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Micellar Effects upon the Alkaline Hydrolysis of 2-(3-Nitrophenoxy)quinoxaline. Effects of Cationic Head Groups.

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***Abstract*:** The rate of alkaline hydrolysis of the novel compound 2-(3-nitrophenoxy)quinoxaline **1** increases with increasing head group size in a series of cationic micellized surfactants ($C_{16}H_{33}NR_3Cl$ and $C_{16}H_{33}NR_3OH$: R = Me, Et, *n*-Pr and *n*-Bu). The reactivity increase with increasing head group size is related to the disruption of the hydration of hydroxide ion. © 1997 Elsevier Science Ltd.

INTRODUCTION

Micelle formation is a non-specific phenomenon that requires that the hydrophobic effect overcomes a net repulsive force between head groups which is reduced by absorption of counter-ions at the micellar surface. Consequently, micelle formation and its effects upon organic reactions is a function of many variables including surfactant concentration and head group type.[1,2] Recently there has been considerable interest on the effect on reaction rates of variation of the micellar head group size.[3-5] The rate of hydroxydehalogenation of 1-chloro-2,4-dinitrobenzene in cetyltrialkylammonium bromide micelles increases as the size of the alkyl groups in the micellar head group increases.[4a] However, for ionic substrates, *e.g.* sodium 2-chloro-3,5-dinitrobenzoate and sodium 4-chloro-3,5-dinitrobenzoate, the magnitude of catalysis decreased as the size of the micellar head group was increased. The second-order rate constants at the micellar surface and the overall rate constants for the reaction of methyl naphthalene-2-sulfonate with Cl^- or Br^- increase with increasing bulk of the surfactant *N*-alkyl group.[5b] Although an increase in the size of the alkyl group decreases the concentration of counter-anions at the micellar surface the overall rate constants of substitution increase.

Rate effects of micellar systems are generally explained in terms of pseudophase models.[1,2,6,7] Reaction occurs in water or at colloidal surfactants that are treated as distinct reaction media. In many systems both reactive and inert counter-ions are present and compete for the micellar surface.[2,6,7] This competition can be described by equations similar to those applied to binding to ion-exchange resins or by equations that include both Coulombic and specific-micelle-ion interactions.[2] The competition is eliminated when reactive ion is the surfactant counter-ion.[8]

In this report, the effect of surfactant head group size upon the basic hydrolysis of the novel compound 2-(3-nitrophenoxy)quinoxaline **1** was investigated in the presence of micellized surfactants that contain non reactive and reactive counter-ion. The surfactants used were cetyltrialkylammonium chlorides ($C_{16}H_{33}NR_3Cl$: R = Me, CTACl; Et, CTEACl; *n*-Pr, CTPACl; *n*-Bu, CTBACl) and cetyltrialkylammonium hydroxides

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($C_{16}H_{33}NR_3OH$: R = Me, CTAOH; Et, CTEAOH; *n*-Pr, CTPAOH; *n*-Bu, CTBAOH).

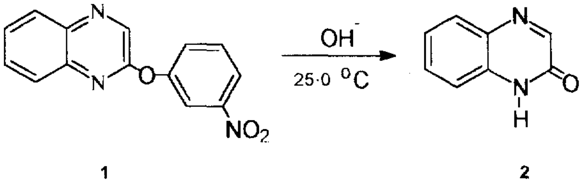
Little work has been published[3a,9-11] so far on the effect of micellar systems upon nucleophilic heteroaromatic substitution upon quinoxaline derivatives, which have synthetic,[12] pharmacological,[13] agricultural[14] and analytical[15] applicability.

Nucleophilic heteroaromatic substitution occurs readily upon quinoxaline derivatives on account of "aza" activation of the heterocyclic ring.[12a,16]

RESULTS AND DISCUSSION

Reactions in the Absence of Surfactant.

The alkaline hydrolysis of 2-(3-nitrophenoxy)quinoxaline **1** leads to the formation of 2-quinoxalone (**2**) (Scheme 1). Repetitive scanning of the spectrum of the reaction mixture showed that no intermediate built up during reaction. The second-order rate constant, k_w, for the basic hydrolysis of **1** at 25.0 °C is 10.2×10^{-2} M^{-1} s^{-1}.



Scheme 1

Reactions in the Presence of Surfactants.

Micellized cetyltrialkylammonium chlorides ($C_{16}H_{33}NR_3Cl$: R = Me, CTACl; R = Et, CTEACl; R = *n*-Pr, CTPACl; R = *n*-Bu, CTBACl) speed the basic hydrolysis of compound **1**. The observed catalysis increased as the size of the micellar head group was increased (Figures 1-4). First-order rate constants increase with increasing surfactant concentration and go through maxima at constant OH^- concentration.

Figures 5-8 present rate constant data for the alkaline hydrolysis of **1** in micellized cetyltrialkylammonium hydroxide ($C_{16}H_{33}NR_3Cl$: R = Me, CTAOH; R = Et, CTEAOH; R = *n*-Pr, CTPAOH; R = *n*-Bu, CTBAOH) in the absence and presence of added OH^-. Reaction is speeded by cationic micelles. Rate constants increase with surfactant concentration and become constant with fully bound substrate. The second-order rate constants at the micellar surface increase with increasing head group size.

Quantitative Kinetic Treatment.

The treatment of micellar catalysis is based on the assumption that reaction occurs in the micellar and aqueous pseudophases, and that equilibrium is maintained between reactants in the two pseudophases.[2,6,7] Aqueous micelles speed bimolecular reaction by bringing reactant together and the enhancements can be treated quantitatively by estimating reactant concentration at the micellar surface.[2,17]

The overall reactions are illustrated in Scheme 2, where S is the substrate, D_n is the micellized surfactant and k'_W and k'_M are first-order rate constants for reaction in the aqueous and micellar pseudophases, respectively.

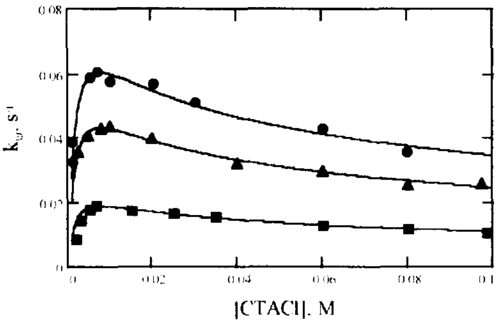


Figure 1. Variation of the first-order rate constant, k_ψ, for the reaction of 2-(3-nitrophenoxy)quinoxaline **1** with OH^- in CTACl. (■) with 0.001 M OH^-; (▲) with 0.01 M OH^-; (●) with 0.3 M OH^-. Curves are calculated.

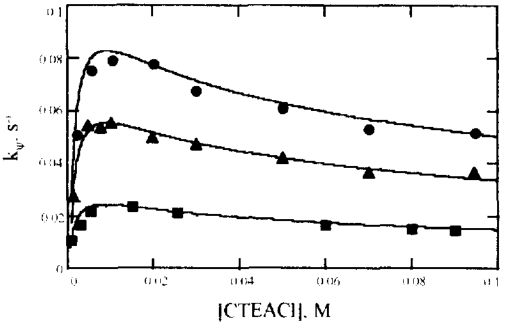


Figure 2. Variation of the first-order rate constant, k_ψ, for the reaction of 2-(3-nitrophenoxy)quinoxaline **1** with OH^- in CTEACl. Symbols as in Figure 1. Curves are calculated.

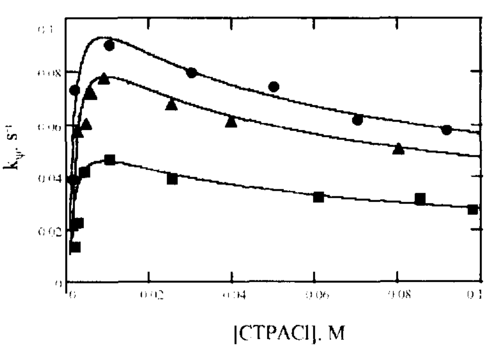


Figure 3. Variation of the first-order rate constant, k_ψ, for the reaction of 2-(3-nitrophenoxy)quinoxaline **1** with OH^- in CTPACl. Symbols as in Figure 1. Curves are calculated.

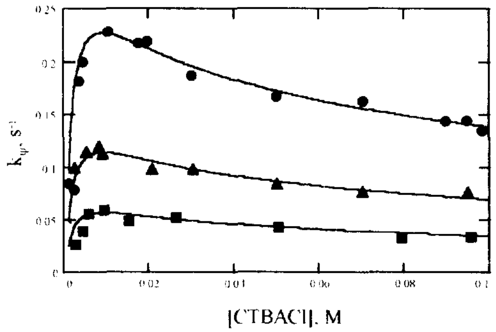
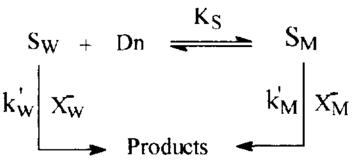


Figure 4. Variation of the first-order rate constant, k_ψ, for the reaction of 2-(3-nitrophenoxy)quinoxaline **1** with OH^- in CTBACl. Symbols as in Figure 1. Curves are calculated.

In Scheme 2 subscripts w and M stand for the aqueous and micellar phases, K_S is the substrate binding constant



Scheme 2

to micellized surfactant, the concentration of which is that of total concentration ([D]) less that of monomeric surfactant, *i.e.* $[D_n]$ = [D] - c.m.c. (the critical micelle concentration, c.m.c., is taken as the concentration of monomeric surfactant). The first-order rate constant for overall reaction, k_ψ, is given by equation (1)[7,18]

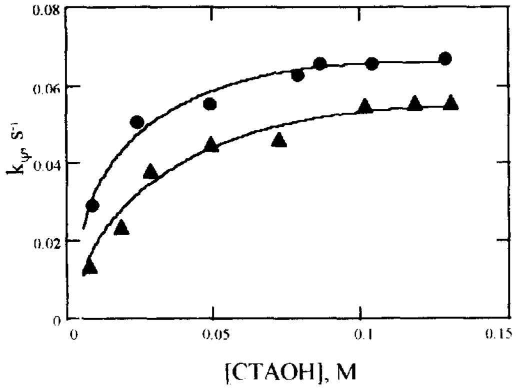


Figure 5. Reaction in CTAOH. (▲) no added NaOH. (●) With added 0.3 M OH⁻. Curves are calculated.

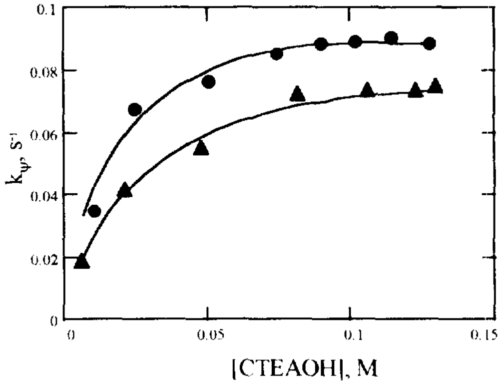


Figure 6. Reaction in CTEAOH. Symbols as in Figure 5. Curves are calculated.

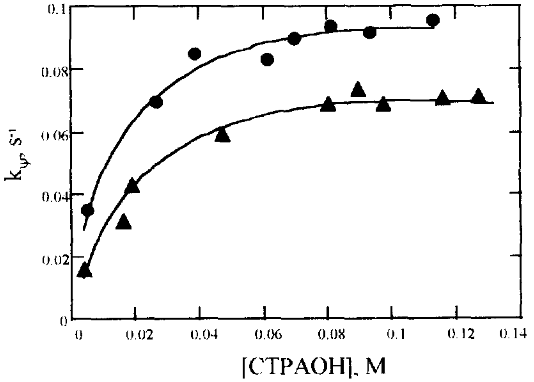


Figure 7. Reaction in CTPAOH. Symbols as in Figure 5. Curves are calculated.

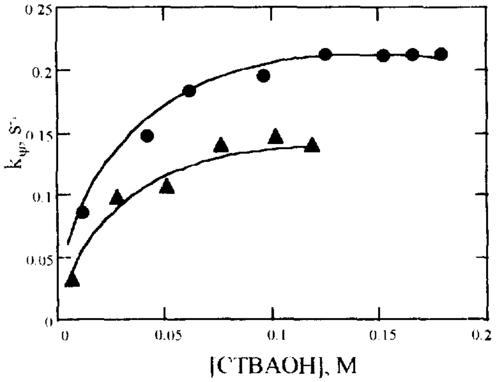


Figure 8. Reaction in CTBAOH. Symbols as in Figure 5. Curves are calculated.

$$k_{\Psi} = \frac{k'_{W} + k'_{M} K_S([D_n] - cmc)}{1 + K_S([D_n] - cmc)} \tag{1}$$

The first-order rate constants, k'_W and k'_M, can be written as second-order rate constants, k_W and k_M, as a mole fraction (the quantities [ ] denote molar concentrations in terms of total solution volume):

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

$$k'_M = k_M m^{OH}_M \tag{3}$$

where k_M, s^{-1}, the second-order rate constant in the micellar pseudophase, is defined in terms of the mole ratio of OH⁻ to surfactant head groups in the micelle.

Reactions in Micelles of Non Reactive Counter-ion Surfactants.

Rate data for reaction of OH^- with compound **1** in aqueous solutions of micellized cetyltrialkylammonium chlorides (R = Me, Et, *n*-Pr, *n*-Bu) can be fitted using a pseudophase model originally proposed by Bunton[19a] [eqns. (1)-(3)], in which the distribution of OH^- between the aqueous and micellar pseudophases is written in terms of the mass-action-like eqns. (4) and (5)

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

$$K'_X = [X^-_M]/([X'_W]([Dn]-[OH'_M]-[X'_M])) \tag{5}$$

The model has been extensively applied by Rodenas.[19b] Table 1 shows the estimated rate constants in the micellar pseudophase and the parameters that best fit the kinetic results for the reaction of substrate **1** in micellized CTACl, CTEACl, CTPACl and CTBACl. Solids lines in Figures 1-4 represents the values of k_Ψ calculated with these parameters by eqns. 1,4,5. The fit of theory and experiment is reasonably good. k_w, was measured directly, and k_M and K'_{Cl} were treated as adjustable parameters. Values of K'_{OH} are from the literature (K'_{OH} = 55, 45, 25 and 12 for CTA^+, $CTEA^+$, $CTPA^+$ and $CTBA^+$ respectively).[4d,8] The cmc values decrease modestly with increasing head-group bulk.

Table 1. Fitting Parameters for the Reaction of 2-(3-Nitrophenoxy)quinoxaline with OH^- ion in non reactive counter-ion micelles.[a]

Surfactant	K_{Cl}	10^3 cmc M	$10\,[OH^-_T]^b$ M	$10^3\,[OH^-_M]^c$ M	$10^3\,[Cl^-_M]^c$ M	$10\,k_M$ s^{-1}
CTACl	125	1.1	0.01			2.4
CTACl	125	1.1	0.1	1.97	3.58	2.3
CTACl	125	1.1	3.0			2.4
CTEACl	110	0.9	0.01			2.9
CTEACl	110	0.9	0.1	1.77	3.45	2.9
CTEACl	110	0.9	3.0			2.9
CTPACl	60	0.8	0.01			9.5
CTPACl	60	0.8	0.1	1.31	2.66	9.4
CTPACl	60	0.8	3.0			9.4
CTBACl	50	0.6	0.01			14.0
CTBACl	50	0.6	0.1	0.747	2.52	14.0
CTBACl	50	0.6	3.0			13.0

[a] At 25.0 °C and with K_S = 8150 M^{-1}, k_W = 10.2×10^{-2} $M^{-1}\,s^{-1}$, K'_{OH} = 55, 45, 25 and 12 M^{-1} for CTA^+, $CTEA^+$, $CTPA^+$ and $CTBA^+$, respectively.[4d,8] [b] Total OH^- concentration. [c] Calculated interfacial counter-ion concentration at [surfactant]= 0.01 M.

Reactions in Micelles of Reactive Counter-ion Surfactants.

For reaction in micelles with reactive counter-ion the distribution of OH^- between aqueous and micellar pseudophases can be fitted to equation (6)[8,19b]

$$K'_{OH} = [OH^-_M]/([OH^-_W]([Dn]-[OH^-_M])) \tag{6}$$

and the fraction of micellar head groups neutralized, β, is given by equation (7)

$$k_\psi = k_M \beta \tag{7}$$

where $\beta = [OH_M]/[D_n]$. Values of β vary significantly when the counter-ion is OH^- unlike other counter-ions such as Cl^- and Br^- which bind specifically as well as electrostatically.[8,19a] The variation of k_ψ for reactions of **1** in solutions of CTAOH can be simulated by using this treatment and the fit is illustrated in Figures 5-8 were solid lines are calculated. The kinetic cmc values are 1.29 mM, 1.18 mM, O.60 mM and 0.50 mM and they were estimated by the method proposed by Broxton.[20]

Table 2 shows the estimated rate constants in the micellar pseudophase and the parameters that best fit the kinetic results for the reaction of substrate **1** in micellized surfactants with reactive counter-ion. The model fits the data up to 0.3 M OH^-. Observed rate constant increase with added OH^-. At the rate maxima, values of k_ψ in CTACl with 0.3 M OH^- are similar to those in CTAOH with added 0.3 M OH^-.

Table 2. Fitting Parameters for Reaction of 2-(3-Nitrophenoxy)quinoxaline **1** with Hydroxide Ion in Micellized Surfactant with Reactive Counter-ion.[a]

Surfactant	$10\,[OH^-_T]$[b] M	$10\,k_M$ s^{-1}	$10^2\,k_2^m$ $M^{-1}\,s^{-1}$
CTAOH		2.40	3.36
CTAOH	3.0	2.50	3.50
CTEAOH		2.90	4.06
CTEAOH	3.0	3.10	4.34
CTPAOH		9.40	13.2
CTPAOH	3.0	9.60	13.4
CTBAOH		14.0	19.6
CTBAOH	3.0	15.3	21.4

[a] At 25.0 °C and with K_S = 8.200 M^{-1}, k_W = 10.2 x 10^{-2} $M^{-1}\,s^{-1}$, K'_{OH} = 55, 45, 25 and 12 M^{-1} for CTAOH, CTEAOH, CTPAOH and CTBAOH, respectively.[4d,8] [b] Concentration of CTAOH + added OH^-, when unspecified OH^- was derived solely from CTAOH.

Micellar rate enhancements of bimolecular ionic reactions are due to increased concentrations in the micelle-water interface,[2] but comparison of second-order rate constants in aqueous and micellar pseudophases requires that concentrations in the latter be expressed as molarity rather than a mole ratio. The reactive molar volume in the micellar pseudophase, V_M, can be taken either as that of the micelle, or of some reaction region on its surface, and estimates of V_M range from 0.14-0.37 L.[6] The second-order rate constant, k_2^m, is given by:

$$k_2^m = k_M V_M \tag{8}$$

and a value for $V_M = 0.14$ L[8] was used in this work.

Influence of the Micellar Head group Size.

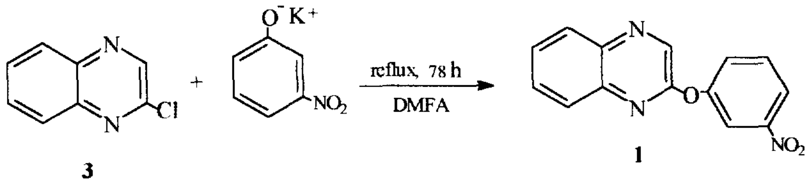
The behavior of an aqueous micelle as a submicroscopic reaction medium depends upon the nature of the head group. The second-order rate constant, k_M, for the alkaline hydrolysis of compound **1** in the micellar pseudophase in both reactive or non reactive counter-ion surfactant micelles increase with head group size. These experimental data indicate that hydration of hydroxide ion is perturbed by an increase in head group hydrophobicity. The rate increase is probably due to the partial exclusion of water from the micellar surface. The reactivity increase with the head group size might be related to disruption of the hydration of the reactive counter-ion.

For both series of surfactants experimental results were fitted with Langmuir coefficients for OH^- that decrease in the head group sequence $Me_3N > Et_3N > Pr_3N > Bu_3N$. In micelles of non reactive counter-ion surfactant, the increase in head group size from methyl to butyl decreases K'_{Cl}, *i.e.*, increases ionic dissociation. A possible interpretation for this result is that the increase in head group size reduces the space available between head groups for counter-ions and increases dissociation of Cl^-.

EXPERIMENTAL

Materials.

Synthesis of 2-(3-nitrophenoxy)quinoxaline **1**. A mixture of 2-chloroquinoxaline[21] **3** (2,0 g, 12 mmol), 3-nitrophenol (8.02 g, 57.7 mmol), potassium hydroxide (2.04 g, 36.4 mmol) and *N,N*-dimethylformamide (15,0 ml) was heated under reflux at 90 °C for 72 h (Scheme 3). After 78 h, TLC showed that no starting material remained. The solution was cooled, the precipitated solid was filtered off and the residue was extracted with dichloromethane. After eliminating the solvent, the product was isolated and recrystallised from CH_2Cl_2 / *n*-hexane to yield 2.18 g (68%) of **1**, m.p. 119-120 °C. IR (KBr) 3098 (C-H, Ph), 1584 (C=C, conj.), 1545 ($-NO_2$), 1222 (C-O-C, as. str.), 1084 (C-O-C, sym. str.), 827 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.78 (s, 1H, H-3), 8.57-8.15 (m, 3H, Ph-H), 7.98-7.50 (m, 5H, Ph-H). MS: m/e (%) 267 (100, M^+), 129 (52, $M^+-C_6H_6O$), 102 (50, M^+-HCN). Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.9; H, 3.39; N, 15.7. Found: C, 62.7; H, 3.44; N, 15.8.



Scheme 3

Synthesis of surfactants. The preparation and purification of the surfactants has been described.[4d,5b] There were no minima in plots of surface tension of purified surfactants against log surfactant concentration.

Kinetics. Reactions were followed spectrophotometrically in aqueous solution at 25 °C in a Perkin-Elmer Lambda II UV-Visible instrument at 362 nm by using the λ_{max} of the 2-quinoxalone. Substrate concentration was 6.0×10^{-5} M and was added to the reaction solution in MeCN so that the final solution contained 0.1% organic solvent. Reactions were clearly first order up to 95% under all conditions. The first-order rate constants, k_ψ, are in reciprocal seconds.

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