalytic effectiveness.

For micellar assisted reactions, it is reasonable to analyze micellar rate effects in terms of the distribution of reactant between water and micelles only if the reaction is followed under conditions where the existence of submicellar clusters is disproved. It is very easy to miss double rate maxima unless a large number of data points are taken near the cmc. Studies of surfactant effects on reaction rates should cover a wide range of surfactant concentrations below and above the surfactant cmc in order to identify the nature and role of the supramolecular structures affecting rates.

The following conclusions can be drawn for the alkaline hydrolysis of **1** in the presence of cationic surfactants: (a) submicellar assemblies activate the substrate toward nucleophilic substitution but micelles assist reaction by concentrating both reactants in the small volume of the Stern layer; (b) rate-surfactant concentration profiles depend on substrate concentration; (c) pre-micellar particles are catalytically more effective than micelles; and (d) bulky head groups increase nucleophile reactivity.

EXPERIMENTAL

Materials. The preparation and purification of the

substrate have been described.¹⁶ The surfactants were samples used in earlier work.³ In neutral solution, a condition where the spontaneous hydrolysis of **1** is negligible, cmc values were determined in the presence of the substrate and from plots of surface tension versus log[surfactant] (Table 1). Surface tensions were measured at room temperature on a Fisher du Noüy-type tensiometer.

Kinetics. Reactions were followed spectrophotometrically at 362 nm following the appearance of product **2** at 25.0°C in a Perkin-Elmer Lambda II spectrometer. Substrate was added as a freshly prepared solution in MeCN so that the final reaction solution contained 0.1% MeCN. Observed rate constants are given in reciprocal seconds. Values of k_{ψ} were calculated by using the integrated first-order rate equation with correlation coefficients of 0.999 or better. Some reactions were run following the appearance of 4-bromophenoxide ion at 243 nm; rate values are within 3% agreement with values measured at 362 nm. Reaction solutions were prepared in distilled, deionized, CO₂-free water.

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