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Catalysis and Inhibition of the Alkaline Hydrolysis of Benzocaine and Analogs by a Cationic Surfactant

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The first-order rate constants for the alkaline hydrolysis of ethyl benzoate and ethyl *p*-nitro- and *p*-aminobenzoates (benzocaine), catalyzed by CTAB, a cationic surfactant, were measured at 25° in the presence of sodium hydroxide and sodium bromide. Although the alkaline hydrolysis of esters is generally accelerated by cationic micelles, that of the three benzoates tended to be inhibited by CTAB micelles under the following conditions: (i) at high CTAB concentrations, (ii) at high concentrations of sodium hydroxide, (iii) at high concentrations of an added salt (including buffer components), (iv) at high ester concentrations, and (v) for compounds possessing a small value of the Hammett substituent constant. These effects were explained quantitatively on the basis of a theory in which the total counterion concentration is assumed to remain constant regardless of the concentrations of CTAB, sodium bromide, and sodium hydroxide, and in which the association constant for a CTAB micelle and an ester, the degree of counterion binding to CTAB micelles, the ion-exchange constant, and a relative rate constant are taken as parameters.

Keywords——micellar inhibition; surface pH; ion-exchange; Hammett equation; benzocaine; alkaline hydrolysis; drug stabilization

Introduction

Extensive studies of the effects of surfactant micelles on chemical reactions have been made in relation to the synthesis of organic compounds, the stabilization of drugs in aqueous media, enzymatic catalyses, and reactions at biomembrane surfaces (since micelles can be regarded as a model of enzymes and biomembranes[2]). Most of the studies published before 1975 have been summarized in a book.[2]

In most cases, micellar effects are explicable on the basis of simple electrostatic considerations, such as those set forth by Hartley:[3] cationic micelles enhance the rates of reactions of nucleophilic anions with unchanged compounds, whereas anionic micelles retard them, but catalyze reactions involving cations. Uncharged and zwitterionic micelles will have little or no effect on reaction rates.[2] A different tendency was observed, however, in the alkaline hydrolysis of aliphatic esters. In this case both cationic and anionic surfactants have been found to retard the rate of hydrolysis of esters,[2] *e. g.*, acetyl salicylate,[4] ethyl benzoate,[5] and acyl choline chloride and iodide.[4]

According to Riegelman,[6] the alkaline hydrolysis of ethyl *p*-aminobenzoate (benzocaine) is catalyzed by hexadecyltrimethylammonium bromide (CTAB) at low concentrations above the critical micellization concentration (cmc), and inhibited at higher concentrations. On the other hand, Meakin *et al.*[7] reported that the alkaline hydrolysis of aromatic esters possessing

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[1] Location: *Misasagi, Yamashina-ku, Kyoto 607, Japan.*

[2] J.H. Fendler and E.J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York, 1975, Chapters 4—8.

[3] G.S. Hartley, *Trans. Faraday Soc.*, **30**, 444 (1934).

[4] H. Nogami, S. Awazu, and N. Nakajima, *Chem. Pharm. Bull.*, **10**, 503 (1962); H. Nogami, S. Awazu, and M. Iwatsuru, *ibid.*, **11**, 1251 (1963).

[5] A.G. Mitchell, *J. Pharm. Pharmacol.*, **14**, 172 (1962).

[6] S. Riegelman, *J. Am. Pharm. Assoc.*, **49**, 339 (1960).

[7] B.J. Meakin, I.K. Winterborn, and D.J.G. Davies, *J. Pharm. Pharmacol.*, **23**, *Suppl.*, 25S (1971).

an amino group in the *para*-position, such as benzocaine, was inhibited by CTAB at any concentration, whereas that of esters possessing a nitro group in the *para*-position, such as ethyl *p*-nitrobenzoate, was catalyzed by CTAB. This difference in the effects of CTAB was explained on the basis of the character of the *p*-nitro and *p*- amino groups.[7,8] A recent study,[9] however, found that the alkaline hydrolysis of 2-diethylaminoethyl *p*-nitrobenzoate, as well as that of 2-diethylaminoethyl *p*-aminobenzoate (procaine), was inhibited by CTAB.

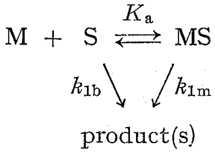
In this work, we studied the effects of CTAB on the alkaline hydrolysis of ethyl *p*-aminobenzoate, ethyl benzoate, and ethyl *p*-nitrobenzoate. Micellar catalysis or inhibition of these reactions depended on experimental conditions, such as the concentrations of CTAB, hydroxide ions, and sodium bromide, and the kind of substituents of these benzoates, and these results together with apparently exceptional and controversial data were analyzed theoretically.

Theory

Our theoretical basis took into consideration the following factors, which are involved in the micellar effects on chemical reactions. It was assumed that chemical reactions proceed simultaneously in the bulk solution and at the micellar surface, where the concentrations of esters and hydroxide ions, as well as the rate constants, are different. An ion-exchange model is suitable for dealing quantitatively with these factors.[10,11]

This model was developed under the following assumptions and conditions. The concentration of cationic surfactant, C_t, is sufficiently low for the intermicellar interaction to be negligible, and is much higher than that of esters, so that the presence of this reactant has no effect on micellar properties. The ester linkage of the reactant is located at the micellar surface. All counterions, *viz.* ions I and X, are univalent and hydrophilic. The total concentration of ester and that of hydroxide ions are kept constant. The cmc, C_c does not depend on the surfactant concentration. Similar assumptions form the basis of other theories.[11] Symbols used here are summarized in the appendix.

We will consider a reaction depicted as



$$\begin{tikzcd} M + S \arrow[rr, shift left, "K_a"] \arrow[dr, "k_{1b}"'] & & MS \arrow[ll, shift left] \arrow[dl, "k_{1m}"] \\ & \text{product(s)} & \end{tikzcd} \tag{1}$$

Here an ester S associates a micelle M, forming a complex MS, and the ester reacts simultaneously in the bulk solution and on micelles under first-order conditions.

The observed first-order rate constants, k_1, can be written as[10-12]

$$k_1 = \frac{k_{1b} + k_{1m}K_a(C_t - C_c)}{1 + K_a(C_t - C_c)} \tag{2}$$

Taking into account that the concentrations of a catalytically active ion, I, in the bulk solution and at the micellar surface generally depend on the reaction conditions, we can rewrite Eq. (2) as[11]

$$k_1 = \frac{k_{2b}[\mathrm{I}]_b + k_{2m}[\mathrm{I}]_m K_a(C_t - C_c)}{1 + K_a(C_t - C_c)} \tag{3}$$

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[8] I.K. Winterborn, B.J. Meakin, and D.J.G. Davies, *J. Pharm. Sci.*, **63**, 64 (1974).

[9] H. Tomida, T. Yotsuyanagi, and K. Ikeda, *Chem. Pharm. Bull.*, **26**, 148 (1978).

[10] L.S. Romsted, "Solubilization, Micellization, and Microemulsions," Vol. 2, ed. by K.L. Mittal, Plenum, New York, 1977, p. 509.

[11] N. Funasaki, *J. Phys. Chem.*, **83**, 1998 (1979) and references cited therein.

[12] N. Funasaki, *J. Colloid Interface Sci.*, **64**, 461 (1978).

Following Romsted,[10] we assume that the total counterion concentration at the micellar surface remains constant, regardless of the concentration and kind of counterions and those of surfactants:

$$[\mathrm{I}]_\mathrm{m} + [\mathrm{X}]_\mathrm{m} = \beta s \tag{4}$$

Here $[\mathrm{X}]_\mathrm{m}$ is the concentration of catalytically inactive ions, X, at the micellar surface, and s is a concentration expressed as moles of micellized surfactant divided by the volume of the Stern layer, which is present at the micellar surface.

We define the ion-exchange constant, K_IX, for the ions I and X as

$$K_\mathrm{IX} = \frac{[\mathrm{I}]_\mathrm{b}[\mathrm{X}]_\mathrm{m}}{[\mathrm{I}]_\mathrm{m}[\mathrm{X}]_\mathrm{b}} \tag{5}$$

The material balance of ion X yields

$$C_\mathrm{t} + C_\mathrm{S} = [\mathrm{X}]_\mathrm{m}(C_\mathrm{t}-C_\mathrm{c})/s + [\mathrm{X}]_\mathrm{b} \tag{6}$$

Also, the material balance of ion I yields

$$[\mathrm{I}]_\mathrm{t} = [\mathrm{I}]_\mathrm{m}(C_\mathrm{t}-C_\mathrm{c})/s + [\mathrm{I}]_\mathrm{b} \tag{7}$$

Elimination of $[\mathrm{I}]_\mathrm{b}$, $[\mathrm{X}]_\mathrm{m}$, and $[\mathrm{X}]_\mathrm{b}$ from Eq. (4)—(7) yields a quadratic equation:

$$\begin{aligned}(K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})[\mathrm{I}]_\mathrm{m}^2 + \{K_\mathrm{IX}(C_\mathrm{t}+C_\mathrm{S}) + [\mathrm{I}]_\mathrm{t} \\ - (K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})\beta\}s[\mathrm{I}]_\mathrm{m} - \beta s^2[\mathrm{I}]_\mathrm{t} = 0\end{aligned} \tag{8}$$

The concentration of catalytically active ions at the micellar surface can be expressed as a root of Eq. (8):

$$[\mathrm{I}]_\mathrm{m} = \frac{-\{K_\mathrm{IX}(C_\mathrm{t}+C_\mathrm{s})+[\mathrm{I}]_\mathrm{t}-(K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})\beta\}s+[\{K_\mathrm{IX}(C_\mathrm{t}+C_\mathrm{s})+[\mathrm{I}]_\mathrm{t}-(K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})\beta\}^2+4(K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})\beta[\mathrm{I}]_\mathrm{t}]^{1/2}s}{2(K_\mathrm{IX}-1)(C_\mathrm{t}-C_\mathrm{c})} \tag{9}$$

From Eq. (3), (7), and (9), we can predict the k_1 *vs.* C_t relation, using the parameter shown in Table I. The degree of counterion binding, β, has already been determined by *p*Br measurements.[12] The value of the ion-exchange constant, K_OHBr, was reported to be 5[13] and 40[14] from analyses of CTAB-catalyzed reactions. We employed a value of $K_\mathrm{OHBr}=10$, which was determined from an analysis of the dissociation constant of a pH indicator solubilized on CTAB micelles.[11] The value of s has been estimated to be 2.86,[15] 3.0,[10] 3.85,[16] and 7.1[13] M. The cmc value was calculated from an empirical equation obtained in solutions with various sodium bromide concentrations.[12]

Table I. Values of Parameters

Parameter	Value	Basis of estimation
β	0.802	*p*Br measurements[12]
K_OHBr	10	Taken from ref. 11
s	3	Micelle dimension[10]
C_c	$10^{-4.61}(C_\mathrm{c}+C_\mathrm{S}+[\mathrm{OH}]_\mathrm{b})^{-0.6}$	Taken from ref. 12
ρ_b	1.56	Taken from Fig. 6
ρ_m	2.15	Taken from Fig. 6

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13) C.A. Bunton, N. Carrasco, S.K. Huang, C.H. Paik, and L.S. Romsted, *J. Am. Chem. Soc.*, **100**, 5420 (1978).

14) M. Almgren and R. Rydholm, *J. Phys. Chem.*, **83**, 360 (1979).

15) A.K. Yatsimirski, K. Martinek, and I.V. Berezin, *Tetrahedron*, **27**, 2855 (1971).

16) K. Martinek, A.K. Yatsimirski, A.P. Osipov, and I.V. Berezin, *Tetrahedron*, **29**, 963 (1973).

Experimental

Materials——CTAB from Nakarai Chemicals Co. was recrystallized from a mixture of ethanol and acetone (1: 1) after extraction with diethyl ether; the purified specimen showed no minimum in the surface tension *vs.* log surfactant concentration curve. Ethyl *p*-nitrobenzoate, ethyl benzoate, and ethyl *p*-aminobenzoate were purchased from Tokyo Kasei Organic Chemicals Co. Ethyl *p*-nitrobenzoate was recrystallized from 70% ethanol. Other reagents were used without further purification. The ion-exchanged water was distilled twice before use.

Methods——Kinetic measurements were carried out spectrophotometrically with a Shimadzu UV-210 double beam spectrophotometer equipped with a cell holder through which water from a thermostated bath (25°) was continuously circulated. Each reaction mixture was made up of 3 ml of a sodium hydroxide and sodium bromide solution and 3—10 µl of an acetonitrile solution of 0.01 M ester. First-order rate constants were obtained in the usual manner.[11,12,17]

The association constant for ethyl *p*-nitrobenzoate and a CTAB micelle was determined by solubility measurements as already reported.[12]

Results

Ethyl *p*-Aminobenzoate (Benzocaine)

Riegelman[6] investigated the effect of CTAB on the alkaline hydrolysis of ethyl *p*-aminobenzoate in 0.04 M sodium hydroxide solution at 30°, and found that CTAB at 1.8 mM accelerated this reaction, whereas CTAB at higher concentrations decelerated it. On the other hand, Meakin *et al.*[7] measured the rate of this reaction at a pH of 10.64 (0.2 M sodium carbonate and 0.2 M sodium hydrogen carbonate buffer) and at 25°. These authors found that this reaction was retarded by CTAB at all concentrations investigated.

With these studies in mind, we investigated the effect of CTAB at various sodium hydroxide concentrations. As shown in Fig. 1, at low sodium hydroxide concentrations (0.005 and 0.02

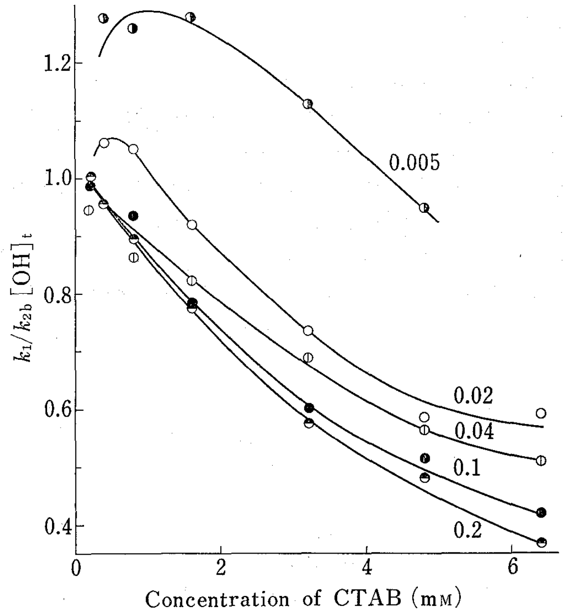

Fig. 1. Relative Rates of Hydrolysis of Ethyl *p*-Aminobenzoate plotted against the CTAB Concentration at Various Sodium Hydroxide Concentrations and at 25°

◑, 0.005 M; ○, 0.02 M; ⦶, 0.04 M; ●, 0.1 M; ⊖, 0.2 M.
The number attached to each line indicates the sodium hydroxide concentration (M).

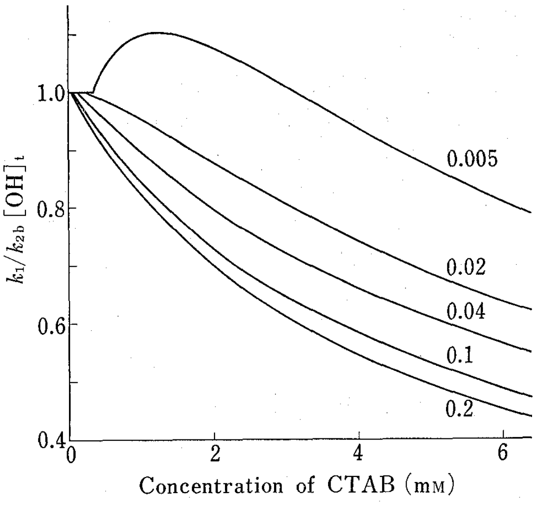

Fig. 2. Calculated Relative Rates of Hydrolysis of Ethyl *p*-Aminobenzoate plotted against the CTAB Concentration at Various Sodium Hydroxide Concentrations and at 25°

The number attached to each line indicates the sodium hydroxide concentration (M).

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[17] N. Funasaki, *J. Phys. Chem.*, **83**, 237 (1979).

Table II. Kinetic and Equilibrium Parameters

Substituent	C_s(M)	K_a(M^{-1})	k_{2b}(M^{-1} min^{-1})	r	σ[a]
p-NO_2	0	240[b]	28.4	0.080	0.778
	0.01	240	26.8	0.080	0.778
	0.1	240[c]	22.8	0.080	0.778
p-H	0	220	1.80	0.028	0
	0.1	220[c]			
p-NH_2	0	250	0.183	0.010	−0.66
	0.1	250[c]	0.183	0.010	−0.66

a) Taken from ref. 18.
b) This work.
c) Calculated by using the partition constant8) and partial specific volume of CTAB micelles.19) The ionic strength may be higher than 0.1 M.

M), CTAB accelerated this reaction at relatively low concentrations above the cmc, and decelerated it at higher concentrations. At higher sodium hydroxide concentrations, however, CTAB inhibited this reaction at all concentrations above the cmc. In the absence of CTAB, k_{1b} was proportional to the total sodium hydroxide concentration, and the second-order rate constant, k_{2b}, in bulk solution was evaluated from this linear relationship, as shown in Table II.

By using the partition constant8) of ethyl p-aminobenzoate between the bulk solution and the CTAB micelle as well as the partial specific volume19) of the CTAB micelle, we can estimate the association constant of ethyl p-aminobenzoate with CTAB micelles. Table II includes the association constant thus obtained.

By employing a value of k_{2m}/k_{2b}, *viz.* $r=0.010$, we calculated theoretical values of k_1 from Eq. (3), (7), and (9). As shown in Fig. 2, these theoretical curves effectively reproduced the trends of the observed data in Fig. 1. That is, as the total concentration of hydroxide ions and that of CTAB decrease, the concentration of hydroxide ions onto CTAB micelles, *viz.* $[OH]_m/[OH]_t$, becomes greater, and therefore rate enhancement can occur. At high concentrations of hydroxide ions and CTAB, however, the reaction rate is reduced because of the very low reactivity, *viz.* $k_{2m} \ll k_{2b}$, at the micellar surface, even if hydroxide ions are somewhat concentrated onto CTAB micelles, *viz.* $[OH]_m > [OH]_b$.

As shown in Fig. 3, the addition of 0.1 M sodium bromide in 0.02 M (●) and 0.2 M (○) sodium hydroxide solutions slightly decreased the rate of alkaline hydrolysis of ethyl p-aminobenzoate in the presence of CTAB (*cf.* Fig. 2). The solid line is calculated from Eq. (3), (7), and (9), employing the parameters for ethyl p-aminobenzoate given in Tables I and II. This line did not depend significantly on sodium hydroxide concentration in the range of 0.02 M to 0.2 M. The agreement between theory and experiment is fairly good. The broken line is calculated from Eq. (7) and (9) as well as Eq. (10):

$$k_1 = \frac{k_{2b}[I]_b}{1+K_a(C_t-C_c)} \tag{10}$$

This line also did not depend significantly on sodium hydroxide concentration in the range of 0.02 M to 0.2 M. Equation (10) is applicable to the case where $k_{2b}[I]_b \gg k_{2m}[I]_m K_a(C_t-C_c)$.

Since $k_{2m} \ll k_{2b}$ in the case of ethyl p-aminobenzoate and $[I]_m/[I]_b$ is smaller because of the presence of sodium bromide at a high concentration of 0.1 M, the solid and broken lines are very, close, as shown in Fig. 3. That is, the reaction takes place largely in the bulk solution and the extent of inhibition is determined by the magnitude of the association constant. Such a case arises in the alkaline hydrolysis of procaine, the rate of which was shown to depend on the magnitude of the association constant for micelles rather than on the charge type of the micelles.9)

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18) D.H. McDaniel and H.C. Brown, *J. Org. Chem.*, 23, 420 (1958).
19) C. Tanford, Y. Nozaki, J.A. Reynolds, and S. Makino, *Biochemistry*, 13, 2369 (1974).

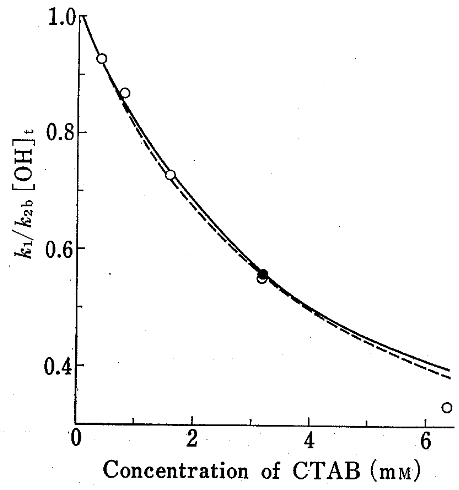

Fig. 3. Effects of Addition of 0.1 M Sodium Bromide on the Relative Rates of Hydrolysis of Ethyl *p*-Aminobenzoate in 0.02 M (●) and 0.2 M (○) Sodium Hydroxide Solutions at 25°

The solid and broken lines were calculated from Eqs. (3) and (10), respectively, with Eqs. (7) and (9).

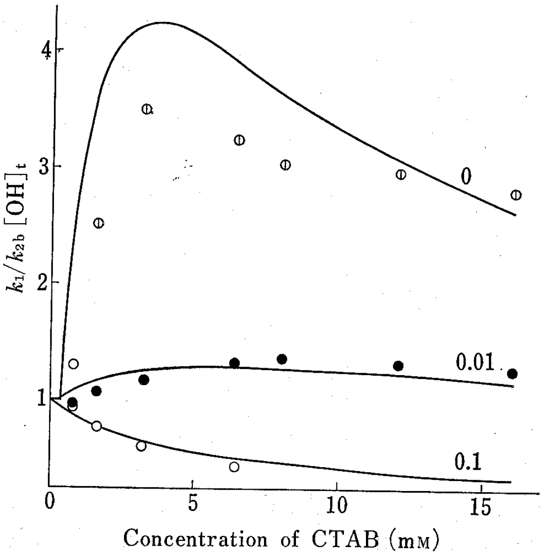

Fig. 4. Relative Rates of Hydrolysis of Ethyl *p*-Nitrobenzoate plotted against the CTAB Concentration at 0.005 M Sodium Hydroxide Solution at Various Sodium Bromide Concentrations and at 25°

The number attached to each line indicates the concentration (M) of sodium bromide added.

The solid lines were calculated from Eqs. (3), (7), and (9).

This does not conflict with the electrostatic theory,[9] but means that the electrostatic effect is minimized by the presence of a large amount of a salt (0.2 M).

Ethyl *p*-Nitrobenzoate

Meakin *et al.* reported that CTAB catalyzed the alkaline hydrolysis of ethyl *p*-nitrobenzoate.[7,8] Figure 4 shows the effect of CTAB on the alkaline hydrolysis of ethyl *p*-nitrobenzoate in 0.005 M sodium hydroxide solution. In this figure, the number on each curve indicates the concentration of sodium bromide added. The solid lines were calculated from Eq. (3), (7), and (9) by employing the values of K_{OHBr}, β, s, C_c, K_a, and r shown in Tables I and II. In 0.1 M sodium bromide solution, CTAB inhibited this reaction. This reduction can be attributed to the displacement of hydroxide ions from the micellar surface by added bromide ions. CTAB had too limited a solubility to measure the reaction rate at high CTAB concentrations in 0.1 M sodium bromide solution.

Ethyl Benzoate

As shown in Fig. 5, CTAB catalyzed this reaction in 0.005 M sodium hydroxide solution, regardless of the CTAB concentration. In 0.04 M sodium hydroxide solution, however, CTAB at low concentrations catalyzed the hydrolysis, whereas this surfactant inhibited it at high concentrations. These tendencies were simulated by the theoretical curves, which were calculated from Eq. (3), (7), and (9) by employing the values of K_{OHBr}, β, s, C_c, K_a, and r shown in Tables I and II. The agreement between theory and experiment is worse for ethyl benzoate than for ethyl *p*-amino- and *p*-nitrobenzoates.

Chemical Structure *vs.* Reactivity Relationship

Bender[20] reported that the second-order rate constant of alkaline hydrolysis of ethyl benzoate is $1.8\,M^{-1}min^{-1}$ (*cf.* Table II) in water (dielectric constant 80) and $0.0522\,M^{-1}min^{-1}$ in a mixture of 33% dioxane–water (dielectric constant 49) at 25.12°. In general, the rate constant

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[20] M.L. Bender, *J. Am. Chem. Soc.*, 73, 1626 (1951).

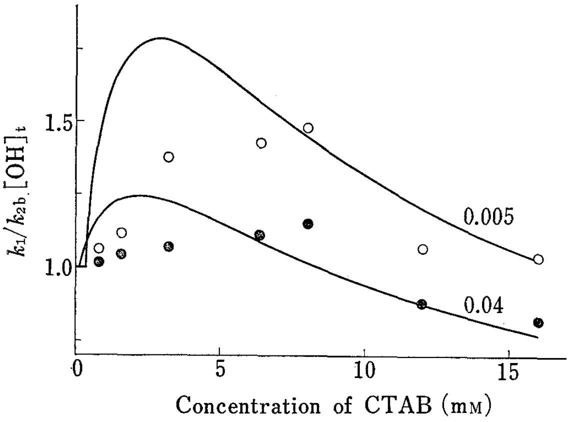

Fig. 5. Relative Rates of Hydrolysis of Ethyl Benzoate plotted against the CTAB Concentration at 25° and at 0.005 M (○) and 0.04 M (●) Sodium Hydroxide

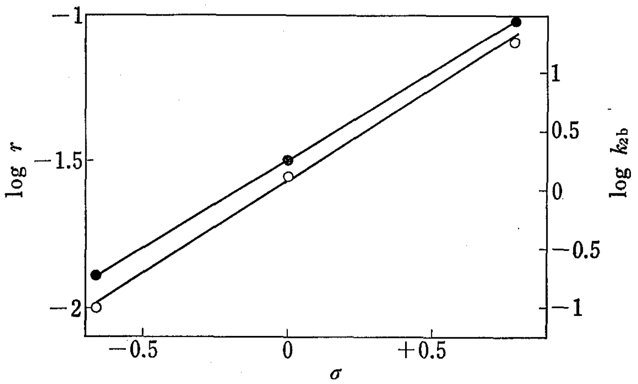

Fig. 6. Plots of log r (○) and log k_{2b} (●) against Hammett's Substituent Constants at 25° for the Three Benzoates

at the micellar surface is smaller than that in aqueous solution, and this result has been rationalized in terms of a lower polarity of the micellar surface.[11,13,21] Since the dielectric constant at the micellar surface is estimated to be about 36,[22] a value of $r=0.028$ seems reasonable in terms of Bender's data.

As shown by the solid circles in Fig. 6, the Hammett equation holds for the three benzoates in water:

$$\log k_{2b} = \rho_b\sigma + \text{constant} \tag{11}$$

A similar equation may hold for these benzoates at the micellar surface:

$$\log k_{2m} = \rho_m\sigma + \text{constant} \tag{12}$$

From Fig. 6, we obtain the following equation:

$$\log r = (\rho_m-\rho_b)\sigma + \text{constant} \tag{13}$$

This equation may hold for other benzoates, as already suggested.[8] The values of ρ_b and ρ_m determined from Fig. 6 are included in Table I, and are close to those already reported.[8]

Discussion

Inhibition of the Alkaline Hydrolysis of Benzoates by Cationic Micelles

In general, the alkaline hydrolysis of esters is catalyzed by cationic micelles.[2] As expected from the present study, the alkaline hydrolysis of the three benzoates tended to be inhibited by CTAB micelles, at least under the following conditions:

(i) When the surfactant concentration is high. Under this condition, since catalytic hydroxide ions at the micellar surface are displaced by bromide ions dissociated from added CTAB, inhibition can occur.

(ii) In solution containing a salt at high concentrations. In such solutions, the hydroxide ion concentration at the micellar surface and the value of $[OH]_m/[OH]_t$ are decreased by catalytically inactive ions, as observed in the cases of ethyl *p*-aminobenzoate (Fig. 3) and ethyl *p*-nitrobenzoate (Fig. 4).

(iii) In solutions containing hydroxide ions at high concentrations. This occurs in the cases of ethyl *p*-aminobenzoate (Fig. 1 and 2) and ethyl benzoate (Fig. 5). As the total concen-

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[21] C.A. Bunton, L.S. Romsted, and H.J. Smith, *J. Org. Chem.*, **43**, 4299 (1978).

[22] P. Mukerjee and A. Ray, *J. Phys. Chem.*, **70**, 2144 (1966); N. Funasaki, *Nippon Kagaku Kaishi*, **1976**, 722.

tration of each counterion, *viz.* OH^- and Br^-, increases, its concentration at the micellar surface also increases. As expected from Eq. (4), the total counterion concentration at the micellar surface remains constant regardless of that in the bulk solution. Hence, as the total hydroxide ion concentration is raised, the concentration of hydroxide ions onto micelles, *viz.* $[OH]_m/[OH]_t$, becomes less. In an extreme case, the total hydroxide ion concentration is higher than βs. In this case, the hydroxide ion concentration in the bulk solution is higher than that at the micellar surface. Since the relative rate, $k_1/k_{2b}[OH]_t$, depends on the value of $[OH]_m/[OH]_t$ rather than on the absolute values of $[OH]_m$ and $[OH]_b$, the addition of CTAB in solutions of high hydroxide ion concentrations can decelerate the alkaline hydrolysis of esters.

(iv) For compounds possessing a small value of Hammett's substituent constant. The alkaline hydrolysis of these compounds is markedly decelerated when the dielectric constant of media decreases. Even if hydroxide ions are more or less concentrated onto CTAB micelles, inhibition can occur.

(v) At high ester concentrations. When the total concentration of an ester is high, many molecules of the ester penetrate into charged micelles. This penetration causes a decrease in the surface charge density of the micelles. As a result, β, which is proportional to the concentration of counterions at the micellar surface, decreases, and inhibition can be induced. In this case, as the total CTAB concentration increases above the cmc, the β value increases asymptotically to that in ester-free solution.

For instance, Mitchell5) reported that the hydrolysis of 0.05 M ethyl benzoate in 0.1 M sodium hydroxide was decelerated by the addition of tetradecyltrimethylammonium bromide at 35°. Blandamer and Reid23) found that a reaction catalyzed by ionic micelles is decelerated by the addition of alcohols, and that the extent of deceleration increases with increase in the chain length of the alcohols. This phenomenon may be explained in terms of the decrease in the surface charge density of the micelles upon penetration by the alcohols.

Effects of Buffers

Most of the reactions catalyzed by surfactants have been carried out in buffer solutions. The presence of buffers, however, may lead to several complications in analyzing the kinetic data.12,17) Some components steming from buffers bind to micelles, driving out catalytically active ions from the micellar surface, and may catalyze or inhibit reactions both in the bulk solution and on micelles.11,12) The present study, therefore, was made in the absence of buffers.

Meakin *et al.*7) studied the CTAB-catalyzed hydrolysis of ethyl *p*-nitrobenzoate at a pH of 10.64, controlled with 0.2 M sodium carbonate and 0.2 M sodium hydrogen carbonate buffer. On the other hand, Romsted10) and others11) developed equations, based on a condition of constant total hydroxide ion concentration, for buffered systems.

With these studies in mind, we compared two theories applicable at a constant total hydroxide ion concentration and at a constant pH, under the reaction conditions employed by Meakin *et al.*7)

Elimination of $[X]_m$ and $[X]_b$ from Eq. (4)—(6) yields, at a constant bulk hydroxide ion concentration:

$$K_{IX}(C_t-C_c)[I]_m^2+\{K_{IX}(C_t+C_s)+[I]_b \\ -K_{IX}(C_t-C_c)\beta\}s[I]_m-[I]_b\beta s^2=0 \tag{14}$$

That is,

$$[I]_m=\frac{-\{K_{IX}(C_t+C_s)+[I]_b-K_{IX}(C_t-C_c)\beta\}s+[\{K_{IX}(C_t+C_s)+[I]_b-K_{IX}(C_t-C_c)\beta\}^2+4K_{IX}(C_t-C_c)[I]_b\beta]^{1/2}s}{2K_{IX}(C_t-C_c)} \tag{15}$$

From Eq. (3) and (15), we can produce theoretical plots of k_1 *vs.* C_t by employing the parameters for ethyl *p*-nitrobenzoate shown in Tables I and II.

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23) M.J. Blandamer and D.J. Reid, *J. Chem. Soc. Faraday I*, **71**, 2156 (1975).

The broken lines thus calculated are shown in Fig. 7, where we neglected the contributions of sodium carbonate and sodium hydrogen carbonate to C_s. The solid lines were calculated from Eq. (3), (7), and (9), employing a total hydroxide ion concentration of 4.37×10^{-4} M (pH 10.64). The data of Meakin *et al.*7) are plotted in this figure.

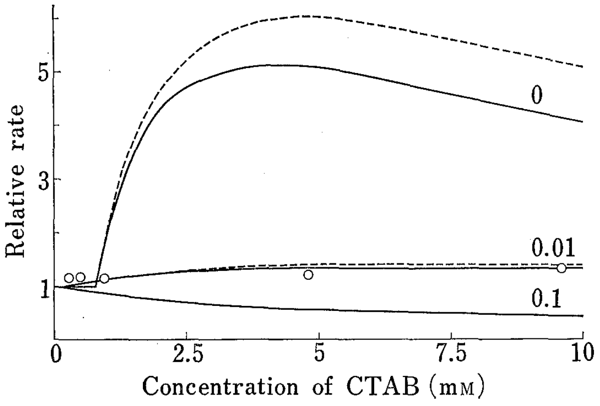

Fig. 7. Relative Rates *vs.* CTAB Concentration at 25°

The broken lines indicate the $k_1/k_{2b}[OH]_b$ *vs.* CTAB concentration relation calculated from Eq. (3) and (15).

The solid lines indicate the $k_1/k_{2b}[OH]_t$ *vs.* CTAB concentration relation calculated from Eq. (3), (7), and (9).

The plots are taken from ref. 7.

The broken line predicts higher rate constants than the corresponding solid line at any salt concentration. As the salt concentration is increased, the two lines become closer, since the amount of hydroxide ions bound to CTAB micelles then decreases. Experimental data were close to those expected at infinite dilution of the buffer in the presence of 0.01 M sodium bromide. When the presence of 0.2 M sodium carbonate and 0.2 M sodium hydrogen carbonate is taken into account, the observed rates seem rather high. Carbonate and hydrogen carbonate ions bind strongly to CTAB micelles, as already estimated from *p*Br measurements,12) and carbonate ions catalyze the hydrolysis of *p*-nitrophenyl carboxylates.17) A similar catalysis by carbonate ions may be involved in the hydrolysis of ethyl *p*-nitrobenzoate.

Limitations of the Present Theory

The assumption that the total counterion concentration is constant, *viz.* Eq. (4), is not rigorous, as already pointed out in analyses of kinetic14) and equilibrium11) measurements. For the three benzoates investigated here, the theoretical plots predict higher values than most of the observed ones, particularly at relatively low concentrations of CTAB above the cmc. Some of this discrepancy is explicable if the degree of hydroxide ion binding to CTAB micelles is lower than that of bromide ions, *viz.* $\beta=0.802$.

In this work, the hydroxide ion concentration at the micellar surface has been discussed theoretically, but not measured experimentally. Some experiments11,12,17,24) have provided data on the concentrations of hydroxide and hydrogen ions at micellar surfaces, and these are consistent with the present theory and experimental results.

The difference between theory and experiment for ethyl benzoate is greater than for ethyl *p*-amino- and *p*-nitrobenzoates; the association constant for ethyl benzoate presented in Table II may be larger than the actual value under the kinetic conditions employed.

Conclusions

Although alkaline hydrolyses of esters are generally catalyzed by cationic micelles, some reactions are known to be inhibited. Such inhibition tends to occur under the following conditions: (i) at high surfactant (cationic) concentrations, (ii) at high hydroxide ion concentrations, (iii) at high concentrations of an added salt (including buffer components), (iv) at high ester concentrations, and (v) for compounds possessing a small value of the Hammett substituent constant. Under some of these conditions, the alkaline hydrolyses of ethyl benzoate and *p*-amino- and *p*-nitrobenzoates were shown to be inhibited by CTAB micelles. These results were

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24) J.W. Larsen and L. Magid, *J. Am. Chem. Soc.*, **96**, 5774 (1974); C.A. Bunton, K. Ohmenzetter, and L. Sepulveda, *J. Phys. Chem.*, **81**, 2000 (1977).

explained quantitatively on the basis of a theory in which the total counterion concentration is assumed to remain constant.

Appendix I. Nomenclature

b: subscript denoting bulk solution
k_1: first-order rate constant for esters
k_2: second-order rate constant for esters and hydroxide ions
m: subscript denoting the micellar surface
r: relative rate constant, *viz.* $k_{2\mathrm{m}}/k_{2\mathrm{b}}$
s: concentration expressed as moles of micellized surfactant molecules divided by the volume of the Stern layer of the micelle
t: subscript denoting the total amount
C_c: critical micellization concentration or cmc
C_s: concentration of a salt, such as sodium bromide
C_t: total concentration of an added surfactant
[I]: hydroxide ion concentration
[X]: bromide ion concentration
K_a: association constant for an ester and a micelle
K_XI: ion-exchange constant for ions I and X
β: degree of counterion binding to micelles
σ: Hammett substituent constant

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