Surfactant Effects on the Reaction of 2-(4-Cyanophenoxy)-Quinoxaline with Hydroxide Ion

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ABSTRACT: A reaction of 2-(4-cyanophenoxy)quinoxaline **1** with hydroxide ion is accelerated by supramolecular aggregates of cetyltrialkylammonium chlorides (alkyl = Me, *n*-Pr, and *n*-Bu). In diluted surfactant solutions, with relatively high substrate concentration (7.0×10^{-5} M), rate constants go through double rate maxima with increase in the surfactant concentration. The first rate maximum is ascribed to a reaction occurring in premicellar aggregates and the second to reaction in micelles. At low substrate concentration (7×10^{-6} M), second-order rate constants in the micellar pseudophase are dependent on the surfactant head-group size, which is related to charge dispersion in the transition state. Nonmicellizing tri-*n*-octylmethylammonium ions (TOAMs) increase the reaction of **1** with hydroxide ion. The observed rate enhancements may be due to the formation of small, hydrophobic aggregates which bind the substrate and promote the nucleophilic substitution reaction. © 2006 Wiley Periodicals, Inc. Int J Chem Kinet 38: 510–515, 2006

INTRODUCTION

Previous studies [1,2] of nucleophilic heteroaromatic substitution of quinoxaline derivatives in the presence of cationic surfactants have provided evidence for the existence of submicellar aggregates that are able to affect reaction rates. In aqueous media, ionic surfactants self-aggregate to form supramolecular structures that bind reactants and alter reactivity [1–6]. Micellar effects on reaction rates and equilibria are generally described by a pseudophase model which treats water and micelles as distinct reaction media [3–5]. The pseudophase model considers reaction either in water or in micelles, and predicts for bimolecular reactions single rate maxima in the rate versus surfactant profiles. The model is known to fail near the critical micelle concentration (cmc) due to the pseudophase assumption [3]. One of the premises of the model is that there should be no interactions between the monomeric surfactant and the substrate, although there are evidences that they interact at surfactant concentrations below the surfactant cmc [1,2,7–9].

In this study, we address the question of what factors allow surfactant self-assemblies to alter reaction rates. Nucleophilic heteroaromatic substitution of 2-(4-cyanophenoxy)quinoxaline **1** (Scheme 1) with OH^- was examined over a wide range of surfactant concentrations, above and below the surfactant

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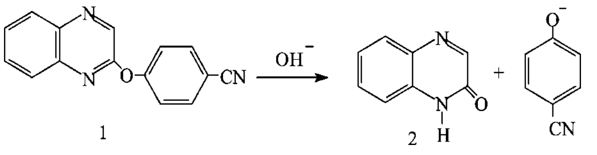


Scheme 1

cmc. Surfactants were hexadecyltrialkylammonium chlorides, $C_{16}H_{33}NR_3Cl$, R = Me (CTACl), R = *n*-Pr (CTPACl), and R = *n*-Bu (CTBACl).

EXPERIMENTAL

Materials

Compound **1** was synthesized in previous studies [10]. Preparation of TOAMs has been described in [11]. Surfactants were synthesized in the earlier work [12]. cmc values were determined by variations in surface tension. In water, cmc values for CTACl and CTBACl are 1.3 and 0.52 mM, respectively.

Kinetics

Kinetic measurements were performed at 25.0°C in a thermostatically controlled cell compartment of a Perkin Elmer, lambda II spectrophotometer. Substrate was added in MeCN so that the final solution contained 0.2 vol% organic solvent. Reactions were followed in redistilled carbon dioxide free water. First-order rate constants, k_ψ, are in reciprocal seconds. The reaction was followed to infinity (10 half-lives) with correlation coefficients ≥ 0.999. Rate constants are mean of three measurements and agreed within 4%.

RESULTS AND DISCUSSION

Reaction in Water

In water, compound **1** reacts with OH^- to produce 2-quinoxalone **2** (Scheme 1). The reaction of **1** with hydroxide ion was followed at 362 nm by monitoring of 2-quinoxalone **2** at 362 nm. At 25.0°C, the second-order rate constant value for the reaction of compound **1** with hydroxide ion is $2.17 \times 10^{-3}\ M^{-1}\ s^{-1}$. In some cases, reactions were also followed by monitoring the appearance of 4-cyanophenoxide ion at 276 nm. Kinetic rate constants obtained by monitoring λ_{max} were in agreement within 3% error.

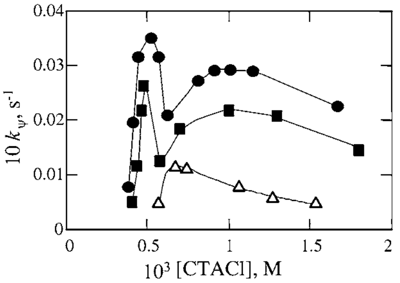


Figure 1 Reaction of compound **1** (7.0×10^{-5} M) with hydroxide ion in the presence of CTACl. ● [NaOH] = 0.03 M; ■ [NaOH] = 0.003 M; △ [NACl] = 0.025 M.

Rate-Surfactant Profiles

Reaction at High Substrate Concentration. Figures 1 and 2 show reaction of **1** (7.0×10^{-5} M) with OH^- (0.003 and 0.03 M) in the presence of CTACl and CTBACl, respectively. At this relatively high substrate concentration, first-order rate constants, k_ψ, for the reaction of **1** with hydroxide ion go through double rate maxima as surfactant concentration increases. Rate effects occur at surfactant concentration below surfactant's cmc in water. Reactions in the presence of CTPACl show the same general tendencies. Double rate maxima are suppressed on addition of NaCl.

Hydrophobic organic substrates such as **1** lower the surfactant cmc by inducing micellization, but this behavior does not explain the observed double rate maxima. A possible interpretation for the observed result is that, in diluted surfactant solutions, the surfactant aggregation induces the formation of premicelles that interact with hydrophobic compound **1** and promotes its nucleophilic substitution.

Surfactant self-association increases rates of bimolecular reactions in different ways [3,8]. Ionic micelles speed bimolecular reactions by bringing reactant together at the micellar surface. Premicelles may activate compound **1** toward hydroxide ion through the formation of transient substrate–ammonium ion complexes. This behavior seems to be associated with

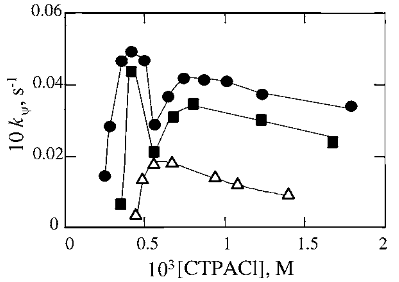


Figure 2 Reaction of compound **1** (7.0×10^{-5} M) with hydroxide ion in the presence of CTBACl. ● [NaOH] = 0.03 M; ■ [NaOH] = 0.003 M; △ [NACl] = 0.025 M.

sparingly water-soluble, hydrophobic substrates whose association with amphiphilic ions decreases hydrocarbon water contact and provides ion–dipole interactions. Substrate hydrophobicity seems to be necessary, but not a sufficient condition for the observation of double rate maxima. A single rate maxima is generally observed for most micellar-assisted reactions. A specific interaction between cationic headgroups and solute might explain the double rate maxima if this interaction leads to the formation of premicelles. It is known that quaternary ammonium headgroups interact favorably with arenes [7,13]. Submicellar aggregates are involved in some nucleophilic aromatic [8] and heteroaromatic [1,2] substitution reactions, and in the attack of OH^- on thiophosphinates [14] where double rate maxima are observed in rate versus surfactant profiles.

The dependence of the first-order apparent rate constant with solute concentration suggests that small aggregates of reactants and surfactant are present in solution, rather than 1:1 adducts, and it appears that there is a cooperative interaction between catalyst and reactants. Micelles have well-defined structures which are not markedly perturbed by addition of substrate, but structures of small submicellar aggregates are probably very sensitive to low concentration of solutes which may bind to them. In diluted surfactant, k_ψ increases with the substrate concentration, and therefore the formation of catalytically active submicellar clusters might be induced by the substrate. Compound **1** may interact with amphiphilic cations to form clusters or premicelles that would attract more hydrophobic solute. Both substrate binding and chemical reactivity should increase with the increasing cluster size.

Rates in premicelles should be much faster than in water if pairing between cationic headgroup and hydroxide ion partially excludes water from the latter. Premicelles must have a significant rate effect, because if these assemblies were kinetically less effective than micelles, rates will increase monotonically to a single rate maximum as premicelles are converted into micelles. One remarkable difference between catalysis by micelles and premicelles is that at a given concentration, micelles are relatively uniform in size and their structures are not very sensitive to reactants, provided that the surfactant concentration is in large excess over reactants. In diluted surfactant solution and at relatively high substrate concentration, the surfactant aggregation may be assisted by a cooperative interaction with solute, whereas micellization does not require such an interaction.

Values of the first rate maxima are higher than those of the second maxima (Figs. 1 and 2). In Table I a comparison is been made between rates in micelles, k_{mic}, and in premicelles, k_{pre}. k_{pre} was estimated in very diluted surfactant solutions by equalizing its value to the highest value of k_ψ (first maximum). Measurements of k_{mic} were made at surfactant concentrations well above the cmc, where compound **1** was fully micellar bound. Results show that reactions in premicelles are faster than in micelles. This result is consistent with a very strong interaction between substrate and surfactant in premicelles, and a relatively loose organization of substrate in the water-rich interfacial region of a cationic micelle.

Figures 1 and 2 show the suppression of the double rate maxima by addition of NaCl. Chloride ion inhibits reaction by competing with OH^- and decreases the cmc converting submicellar aggregates into micelles. Hydroxide ion is a hydrophilic ion with high charge density that is probably weakly bound to submicellar aggregates as it has been found with cationic micelles [15].

Figure 3 shows the first-order rate constants for the reaction of compound **1** with hydroxide ion in the presence of nonmicellizing mesylates. Tri-*n*-octylmethylammonium ions (TOAMs) speed the reaction of compound **1** with hydroxide ion, although these ions do not form micelles. Observed rate enhancements may be due to the formation of clusters of hydrophobic ammonium ions which associate with the substrate

Table I Reaction of Compound **1** with Hydroxide Ion in Micelles and Premicelles[a]

		$\times 10^3 k_\psi$ (s^{-1})	
$\times 10^2$ NaOH (M)	Surfactant	Micelles (k_{mic})	Premicelles[b] (k_{pre})
0.3	CTAC	2.1	2.5
3.0	CTAC	2.9	5.1
0.3	CTPAC	3.2	4.2
3.0	CTPAC	4.1	4.8
0.3	CTBAC	5.3	6.6
3.0	CTBAC	4.4	5.5

[a] At 25.0°C and with 7.0×10^{-5} M substrate.

[b] Values are from maximum values of k_ψ in Figs. 1 and 2.

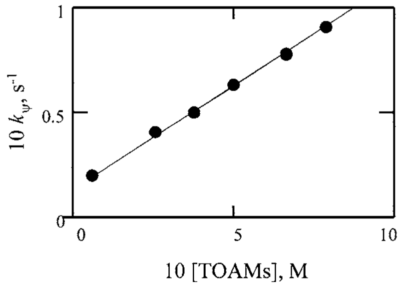


Figure 3 Reaction of compound **1** (7.0×10^{-5} M) with hydroxide ion in the presence of TOAMs. [NaOH] = 0.03 M.

and activate it toward nucleophilic heteroaromatic substitution. Rate enhancements by these nonmicellizing salts have been observed in other bimolecular reactions [1,3,11] and decarboxylation [16]. Compound **1**'s solubility is largely increased on addition of very small amounts of TOAMs suggesting an association between the substrate and the hydrophobic cations.

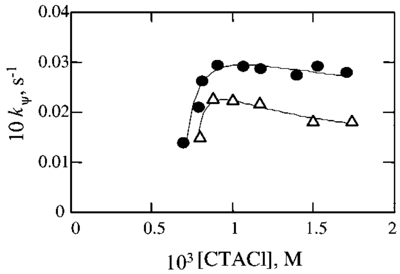


Figure 4 Reaction of compound **1** (7.0×10^{-6} M) with hydroxide ion the presence of CTACl. ● [NaOH] = 0.03 M; Δ [NaOH] = 0.003 M. Curves are calculated.

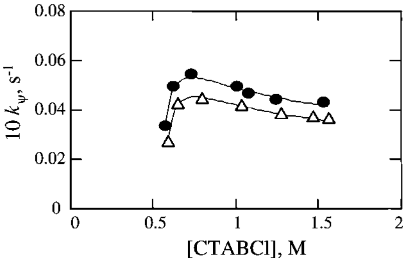
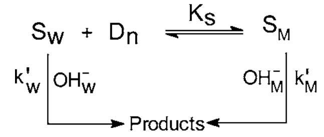


Figure 5 Reaction of compound **1** (7.0×10^{-6} M) with hydroxide ion the presence of CTACl. ● [NaOH] = 0.03 M; Δ [NaOH] = 0.003 M. Curves are calculated.



Scheme 2

Reaction at Low Substrate Concentration. At relatively low substrate concentration (7.0×10^{-6} M), rate versus surfactant concentration profiles for the reaction of compound **1** with hydroxide ion show a single rate maximum (Figs. 4 and 5), a typical behavior for micellar assisted bimolecular reactions [3,5]. Reactions in CTPACl show the same general tendencies. Under these reaction conditions, nucleophilic heteroaromatic substitution of compound **1** with OH^- occurs in micelles. At low substrate concentration, rate-surfactants profiles can be fitted quantitatively to equations which describe reactant distributions in terms of Scheme 2, where subscripts "w" and "M" denote the aqueous and micellar pseudophase, S is the substrate, OH^- is the nucleophile, K_S is the substrate–surfactant binding constant, D_n is the micellized surfactant whose concentration usually is taken as that of total less monomeric surfactant. k'_W and k'_M are, respectively, the first-order rate constants in aqueous and micellar pseudophases.

The overall observed first-order rate constant, k_ψ, is given by Eq. (1) [4]:

$$k_\Psi = \frac{k'_M K_s[OH^-_M]}{1 + K_S([D_n] - \mathrm{cmc})} \tag{1}$$

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:

$$k'_W = k_W[OH^-_W] \tag{2}$$

$$k'_M = k_M m_M^{OH} = k_M[OH_M^{OH}]/([D] - \mathrm{cmc}) \tag{3}$$

$[OH^-{}_w]$ is molarity in terms of total solution volume.

At low substrate concentration, rate data for reaction of OH^- with compound **1** in solutions of cationic surfactants can be described using a pseudophase model (Eqs. (1)–(3)), in which the distribution of OH^- and Cl^- between the aqueous and micellar pseudophases is written in terms of the mass-action-like equations (4) and (5) [15]

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

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

Table II gives values of the parameters that best fit the experimental results for the reaction of compound **1** in cationic micelles. Solid lines in Figs. 4 and 5 represent values of k_Ψ calculated using these parameters by Eqs. (1), (4), and (5). At low substrate concentration,

Table II Fitting Parameters for the Reaction of Substrate **1** with Hydroxide Ion in Micellized Surfactants[a]

Surfactant	$\times 10^2$ [OH_T^-] (M)	K'_{Cl} (M^{-1})	$\times 10^4$ cmc (M)	k_M (s^{-1})	$\times 10k_2{}^m$ (M^{-1} s^{-1})
CTACl	0.3	115	6	1.9	2.5
CTACl	3.0	115	6	1.9	2.5
CTPACl	0.3	60	4	4.1	5.7
CTPACl	3.0	60	4	4.1	5.7
CTBACl	0.3	48	3	5.2	7.2
CTBACl	3.0	48	3	5.2	7.2

[a] At 25.0°C and with $K_s = 9500$ M^{-1}, $k_W = 2.17 \times 10^{-3}$ M^{-1} s^{-1}, $K'_{OH} = 55$, 25, and 12 M^{-1} for CTA^+, $CTPA^+$, and $CTBA^+$, respectively.[15] [Substrate] $= 7.0 \times 10^{-6}$ M.

the model adequately describes rate data for reactions of OH^- with compound **1**, as shown in Figs. 4 and 5. The Langmuir parameters, K_{OH}, are from the literature [17] ($K'_{OH} = 55$ and 12 for CTA^+ and $CTBA^+$, respectively). K'_{Cl}, k_M, and K_S were treated as adjustable parameters. Kinetic cmc values are 7×10^{-4} M, 5×10^{-4} M, and 4×10^{-4} M for CTACl, CTPACl, and CTBACl, respectively, and with 0.03 M NaOH and 7.0×10^{-6} M substrate concentration.

Second-order rate constant, k_M, for the reaction in the micellar pseudophase has dimensions of reciprocal time, and cannot be compared directly with second-order rate constant in water, k_W, the units of which are generally M^{-1} s^{-1}. Second-order rate constants in the micellar pseudophase with the same dimensions, k_2^m, M^{-1} s^{-1} are given by Eq. (6):

$$k_2^m = k_M V_M \tag{6}$$

where V_M is the molar volume of the reactive region at the micellar surface, and the value $V_M = 0.14$ L was taken (estimates of V_M range from 0.14 to 0.35 L) [5b]. Values of k_2^m are based on constant V_M. This value may increase with increasing bulk of the alkyl group. However, for reactions in hexadecyltributylammonium bromide, Bacaloglu et al. [18] found NMR evidence that indicates that V_M does not change markedly with alkyl group bulk because butyl groups do not extend into the water but are "folded-back" toward the micellar surface to reduce water-alkyl group contact.

Substrate orientation or location may also be influenced by headgroup size. Increase in the bulk of the surfactant headgroup should move the reaction center more deeply into the interfacial region.

Rate enhancements for the alkaline hydrolysis of compounds **1** follow the sequence: CTACl < CTPACl < CTBACl (Table II). Several factors may alter the rate of a reaction occurring in micelles with bulky headgroups. There is evidence that headgroup effects on reactivities are larger for bimolecular reactions which have extensive charge delocalization in the transition state as in aromatic nucleophilic substitution and E2 reactions [19]. The extent of the effect is increased by increasing bulk of the surfactant headgroup. For the nucleophilic heteroaromatic substitution of compound **1** with OH^-, there should be extensive charge dispersion in the transition state through the quinoxaline π system, consequently micellar assistance should increase with the bulk of the headgroup.

In conclusion, studies of surfactant effects upon reaction rates should cover a wide range of surfactant concentration below and above the surfactant cmc in order to identify the nature and role of the supramolecular structures affecting rates. In very diluted surfactant solutions, quinoxaline derivative **1** forms associative complexes with submicellar aggregates. These surfactant clusters do not form a discrete reaction region but promote reactivity by their association with the substrate. An increase in the headgroup size favors nucleophilic heteroaromatic substitution reactions where charge is dispersed in the transition state.

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