Determination of the Hydrolysis Kinetics of α-Naphthyl Acetate in Micellar Systems and the Effect of HPMC (Catalyst Present)

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ABSTRACT: The change in the hexadecyltrimethylammonium bromide (CTAB) critical aggregation concentration (CAC) was studied in the presence of various concentrations and grades of hydroxypropylmethyl cellulose (HPMC) using surface tension measurement (duNoüy ring and Wilhelmy plate) and oil red O solubilization. According to the surface tension methods, the CAC was higher than the CTAB critical micelle concentration (CMC). CAC and CMC were not different when the solubilization method was used. Micellar solutions of CTAB have been found to accelerate the hydrolysis of α-naphthyl acetate (α-NA) by *o*-iodosobenzoic acid (IBA), a strong nucleophile. Pseudo-first-order kinetics were utilized for rate constant determination. The observed rate constants for the degradation of α-NA in the presence of varying CTAB concentrations with and without HPMC were analyzed according to the pseudophase model. The micellar rate constants and the micellar binding constants for the substrates were obtained. The presence of HPMC retarded the reaction rate, and the rate constant decreased as the polymer concentration increased. However, there was no obvious difference in the observed rate constants among the different grades of HPMC (Methocel E5®, Methocel E15®, Methocel E50®). The decrease in the rate constant was likely due to the polymer–micelle interaction interfering with substrate binding to the CTAB micelles. J Pharm Sci 96:448–458, 2007

Keywords: micelle; surfactant; polymer; decomposition kinetics; hydroxypropylmethylcellulose; hexadecyltrimethylammonium bromide; hydrolysis; surface tension; solubility; critical micelle concentration

INTRODUCTION

Micellar solutions are of widespread interest due to their varied applications. In some cases, polymers are introduced into these micellar solutions,[1,2] resulting in polymer–surfactant interactions.[3–5] One method that can be utilized to study such interactions is to determine the effect of polymer addition on the critical aggregation concentration (CAC), which is the concentration where surfactant molecules aggregate, or cluster about the polymer molecules.[6] In the absence of polymer, the narrow range of surfactant concentration over which micelles first become detectable is the critical micelle concentration (CMC).[7] The existence of interactions between a polymer and a surfactant can be inferred if the CAC and the CMC are different.

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Surface tension lowering and solubilization are two techniques that can be used for the determination of CMC/CAC.[7,8] In the surface tension method, a plot of surface tension as a function of the logarithm of surfactant concentration is used. In the solubilization method, the solubility of an insoluble molecule is plotted as a function of the logarithm of surfactant concentration. In both methods, a break is identified and used to determine the CMC/CAC.

The observed rates of chemical reactions may be altered in micellar solutions because of the distribution of substrates between the micellar and aqueous phases, in which different environments exist.[8] Therefore, a reaction can be accelerated or inhibited by micelles, depending on the mechanism of the reaction.[9] Berezin et al. proposed an equation (Eq. 1) for the quantitative analysis of bimolecular reactions occurring in micellar systems.[10] Wurster and Patel utilized that equation to analyze the hydrolysis of α-naphthyl acetate (α-NA) in the presence of *o*-iodosobenzoic acid (IBA) and CTAB micelles.[11] Those authors reported that the rate of hydrolysis is enhanced in the presence of CTAB micelles and that the mechanism of the reaction is unchanged, since the entropy of activation is −44.9 cal/mole·K in solutions without surfactant, and −39.3 cal/mole·K in 3 mM CTAB solutions.[11] The negative entropy of activation indicates that the reaction follows a bimolecular mechanism.

$$k_{obs} = \frac{k_b + \bar{k}_m K_{NA} K_{IBA} C}{(1 + K_{NA} C)(1 + K_{IBA} C)} \qquad (1)$$

k_{obs}, observed rate constant; k_b, rate constant in the aqueous phase; K_{NA}, α-NA binding constant; K_{IBA}, IBA binding constant; k_m, micellar rate constant per molar volume; C, CTAB micelle concentration.

In this work, the impact of adding a nonionic polymer, hydroxypropylmethyl cellulose (HPMC), to CTAB micellar solutions on the hydrolysis of α-NA in the presence of IBA is studied thoroughly. As mentioned earlier, polymers are added to micellar systems for a variety of different reasons. One of those reasons is viscosity enhancement so that topical formulations of micellar systems can be prepared. This work is part of an ongoing project to determine the feasibility of making reactive barriers, for topical application, which could protect human beings against inadvertent pesticide exposure. If such formulations are to be successful, it is essential that the exact effects of the added viscosity-inducing polymer be determined. These effects may be on surfactant aggregation behavior, substrate binding to the micelle, and on the substrate reactivity itself.

The changes in reaction rate of α-NA, a model substrate, with changing surfactant concentrations and changing polymer concentrations were studied. In addition, the influence of added electrolytes on the micellar system was also studied. Surface tension and solubilization methods were used to determine the CAC of CTAB in the presence of HPMC. Oil red O, which is very slightly soluble in water, was utilized in the solubilization studies. The reaction kinetics were studied using fluorescence spectrophotometry, and the reaction parameters in Equation 1 were calculated using nonlinear curve fitting software (Kaleidagraph program).

EXPERIMENTAL SECTION

Materials

Three different grades of HPMC: HPMC E5, HPMC E15, and HPMC E50 (Methocel E5®, Methocel E15®, Methocel E50®), were obtained from The Dow Chemical Company (Midland, MI). CTAB, oil red O, α-NA, and IBA were purchased from Sigma Chemical Co. (St. Louis, MO). Monobasic sodium phosphate monohydrate, dibasic sodium phosphate, sodium sulfate, glacial acetic acid, and sodium acetate trihydrate were purchased from Fisher Scientific (Fair Lawn, NJ). All HPMC grades were purified using a dialysis method. A 10% w/w, in water, polymer solution was placed in a dialysis bag (3500 MWCO) and the bag was placed in distilled water. The medium was replaced with fresh distilled water every day until the conductivity of the medium was not different from the freshly distilled water. The other chemicals were used as received.

Methods

Critical Micelle Concentrations of CTAB, HPMC, and CTAB—HPMC Mixed Systems

Surface Tension Measurement. A Surface Tensiomat 21® (semi-automatic model, Fisher Scientific) and a KSV Sigma 7^0 (surface tension/contact angle meter, Type 100L, KSV instrument, Monroe, CT) were employed in these studies. A platinum-iridium duNoüy ring (circumference 5.910 cm,

R/r 52.94) was attached to the Tensiomat 21® and a platinum Wilhelmy plate (19.6-mm wide and 0.1-mm thick) was used with the KSV Sigma 7^0. The CMC of CTAB was determined in water, buffer solution (monobasic sodium phosphate monohydrate and dibasic sodium phosphate), and HPMC solutions (HPMC E5, HPMC E15, and HPMC E50). Four concentrations of polymer solutions, 0.02, 0.1, 0.3, and 0.8% w/v (without CTAB), were prepared in phosphate buffer solution. The total buffer concentration and pH value were controlled at 0.0667 M and 7.40 ± 0.01, respectively.

Various concentrations of CTAB from 0 to 15 mM were prepared in the aforementioned solvent solutions. Sample solutions were placed in a jacketed beaker connected to a circulating water bath maintained at 30°C. Two different aliquots of each solution were measured. The surface tension versus log [CTAB] plot was constructed for each solvent system and the CMC and/or the CAC was calculated from the profile.

Regarding the critical polymer concentration (CPC), the surface tensions of solutions having various concentrations of HPMC E5 were measured. The CPC was obtained from the plot of surface tension versus log [HPMC E5].

Solubilization of Oil Red O. Excess amounts of oil red O were added to screw-cap tubes filled with phosphate buffer, water, or solvent systems containing different concentrations (0.02, 0.1, 0.3, 0.8% w/v) of the three HPMC grades in phosphate buffer solution. The samples were rotated end over end using a sustained-release apparatus (Vanderkamp® Sustained Release Apparatus, Model 103906, VanKel Industries, Inc., Edison, NJ) in a water bath (Vanderkamp®, Model W-1115, VanKel Industries, Inc.) at a controlled temperature of 30°C. The samples were allowed to equilibrate for a period of 48 h, and were then filtered through 0.22 μm Millex®-GV disposable syringe filters (Millipore, Carrigtwohill, Co. Cork, Ireland). The first 3 mL of filtrate was discarded and the collected filtrate was suitably diluted. The concentrations of oil red O were assayed using a UV spectrophotometer (Hewlett Packard HP 8453, Agilent Technology, Palo Alto, CA) at a wavelength of 521.4 nm. Each sample was run in duplicate. The data were utilized to prepare an oil red O solubility versus log [CTAB] plot for each solvent and the CMC or CAC was indicated by the CTAB concentration for which the oil red O solubility increased considerably.

The oil red O solubilities were also determined in solutions having various concentrations of HPMC E5. HPMC E5 aggregation concentration was determined from the profile of oil red O solubility versus log [HPMC E5].

Effect of SO_4^{2-} Ion on CMC

Phosphate buffer solutions, ionic strength of 0.17 M, and phosphate buffer solutions with sodium sulfate, ionic strength of 0.30 M, were prepared with a pH of 7.40 ± 0.01. Various concentrations of CTAB from 0 to 15 mM were prepared in these media. The CMC values of CTAB were determined from both surface tension and oil red O solubility data using the procedures previously described.

Hydrolysis Kinetics of α-NA in Micellar Systems and the Influence of HPMC

The effect of the interaction between HPMC and CTAB was studied using the degradation of α-NA in the presence of a catalyst, IBA. The reaction was performed in phosphate buffer solution, 0.0667 M and pH 7.40 ± 0.01, in the presence and absence of the polymers: HPMC E5, HPMC E15, and HPMC E50. Buffered polymer solutions were prepared at concentrations of 0.02, 0.1, and 0.3% w/v of each HPMC.

To construct the observed rate constant versus CTAB concentration profile, various concentrations of CTAB (0–6.5 mM) were prepared in each reaction medium. The initial concentrations of reactants were 2.0×10^{-4} M of α-NA and 1.0×10^{-4} M of IBA at 30°C. Samples were taken during the kinetic runs and were diluted with pH 4.5 acetate buffer (glacial acetic acid and sodium acetate trihydrate) to quench the reaction.

The amount of α-NA remaining was analyzed using a fluorescence spectrophotometer (Kontron Instruments, Inc., Milano, Italy). The excitation and emission wavelengths used for the analyses of α-NA were 278 and 328 nm, respectively. The data obtained were employed for the determination of the pseudo-first-order rate constants for the decomposition of α-NA. Due to the side reaction between the degradation product, α-naphthol, and the nucleophile, IBA, only the kinetic data up to one and one-half half-life periods were used for the determination of the rate constants.[11] The profile of observed rate constant versus the concentration of CTAB was constructed for each solvent mixture.

Influence of SO_4^{2-} Ions on α-NA Hydrolysis Kinetics in Micellar Systems

Sodium sulfate was added to the buffered reaction medium to reach 0.3 M ionic strength. The solutions were controlled at pH 7.40 ± 0.01 and the total phosphate buffer concentration was kept constant at 0.0667 M. These solvent mixtures were used for preparing various concentrations of CTAB from 0 to 6.5 mM. The initial concentrations of reactants were 2.0×10^{-4} M of α-NA and 1.0×10^{-4} M of IBA at 30°C. Samples were taken and analyzed during the kinetic runs. These experiments were done in duplicate.

α-NA Hydrolysis Kinetics in a CTAB-HPMC Gel System

HPMC gels were prepared from HPMC E50 hydrated in phosphate buffer solution at pH 7.40 ± 0.01 and a total buffer concentration of 0.0667 M. The initial concentrations of reactants were 2.0×10^{-4} M for α-NA and 1.0×10^{-4} M for IBA and the system was controlled at 30°C. The concentration of HPMC E50 was kept constant at 5% w/v, but the concentration of CTAB was varied from 0 to 6 mM. Samples were taken and analyzed during the kinetic runs and a plot of observed rate constant versus CTAB concentration was constructed. These experiments were done in duplicate.

RESULTS AND DISCUSSION

CMC/CAC Values for CTAB, HPMC, and CTAB—HPMC Mixed Systems

Surface Tension Measurement

The CMC of CTAB was determined in water and in buffer solution by measuring the surface tensions of a series of CTAB solutions having different concentrations. As the CTAB concentration increased, the surface tension rapidly dropped to a minimum value and then remained constant. Figure 1 is a typical plot for CMC/CAC determination using the surface tension method. The CMC and CAC values of CTAB in solutions of different HPMC grades and concentrations, which were determined from their surface tension versus log [CTAB] profiles, are reported in Table 1. CPC was observed at 2.66×10^{-6} g/ml.

Regarding the surface tension method, the CMC for CTAB in water was found to be

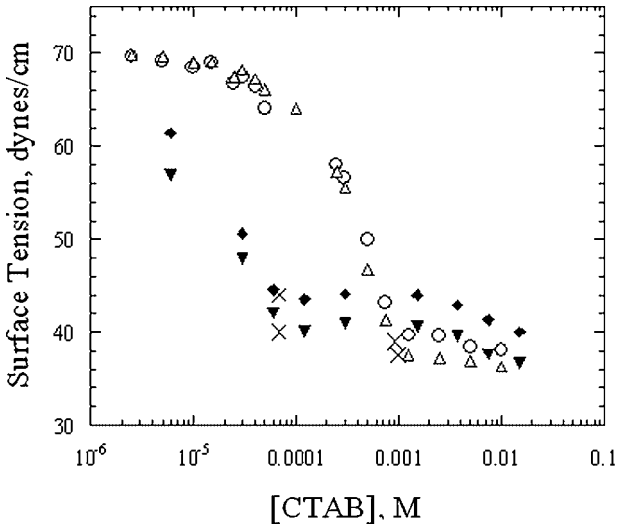

Figure 1. CMC determination for CTAB in water and in phosphate buffer solution (pH 7.40 ± 0.01) at 30°C: (○) water using duNoüy ring, (△) water using Wilhelmy plate, (◆) buffer using duNoüy ring, (▼) buffer using Wilhelmy plate, and (×) the CMC.

9.34×10^{-4} M (Wilhelmy Plate) and 9.36×10^{-4} M (duNoüy Ring) at 30°C. Those values are close to the literature value of 9.2×10^{-4} M at 25°C.[12] In this case, an increase in temperature is likely to cause the small change observed. The disruption of the structured water surrounding the hydrophobic chain apparently predominated over the decrease in hydration of the hydrophilic group as temperature was increased. The CMC for CTAB in the buffer solution was 6.85×10^{-5} M, which is close to the value reported by Patel of 6.8×10^{-5} M.[13] The CMC of CTAB in water was higher than that in buffer because electrolytes from the buffer reduce repulsion between the ionic head groups of the surfactant molecules, thus facilitating micellization. In other words, the increased binding of counterions to the surfactant polar groups causes a decrease in the CMC of the surfactant.[12] A greater electrolyte effect was found when sodium sulfate was added to the system.

The addition of HPMC to the CTAB solution increased the observed concentration of CTAB at the breakpoint in the plot of surface tension versus log [CTAB]. This breakpoint was defined earlier as the CAC and it gives an indication of the interaction between CTAB and HPMC. These interactions caused a redistribution of the CTAB molecules, from the surface to the bulk phase. Since more CTAB molecules distributed to the bulk phase when HPMC was added, more CTAB

Table 1. CMC or CAC of CTAB in Various Media Using Surface Tension and Solubilization Methods at 30°C

	CMC or CAC, M		
	Surface Tension Method		
System	duNoüy Ring	Wilhelmy Plate	Solubilization Method
Water	9.36×10^{-4}	9.34×10^{-4}	5.04×10^{-4}
Phosphate buffer (pH 7.40 ± 0.01)	6.85×10^{-5}	6.83×10^{-5}	1.20×10^{-4}
Na_2SO_4 in phosphate buffer (pH 7.40 ± 0.01)	—	6.11×10^{-5}	1.02×10^{-4}
HPMC E5 (% w/v)			
0.02	1.26×10^{-4}	1.14×10^{-4}	1.10×10^{-4}
0.1	1.20×10^{-4}	1.23×10^{-4}	1.13×10^{-4}
0.3	1.17×10^{-4}	1.22×10^{-4}	1.10×10^{-4}
0.8	1.10×10^{-4}	1.25×10^{-4}	1.10×10^{-4}
HPMC E15 (% w/v)			
0.02	1.33×10^{-4}	1.19×10^{-4}	1.20×10^{-4}
0.1	1.12×10^{-4}	1.03×10^{-4}	1.20×10^{-4}
0.3	1.04×10^{-4}	8.44×10^{-5}	1.20×10^{-4}
0.8	1.10×10^{-4}	1.01×10^{-4}	1.20×10^{-4}
HPMC E50 (% w/v)			
0.02	1.05×10^{-4}	1.17×10^{-4}	1.20×10^{-4}
0.1	1.08×10^{-4}	1.06×10^{-4}	1.20×10^{-4}
0.3	1.09×10^{-4}	1.06×10^{-4}	1.20×10^{-4}
0.8	1.24×10^{-4}	1.18×10^{-4}	1.20×10^{-4}

molecules were needed to reach the CMC. This explanation was supported by the effect of HPMC on the surface tension. The initial decrease in surface tension upon CTAB addition was more rapid in the absence of HPMC than in the presence of HPMC. Lundqvist et al. also observed a CAC higher than the CMC in a study of CTAB-starch polysaccharides binding.[14] Similar behavior was also observed in the presence of Carbopol and Tween 80.[15] The initial slope of surface tension versus log [Tween 80] was less in the presence of 0.25% Carbopol, since the surface excess of Tween 80 at the air/water interface was decreased as the surfactant was adsorbed by the polymer and drawn into the bulk solution. According to the Gibbs adsorption equation, the relationship between change in surface tension ($d\gamma$) and the surface excess (Γ_1) of a surfactant is given by:

$$d\gamma = -2RT\Gamma_1 d \ln C \qquad (2)$$

where, T and C represent the absolute temperature and the surfactant concentration, respectively, and R is the gas constant.

Surface excesses from the experiments are reported in Table 2. The results confirmed that the surface excess of CTAB was lowered when HPMC was added to the system. In buffer solution,

Table 2. Surface Excesses of CTAB in Various Media

	Surface Excess, Mole/cm^2 ($10^{11}\times$)	
System	duNoüy Ring	Wilhelmy Plate
Water	9.01	10.8
Phosphate buffer (pH 7.40 ± 0.01)	14.3	12.5
Na_2SO_4 in phosphate buffer (pH 7.40 ± 0.01)	—	13.1
HPMC E5 (% w/v)		
0.02	5.54	5.63
0.1	6.66	5.40
0.3	5.90	5.36
0.8	5.74	5.05
HPMC E15 (% w/v)		
0.02	6.20	6.09
0.1	7.46	6.11
0.3	6.60	6.48
0.8	6.21	5.90
HPMC E50 (% w/v)		
0.02	7.11	6.11
0.1	7.29	6.44
0.3	6.31	6.22
0.8	6.62	6.02

the surface excess increased because the effective charge of the hydrophilic groups on the CTAB molecules was decreased by the buffer salts, leading to an increase in the efficiency of adsorption of CTAB at the surface.[12]

Neither HPMC concentration nor grade affected the CAC. This result was surprising, and the explanation is not definitively known. One possible explanation is that the lowest HPMC concentration used in this work, 0.02%, was large enough to satisfy the possible interactions with CTAB. Therefore, further increase in HPMC concentration had no impact.

Solubilization of Oil Red O

The solubility of oil red O in CTAB solution dramatically increased above the CMC. Figure 2 shows typical solubility profiles obtained from this study. The CMC was defined as the point where the solubility abruptly increased. In buffer solution, the introduction of HPMC into the system did not alter the break point of the profile. The CMC or CAC values for CTAB in the different solvent systems using the solubilization method are reported in Table 1. According to solubility studies (not shown in Tab. 1), the HPMC (only) solutions did not dissolve oil red O at any of the tested concentrations.

HPMC is surface active and reduces the surface tension of aqueous systems, but the HPMC solutions did not dissolve oil red O at any of the tested concentrations. The reason is that HPMC does not form micelles. Micelle formation requires both hydrophobic and hydrophilic regions in the molecular structure.[16]

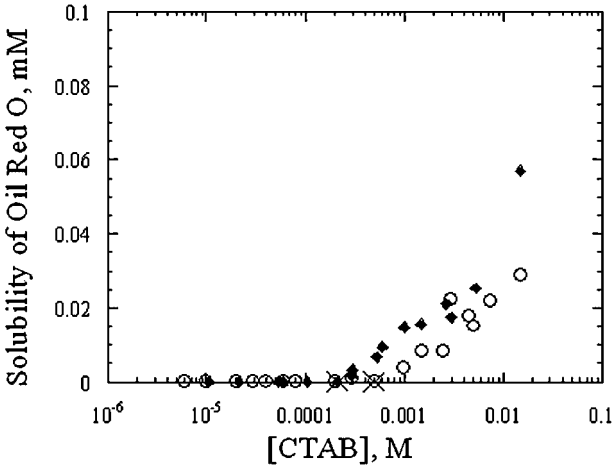

Figure 2. CMC determination for CTAB using the solubilization method at 30°C: (○) water, (◆) phosphate buffer solutions, and (×) the CMC.

The solubilization results confirmed that the CMC of CTAB in water was higher than that in buffer. Using the solubilization method, the CMC of CTAB in buffer was 1.2×10^{-4} M, which was higher than that obtained from the surface tension method (6.8×10^{-5} M). This difference may be real or it may be an artifact. It may be that, when the number of micelles was small, oil red O solubility changes could not be detected.

Effect of SO_4^{2-} Ion on CMC

The CMC of CTAB in a buffered sodium sulfate solution was determined to be 6.11×10^{-5} M using surface tension measurement and 1.02×10^{-4} M using the solubilization technique. For experiments involving water without electrolytes, the CMC from the solubilization method was less than that obtained from the surface tension methods. In most cases, the decrease in the CMC caused by the introduction of a solubilizate is attributed to changes in the activity of the surfactant and, consequently, in the concentration of monomeric surfactant in the bulk phase.[12] The solubilizate influence was not observed in the buffer solution because the reduction of the CMC due to the electrolyte effect was more dominant than the increase in the CMC due to the solubilizate effect.

Hydrolysis Kinetics of α-NA in Micellar Systems and the Influence of HPMC

Throughout this work, excellent correlations were observed between log [α-NA] and time, which supports pseudo-first-order kinetics.[11] The presence of 2.65 mM CTAB enhanced the IBA-catalyzed α-NA hydrolysis as much as 68 times compared to the same system without CTAB micelles. The catalytic effect of micellar media on bimolecular reactions can occur in two ways: (1) concentrating reactants in a small volume and providing a concentration advantage to the reaction, and (2) providing a medium effect to change the activities of substrates. Micelles may provide a medium effect that changes the reactivities of both the substrate and the reactive ion. This effect arises from a combination of orientation, microviscosity, polarity, and charge effects.[17] Since the microviscosity of micelles is much higher than the viscosity of the surrounding homogeneous solvent, substrate molecules incorporated in

micelles have less translational and rotational freedom and this is reflected in their reactivities. For some reactions, electrostatic and hydrophobic interactions between the substrate and micelle may influence the activation energy.[8]

Typical observed rate constant versus CTAB concentration profiles in the presence and absence of HPMC are presented in Figures 3 and 4. The shapes of all of the plots follow the same pattern as the system without HPMC. Regarding Equation 1, the pseudophase parameters were obtained using nonlinear curve fitting and the results are tabulated in Tables 3–5.

As seen in Figures 3 and 4, a maximum in the observed rate constant versus surfactant concentration profile was reached. The reason is that, as CTAB micelle concentration was increased, a concentration was reached for which essentially all of the reactants were bound to micelles. After this point, an increase in the number of CTAB micelles decreased the micellar concentrations of substrates, causing lower observed rate constants.

Regarding the pseudophase parameters before the addition of HPMC, the micellar rate constant, k_m, was found to be 1.4×10^{-4} min^{-1}, assuming that the molar volume of CTAB in the micellar form was 0.25 M^{-1}. This micellar rate constant was less than that observed for the reaction conducted in the absence of the surfactant, k_b, which was 6.2×10^{-4} min^{-1}. The enhancement of reaction rate is, therefore, due to the increased

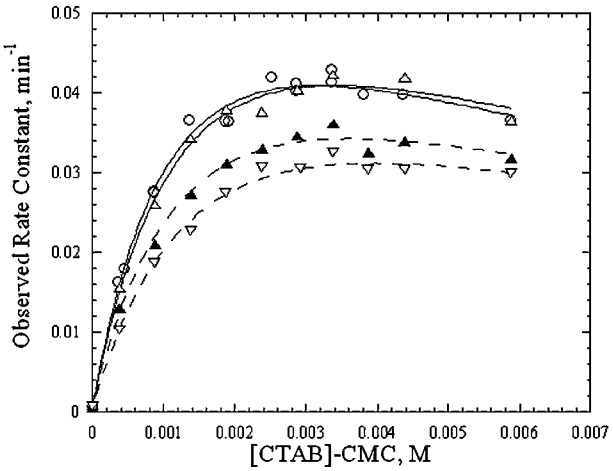

Figure 3. Observed rate constant for α-NA hydrolysis versus CTAB concentration with added HPMC E5 in pH 7.40 ± 0.01 phosphate buffer at 30°C: (○) buffer, (△) 0.02% HPMC E5, (▲) 0.1% HPMC E5, and (▽) 0.3% HPMC E5.

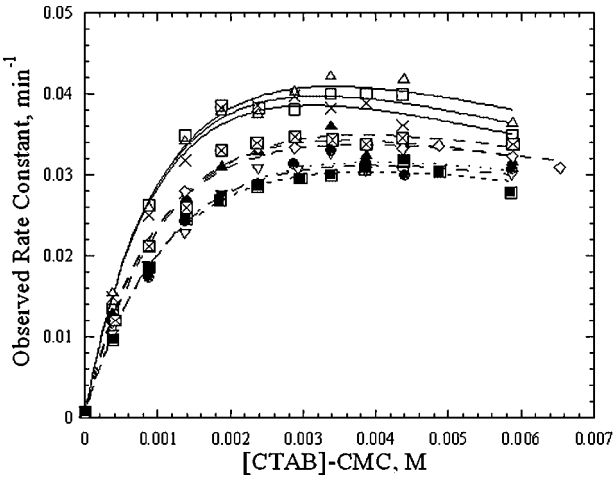

Figure 4. Observed rate constant for α-NA hydrolysis versus CTAB concentration with added HPMC at different concentrations in pH 7.40 ± 0.01 phosphate buffer at 30°C: (△) 0.02% HPMC E5, (×) 0.02% HPMC E15, (□) 0.02% HPMC E50, (▲) 0.1% HPMC E5, (◇) 0.1% HPMC E15, (⊠) 0.1% HPMC E50, (▽) 0.3% HPMC E5, (●) 0.3% HPMC E15, and (■) 0.3% HPMC E50.

concentration of the reactants in the micellar pseudophase and not due to an enhancement of the reactivity in the micellar environment. The lowering of the reaction rate constant in the micellar pseudophase, compared to the bulk phase, is normally attributed to such factors as microviscosity or orientational effects.

Patel[13] reported that the activation energy of the reaction was 11.5 kcal/mole in the system without any surfactant present (pH 7.5), and 11.1 kcal/mole in the system with 3 mM CTAB (same pH). These two activation energies are essentially equal. This information further supports the notion that the acceleration in reaction rate afforded by the micellar solution is due to a concentration effect.

Nardviriyakul studied the degradation of dicapthon in a micellar CTAB system in the presence of IBA (25°C). The reported substrate binding constants for IBA and dicapthon were 120 and 2749 M^{-1}, respectively.[18] In these current studies, the degradation of α-NA in a micellar CTAB system containing IBA was studied at 30°C. The substrate binding constants were found to be 174 and 541 M^{-1} in phosphate buffer solution. Based on this information, it can be deduced that 174 and 541 M^{-1} were for IBA and the α-NA binding constants, respectively. The difference between the IBA binding constant found in this work and the previously reported value might be due to a

Table 3. Summary of the Parameter Estimates Obtained From the Analysis of the Rate Constant Versus Surfactant Concentration Data in the System With HPMC E5

Pseudophase Parameters	Concentration of HPMC E5, % w/v[b]			
	0% HPMC	0.02% HPMC	0.1% HPMC	0.3% HPMC
K_{IBA} (M^{-1})	174 (14)	151 (12)	146 (12)	120 (11)
K_{NA} (M^{-1})	541 (35)	517 (33)	494 (31)	455 (30)
$\overline{k}_m$(M/min)	5.7×10^{-4} (0.2×10^{-4})	6.4×10^{-4} (0.2×10^{-4})	5.6×10^{-4} (0.2×10^{-4})	5.9×10^{-4} (0.2×10^{-4})
k_m (min^{-1})[a]	1.4×10^{-4}	1.6×10^{-4}	1.4×10^{-4}	1.5×10^{-4}
k_b (min^{-1})	6.2×10^{-4} (0.1×10^{-4})	7.0×10^{-4} (0.0×10^{-4})	5.4×10^{-4} (0.1×10^{-4})	8.0×10^{-4} (0.0×10^{-4})
C_{opt} (M)[c]	3.2×10^{-3}	3.5×10^{-3}	3.7×10^{-3}	4.2×10^{-3}
R^2	0.993	0.991	0.991	0.991

[a]Assuming a molar volume for CTAB in the micellar form of 0.25 M^{-1}.
[b]The number between brackets is the standard error.
[c]CTAB concentration at the highest rate constant.

change in either the reaction components or the temperature, or both. Temperature, for example, alters micelle formation and increases the dissociation constant of weak acids.[12,19]

Upon HPMC addition, the cationic surfactant still had an effect on the hydrolysis of α-NA. However, HPMC addition resulted in a decrease in the observed rate constant at any given CTAB concentration. The higher the HPMC concentration, the lower was the rate constant. The reason is that the binding constants of both IBA and α-NA decreased systematically as the concentration of HPMC increased. For example, the IBA and the α-NA binding constants decreased from 174 to 120 M^{-1} and from 541 to 455 M^{-1}, respectively, when the concentration of HPMC E5 was increased from 0.0 to 0.3% w/v. On the other hand, the micellar rate constant, k_m, did not appear to be affected by the addition of HPMC and it remained within the range of 1.4×10^{-4} to 1.6×10^{-4} min^{-1} for HPMC E5 concentrations of 0.02, 0.1, and 0.3% w/v. When the results from different grades of HPMC were compared, the observed rate constants did not seem to be influenced by HPMC grade (Fig. 4).

The aforementioned results indicate that the decrease in the observed reaction rate constants upon the addition of HPMC was due to decreased substrate binding. Therefore, substrate concentrations in the micellar pseudophase were lower than before the addition of polymer, but the reactivity in the micellar environment was not decreased. Furthermore, the viscosity increase in the bulk phase resulting from the addition of the polymer was not responsible for the decrease in the reaction rate constant. If that had been the case, then the observed rate constants should have decreased more when HPMC E15 or HPMC E50 was added than when HPMC E5 was added, since

Table 4. Summary of the Parameter Estimates Obtained From the Analysis of the Rate Constant Versus Surfactant Concentration Data in the System With HPMC E15

Pseudophase Parameters	Concentration of HPMC E15, % w/v[b]			
	0% HPMC	0.02% HPMC	0.1% HPMC	0.3% HPMC
K_{IBA} (M^{-1})	174 (14)	166 (14)	148 (6)	120 (12)
K_{NA} (M^{-1})	541 (35)	537 (37)	492 (16)	451 (34)
$\overline{k}_m$(M/min)	5.7×10^{-4} (0.2×10^{-4})	5.6×10^{-4} (0.0×10^{-4})	5.5×10^{-4} (0.1×10^{-4})	6.0×10^{-4} (0.2×10^{-4})
k_m (min^{-1})[a]	1.4×10^{-4}	1.4×10^{-4}	1.4×10^{-4}	1.5×10^{-4}
k_b (min^{-1})	6.2×10^{-4} (0.1×10^{-4})	7.0×10^{-4} (0.0×10^{-4})	6.0×10^{-4} (0.0×10^{-4})	7.0×10^{-4} (0.0×10^{-4})
C_{opt} (M)[c]	3.2×10^{-3}	3.3×10^{-3}	3.7×10^{-3}	4.3×10^{-3}
R^2	0.993	0.990	0.997	0.987

[a]Assuming a molar volume for CTAB in the micellar form of 0.25 M^{-1}.
[b]The number between brackets is the standard error.
[c]CTAB concentration at the highest rate constant.

Table 5. Summary of the Parameter Estimates Obtained From the Analysis of the Rate Constant Versus Surfactant Concentration Data in the System With HPMC E50

Pseudophase Parameters	Concentration of HPMC E50, % w/v[b]			
	0% HPMC	0.02% HPMC	0.1% HPMC	0.3% HPMC
K_{IBA} (M^{-1})	174 (14)	165 (15)	144 (12)	126 (10)
K_{NA} (M^{-1})	541 (35)	544 (40)	487 (29)	470 (27)
$\overline{k}_m$(M/min)	5.7×10^{-4} (0.2×10^{-4})	5.7×10^{-4} (0.4×10^{-4})	5.7×10^{-4} (0.4×10^{-4})	5.5×10^{-4} (0.1×10^{-4})
k_m (min^{-1})[a]	1.4×10^{-4}	1.4×10^{-4}	1.4×10^{-4}	1.4×10^{-4}
k_b (min^{-1})	6.2×10^{-4} (0.1×10^{-4})	7.0×10^{-4} (0.0×10^{-4})	6.7×10^{-4} (0.4×10^{-4})	7.1×10^{-4} (0.1×10^{-4})
C_{opt} (M)[c]	3.2×10^{-3}	3.3×10^{-3}	3.7×10^{-3}	4.1×10^{-3}
R^2	0.993	0.988	0.990	0.992

[a]Assuming a molar volume for CTAB in the micellar form of 0.25 M^{-1}.
[b]The number between brackets is the standard error.
[c]CTAB concentration at the highest rate constant.

the same concentration of HPMC E15 or HPMC E50 provides higher viscosities than HPMC E5.

Influence of SO_4^{2-} Ions on α-NA Hydrolysis Kinetics in Micellar Systems

The plots of observed rate constant versus micellar CTAB concentrations are presented in Figure 5. Nonlinear curve fitting was employed to calculate the pseudophase parameters reported in Table 6.

The addition of sodium sulfate caused a decrease in the observed rate constant at any CTAB concentration. The effect was not due to a change in reaction rate constant in the bulk phase, k_b, or the micellar rate constant, k_m. Sodium sulfate changed CTAB micelle formation, as indicated by the decrease in the CMC. Moreover, the addition of electrolytes to a micellar solution will cause competition between ionic species having the same charge, including reactive counterions in the Stern layer.[17] Thus, nonreactive counterions can interfere with the binding of reactive counterions causing rate inhibition.[13,18]

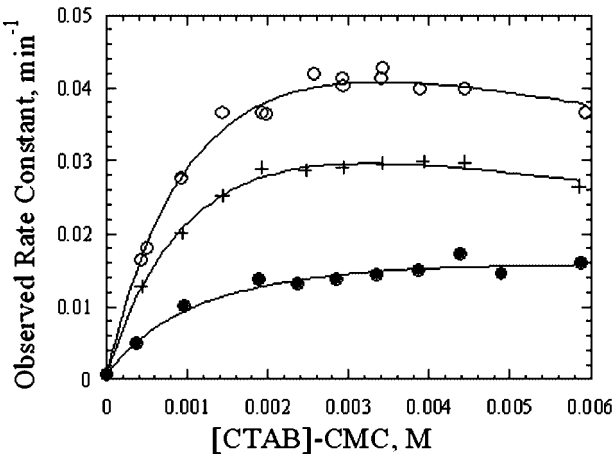

Figure 5. Observed rate constants for α-NA hydrolysis with CTAB-sodium sulfate and CTAB-HPMC gel at 30°C: (○) buffer, (+) sodium sulfate in buffer, and (●) 5% HPMC E50.

The calculated binding constants for the substrates from the pseudophase model supported this explanation. Sodium sulfate reduced the IBA binding constant from 174 to 98 M^{-1}. Conversely, the α-NA binding constant increased from 541 to 763 M^{-1}. The decrease in the IBA binding constant could be explained as follows. The anionic form of IBA (IBA^-) had to compete with SO_4^{2-} to bind to the polar head groups of the CTAB molecules. Since SO_4^{2-} carries a higher charge than IBA^-, it competes very effectively. SO_4^{2-} also compressed the electrical double layer surrounding the positively-charged head groups of CTAB and increased the aggregation number. The higher aggregation number should result in a greater volume in the palisade region of the micelle. This would likely increase the available region for solubilization of α-NA, a neutral substrate.

For one and one-half half-lives, the α-NA degradation (in the presence of IBA) was found to follow pseudo-first-order kinetics. Thus, a change in the amount of α-NA in the reaction region should not affect the reaction rate constant. On the other hand, the observed rate constant was dependent on the amount of IBA in the reaction region. The smaller the amount of IBA in the reaction region, the lower was the observed rate constant. The ionic strength of the system with sodium sulfate was 0.3 M, whereas that of the phosphate buffer solution alone was 0.17 M.

Table 6. Summary of the Parameter Estimates Obtained From the Analysis of the Rate Constant Versus Surfactant Concentration Data in Sodium Sulfate and CTAB-HPMC Gel Systems

	System[b]		
Pseudophase Parameters	Phosphate Buffer	Sodium Sulfate in Phosphate Buffer	CTAB-HPMC (5% w/v HPMC E50) Gel in Phosphate Buffer
K_{IBA} (M^{-1})	174 (14)	98 (9)	84 (17)
K_{NA} (M^{-1})	541 (35) .	763 (48)	448 (56)
$\overline{k}_m$(M/min)	5.7×10^{-4} (0.2×10^{-4})	5.5×10^{-4} (0.1×10^{-4})	3.8×10^{-4} (0.2×10^{-4})
k_m (min^{-1})[a]	1.4×10^{-4}	1.4×10^{-4}	9.5×10^{-5}
k_b (min^{-1})	6.2×10^{-4} (0.1×10^{-4})	6.1×10^{-4} (0.0×10^{-4})	7.2×10^{-4} (0.2×10^{-4})
C_{opt} (M)[c]	3.2×10^{-3}	3.6×10^{-3}	5.0×10^{-3}
R^2	0.993	0.990	0.971

[a]Assuming a molar volume for CTAB in the micellar form of 0.25 M^{-1}.
[b]The number between brackets is the standard error.
[c]CTAB concentration at the highest rate constant.

Changes in ionic strength result in changes in the activity coefficients of the substrates and of the substrates in the transition state (γ_{NA}, γ_{IBA}, and γ_{NA-IBA}). However, this reaction involves a neutral species and an ion, which means that the primary salt effect on the rate constant is not important. γ_{NA} is approximately unity and γ_{IBA} and γ_{NA-IBA} decrease to approximately the same extent. Additionally, there were no significant differences between the observed rate constants with and without sodium sulfate when no CTAB was added. Changes in ionic strength also caused the pK_a of IBA to change (secondary salt effect). Using the Davies equation, the difference in the apparent pK_a of IBA was approximately 0.035 pH units lower, which is small. Therefore, sodium sulfate retarded the catalytic ability of CTAB by decreasing the IBA binding constant without, apparently, changing the reaction environment.

α-NA Hydrolysis Kinetics in a CTAB-HPMC Gel System

The observed rate constant profile in the CTAB-HPMC gel system was compared to that of the buffer samples (without polymer), as presented in Figure 5. The bimolecular reaction equation for the pseudophase model was fit to the rate constant data and the parameters are reported in Table 6.

HPMC E50 was selected for preparing gel-like samples. Since the difference in the rate constants between the HPMC gel system without CTAB and the buffer solution without CTAB was not large, gel conditions were not likely to disturb the reaction in the bulk phase. However, gel conditions did seem to disturb the micellar pseudophase. In the micellar pseudophase, the high concentration of HPMC E50 diminished the concentration advantage, as evidenced by the decreased substrate binding constants and the lowered reaction rate constant, k_m. Moreover, the decrease in k_m implied that the high concentration of the polymer might have impeded the bimolecular reaction, possibly through environmental effects. This could occur through orientation effects on the substrates.

CONCLUSION

The formation of CTAB micelles was facilitated by the addition of electrolytes. According to the surface tension experiments, the surface tension became lower when HPMC was added to the surfactant solutions. The CAC was found to be higher than the CMC when surface tension was measured. The solubilization method did not show a difference between the CAC and the CMC. The α-NA degradation with IBA present was accelerated in the micellar environment due to the concentration effect. When either HPMC or sodium sulfate was introduced into the solutions containing micellar CTAB, the observed reaction rate constant decreased. In both cases, this was due to a decrease in the binding constants of the reactants to the micelles. In the first case, the addition of sodium sulfate decreased IBA binding. In the second case, HPMC decreased both α-NA and IBA binding.

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