

one-half the summation of the critical concentrations of the two individual alcohols (Table III). The effect of the alcohols on red cells appeared to be strictly an additive one and did not depend on one of the alcohols being at or near its critical concentration.

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## Influence of Cetrimonium Bromide on Base-Catalyzed Hydrolysis of *p*-Substituted Ethyl Benzoates

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**Abstract** □ The effect of cetrimonium bromide at a concentration above its CMC on the base-catalyzed hydrolysis of eight *p*-substituted ethyl benzoates was investigated. The *p*-substituents were chosen on the basis of their Hammett substituent constants and included nitro, cyano, acetyl, fluoro, hydrogen, methoxy, amino, and dimethylamino. Of these, the nitro and cyano esters showed an increase in rate in the presence of cetrimonium bromide whereas all the others showed a decrease in rate. Micellar rate constants were calculated from both kinetic and gel filtration data. Treatment of the results according to the Hammett relationship for the effect of *p*-substituents on the rate of aromatic side-chain reactions led to the hypothesis that the observed rate modifications are dependent not only on the *p*-substituent and the surface pH of the micelle but also on the dielectric constant at the surface of the micelle.

**Keyphrases** □ Cetrimonium bromide—effect on base-catalyzed hydrolysis of eight *p*-substituted ethyl benzoates, Hammett considerations □ Benzoates, ethyl, *p*-substituted—effect of cetrimonium bromide on base-catalyzed hydrolysis, Hammett considerations □ Hydrolysis, base catalyzed, *p*-substituted ethyl benzoates—effect of cetrimonium bromide, Hammett considerations

In recent years, there have been a number of investigations into the modifying effect of surfactants on the rates of organic reactions, both with regard to their influence on drug stability and as models for enzymatic and other biological reactions, and several reviews have been written on the subject (1-3). Much published work, however, is not easily interpreted and the mechanisms by which surfactants exert their influences are not fully understood.

The modifying effect of surfactants on the kinetics of hydrolysis reactions results from the fact that the rate of reaction for the substrate, which is often an

ester associated with the micelles, differs from that in the bulk phase. The observed rate constant is, therefore, determined by the aqueous and micellar rate constants and the fraction of the substrate associated with the micelles, as represented by Eq. 1:

$$k_{\text{obs}} = k_m F_m + k_w F_w \quad (\text{Eq. 1})$$

where  $k_{\text{obs}}$ ,  $k_m$ , and  $k_w$  are the observed, micellar, and aqueous reaction rate constants, respectively, and  $F_m$  and  $F_w$  are the fractions of the ester associated with the micelles and the aqueous phase, respectively.

The rate of the micellar reaction depends upon the site of association of the drug with the micelle. Penetration of the substrate into the hydrocarbon interior would result in protection from attack and would reduce the rate considerably. NMR (4) and UV (5) spectroscopic measurements, however, indicate that simple aromatic esters are solubilized at, or close enough to, the micellar surface for electrostatic interactions between the surface and attacking species to have an effect; therefore, the ionic nature of the surfactant is of importance. Simple electrostatic theory (6) would predict that the base-catalyzed hydrolysis of an uncharged ester will be enhanced in the presence of cationic micelles and retarded in the presence of anionic micelles; conversely, the acid-catalyzed hydrolysis will be enhanced by anionic and retarded by cationic micelles.

Contrary to this theory, it was previously reported that the presence of cetrimonium bromide (I) at concentrations above its critical micelle concentration (CMC) increases the rate of base-catalyzed hydroly-

sis of ethyl *p*-nitrobenzoate and *p*-nitrophenyl acetate but decreases the rate for *p*-aminophenyl acetate and ethyl *p*-aminobenzoate (7). This difference in the nature of the effect of I was postulated to be dependent upon the net charge on the *p*-substituent, the nitro group with a net  $\delta^-$  charge causing an increase in rate and the amino group with a net  $\delta^+$  charge causing a decrease in rate. The nature of the rate modification, therefore, appeared to be dependent upon the combined inductive and mesomeric effect of the *p*-substituent on the benzene ring, electron-withdrawing groups having a negative charge and electron-releasing groups having a positive charge, influencing the orientation of the ester with respect to the micellar surface.

This report concerns the investigations into the effect of  $4.8 \times 10^{-3} M$  I, which is above the CMC under the experimental conditions used, on the base-catalyzed hydrolysis of eight *p*-substituted ethyl benzoates under identical conditions. These esters have different combined inductive and mesomeric effects as defined by their Hammett substituent constants (8).

### EXPERIMENTAL

**Esters**—The eight esters used are listed in Table I, together with the values of their Hammett substituent constant (8). The esters that were commercially available were reagent grade; the others were synthesized using standard methods. In each case, they were further purified by two recrystallization or redistillation processes and stored under anhydrous conditions. Full details of the preparatory and purification techniques are available (9).

**Surfactant**—Cetrimonium bromide (cetyl trimethyl ammonium bromide) (I) was prepared and purified as previously described (7).

**Buffer Solutions**—Delory and King's carbonate-bicarbonate buffer at pH 9.20 was used for all kinetic investigations (10).

**Water**—Freshly distilled water from an all-glass still was used.

**pH Measurements**<sup>1</sup>—The pH meter and electrode systems were standardized prior to each pH determination using sodium tetraborate buffer (11).

**Kinetic Investigations**—All experiments were carried out using a  $4 \times 10^{-5} M$  solution of the appropriate ester at pH 9.2 and 25°, alone and in the presence of  $4.8 \times 10^{-3} M$  surfactant.

Two hundred milliliter samples of carbonate-bicarbonate buffer alone and of buffer containing  $5.0 \times 10^{-3} M$  I at pH 9.20 were prepared and equilibrated to 25°. The pH was measured and, if necessary, adjusted to pH 9.20 by the addition of up to 0.5 ml of the appropriate standard solution. To 96 ml of the solution in a 100-ml volumetric flask was added 4 ml of a  $10^{-3} M$  aqueous solution of the ester. The flask was then stoppered and placed in a constant-temperature bath at  $25 \pm 0.1^\circ$ . A sample was immediately removed for assay and at appropriate time intervals afterward.

**Assay Procedures**—All esters were assayed by direct spectrophotometric<sup>2</sup> measurement of the samples removed from the reaction flask by a method similar to that of Higuchi *et al.* (12). The addition of surfactant on occasion caused a change in the  $\lambda_{max}$  and extinction values, resulting in slight modifications of the basic method. In these cases, the validity of the procedure was confirmed for the assay in the presence and absence of surfactant (9).

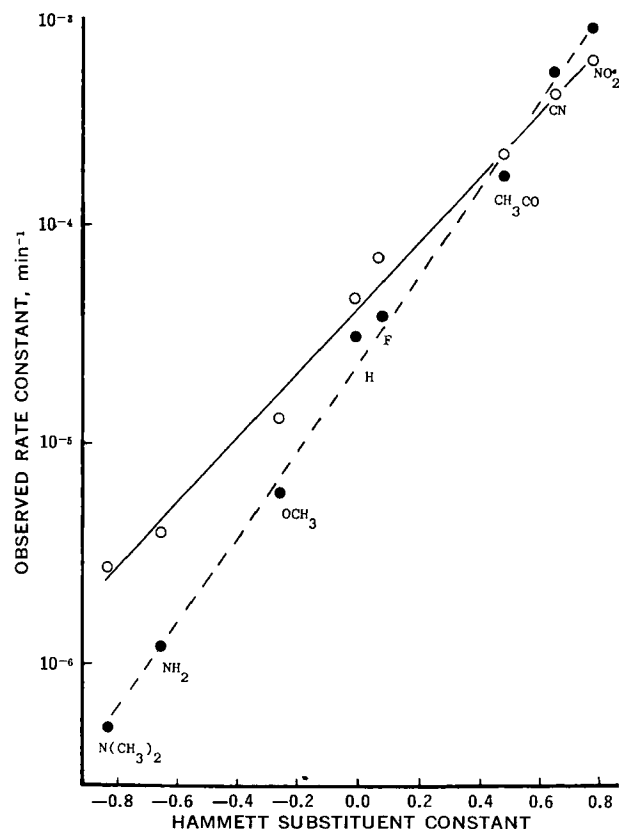
**Treatment of Results**—In all cases, the hydrolysis followed first-order kinetics. The observed first-order rate constants ( $k_{obs}$ ), each with its associated standard error, were obtained from the log percentage concentration-time data by means of a computerized least-squares regression analysis. Duplicate experiments were

**Table I**—Effect of  $4.8 \times 10^{-3} M$  I on the Rates of Hydrolysis of *p*-Substituted Ethyl Benzoates with Different Hammett Substituent Constant Values at a Concentration of  $4 \times 10^{-5} M$  in Carbonate-Bicarbonate Buffer at pH 9.2 and 25°

| <i>p</i> -Substituent | Hammett Substituent Constant, $\sigma$ | Rate Constant in Absence of Surfactant, $\text{min}^{-1}$ | Rate Constant in Presence of Surfactant, $\text{min}^{-1}$ |
|-----------------------|--|---|--|
| Dimethylamino         | -0.83                                  | $2.74 \times 10^{-6}$                                     | $4.98 \times 10^{-7}$                                      |
| Amino                 | -0.66                                  | $3.41 \times 10^{-6}$                                     | $1.17 \times 10^{-6}$                                      |
| Methoxy               | -0.27                                  | $1.34 \times 10^{-5}$                                     | $5.96 \times 10^{-6}$                                      |
| Hydrogen              | 0.00                                   | $4.68 \times 10^{-5}$                                     | $3.03 \times 10^{-5}$                                      |
| Fluoro                | 0.06                                   | $7.04 \times 10^{-5}$                                     | $3.93 \times 10^{-5}$                                      |
| Acetyl                | 0.50                                   | $2.19 \times 10^{-4}$                                     | $1.70 \times 10^{-4}$                                      |
| Cyano                 | 0.66                                   | $4.08 \times 10^{-4}$                                     | $5.11 \times 10^{-4}$                                      |
| Nitro                 | 0.78                                   | $6.02 \times 10^{-4}$                                     | $8.12 \times 10^{-4}$                                      |

performed in all cases, and no significant differences in rates were observed (9).

**Partition Coefficients ( $K_p$ )**—Partition coefficients for the esters between surfactant micelles and the aqueous phase were obtained by the gel filtration technique of Herries *et al.* (9, 13). Determinations at 25 and 50° were carried out in sodium chloride solutions of the same ionic strength as the buffers used in the kinetic experiments. This technique was used because the more conventional methods of determination, such as equilibrium dialysis and solubility, cannot be used due to the lack of suitable membranes for relatively low molecular weight ionic surfactants and the instability of some esters even at more neutral pH values. This instability requires determinations to be completed within hours rather than days, and it is also the reason for carrying out



**Figure 1**—Plots of the observed rate constant against Hammett substituent constant for the hydrolysis of *p*-substituted ethyl benzoates at a concentration of  $4 \times 10^{-5} M$  in carbonate-bicarbonate buffer at pH 9.2 and 25° in the absence (○—) and in the presence (●—) of  $4.8 \times 10^{-3} M$  of I.

<sup>1</sup> Performed with a Pye Dynacap pH meter fitted with a Pye Ingold 405 combined electrode and 622 thermal resistor.

<sup>2</sup> Unicam SP500 spectrophotometer was used for all measurements.

**Table II**—Values of the Partition Coefficient,  $K_p$ , and Micellar Rate Constant,  $k_m$ , for the Different Esters Calculated from Gel Filtration Data and Corrected Values  $K_p'$  and  $k_m'$  Calculated from Kinetic Data

| <i>p</i> -Substituent | Hammett Constant, $\sigma$ | Partition Coefficient by Gel Filtration, $K_p$ | Corrected Partition Coefficient, $K_p'$ | Micellar Rate Constant, $\text{min}^{-1}$ , from Gel Filtration, $k_m$ | Corrected Micellar Rate Constant, $\text{min}^{-1}$ , $k_m'$ |
|-----------------------|----------------------------|--|---|--|--|
| Dimethylamino         | -0.83                      | 2268   | 5670                                    | $-1.07 \times 10^{-7}$   | $2.61 \times 10^{-7}$  |
| Amino                 | -0.66                      | 686  | 1715                                    | $-8.30 \times 10^{-7}$   | $3.81 \times 10^{-7}$  |
| Methoxy               | -0.27                      | 1234   | 3085                                    | $2.29 \times 10^{-6}$  | $4.51 \times 10^{-7}$  |
| Hydrogen              | 0.00                       | 601  | 1503                                    | $1.34 \times 10^{-6}$  | $2.36 \times 10^{-6}$  |
| Fluoro                | 0.06                       | 691  | 1728                                    | $1.19 \times 10^{-5}$  | $2.85 \times 10^{-5}$  |
| Acetyl                | 0.50                       | 523  | 1308                                    | $1.13 \times 10^{-4}$  | $1.48 \times 10^{-4}$  |
| Cyano                 | 0.66                       | 384  | 960                                     | $6.22 \times 10^{-4}$  | $5.76 \times 10^{-4}$  |
| Nitro                 | 0.78                       | 666  | 1665                                    | $1.00 \times 10^{-3}$  | $8.88 \times 10^{-4}$  |

gel filtration in neutral salt solution. For an unionized ester, the partition coefficient should be independent of pH.

### RESULTS AND DISCUSSION

The results for the hydrolysis of the esters in the absence and presence of I (Table I) are the mean of the duplicate experiments. It can be seen that the presence of I causes an increase in rate for the *p*-nitro and *p*-cyano substituents but a decrease for all other substituents studied.

The Hammett relationship for the effect of *p*-substituents on the rates of aromatic side-chain reactions, such as the hydrolysis of ethyl benzoate, may be represented by Eq. 2:

$$\log \frac{k}{k_0} = \sigma \rho \quad (\text{Eq. 2})$$

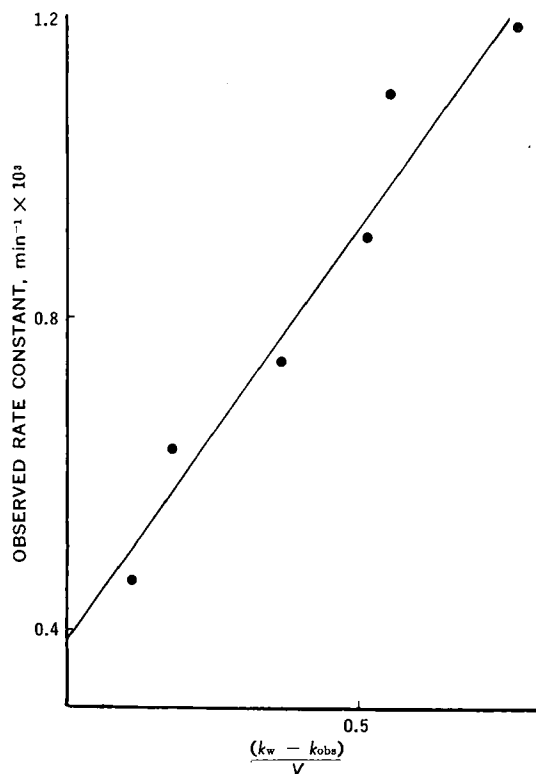
where  $k$  and  $k_0$  are the rate constants for the reaction of the substituted and unsubstituted compounds, respectively;  $\sigma$  is the Hammett substituent constant and is dependent upon the substituent but independent of the reaction conditions; and  $\rho$  is the reaction constant, which is dependent upon the reaction, the con-

ditions under which it takes place, and the nature of the side chain undergoing reaction (14).

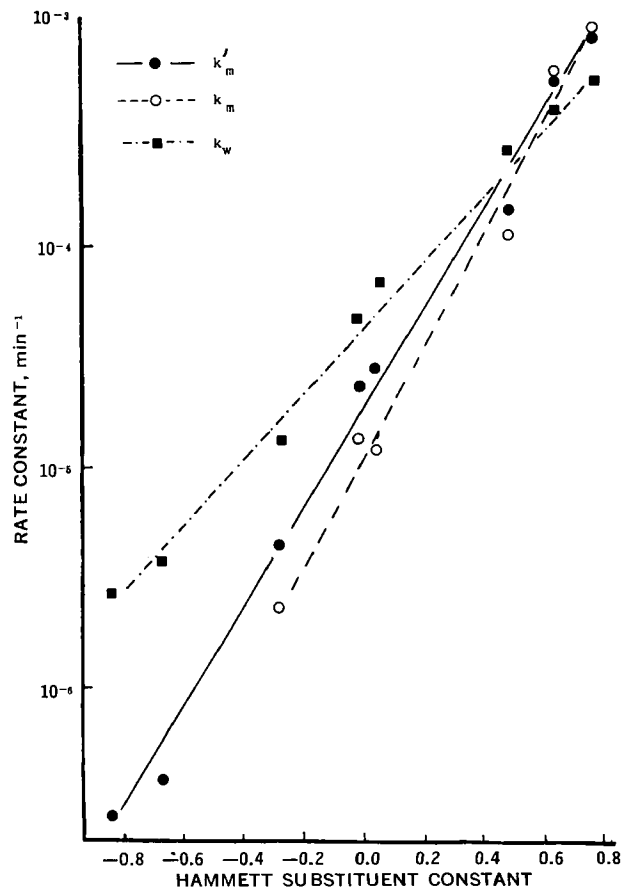
If this relationship is obeyed, a plot of the rate constant on a log scale versus the Hammett substituent constant  $\sigma$  should be linear with a slope equal to the reaction constant  $\rho$ . Plots of this form for the eight *p*-substituted ethyl benzoates both in the presence and absence of I are shown in Fig. 1, the calculated values of  $\rho$  being 1.98 and 1.49, respectively.

Consideration of the kinetics of micellar reactions as represented by Eq. 1 indicates that four variables ( $k_m$ ,  $k_w$ ,  $F_m$ , and  $F_w$ ) can influence the observed rate constant. Therefore, the good linear relationships shown in Fig. 1 are perhaps somewhat surprising.

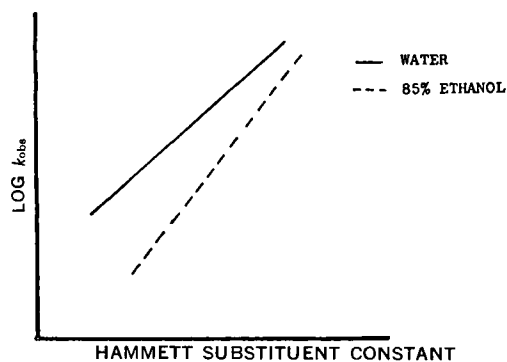
From the plot of  $\log k_{\text{obs}}$  against  $\sigma$  in the absence of I, it is clear that  $k_w$  is directly related to the substituent constant. Values of  $F_m$  and  $F_w$  are dependent upon the partition coefficients for the



**Figure 2**—Plot of  $k_{\text{obs}}$  against  $(k_w - k_{\text{obs}})/V$  to determine the partition coefficient between micelles of I and the aqueous phase for ethyl *p*-aminobenzoate in glycine buffer at pH 10.39 and 50°.



**Figure 3**—Plots of aqueous and micellar rate constants against Hammett substituent constant for the hydrolysis of *p*-substituted ethyl benzoates in carbonate-bicarbonate buffer at pH 9.2 and 25°.



**Figure 4**—Diagrammatic representation of data plotted according to the Hammett relationship to show the effect of dielectric constant on the base-catalyzed hydrolysis of *p*-substituted ethyl benzoates.

esters between I micelles and the aqueous phase. Values of the partition coefficients,  $K_p$ 's, as measured by the gel filtration technique are shown together with substituent constants in Table II. Although  $K_p$  varies with the substituent, there is no direct correlation with  $\sigma$ , which is indicative that the micellar rate constant,  $k_m$ , is varying for each individual ester.

The micellar rate constants may be calculated from a knowledge of  $K_p$ ,  $k_w$ ,  $k_{obs}$ , and  $V$ , the volume fraction of the micellar phase, by application of Eq. 3:

$$k_{obs} = k_w \frac{(1-V)}{(1-V) + K_p V} + k_m \left( 1 - \frac{(1-V)}{(1-V) + K_p V} \right) \quad (\text{Eq. 3})$$

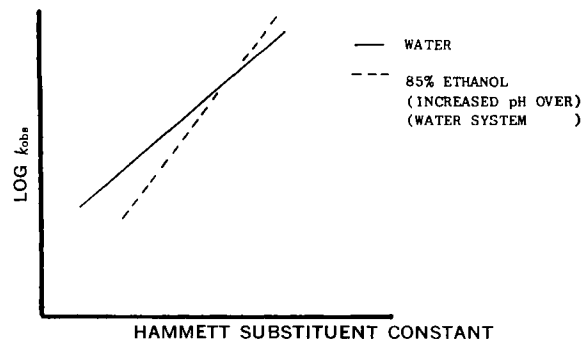
Micellar rate constants calculated from Eq. 3 are shown in Table II. The calculated rate constants for the amino and dimethylamino substituents are *negative* and cannot be accounted for by errors in the experimental rate constants. The most likely explanation of these negative rates is that the value of  $K_p$  obtained from gel filtration does not represent the true partitioning in the hydrolyzing system.

An alternative estimate of  $K_p$  can be obtained from the kinetic data by application of Eq. 4:

$$k_{obs} = \frac{(1-V)}{K_p} \left( \frac{k_w - k_{obs}}{V} \right) + k_m \quad (\text{Eq. 4})$$

This equation may be obtained by rearrangement of Eq. 3, assuming that  $k_m$  is constant for any given ester and set of hydrolysis conditions and is independent of surfactant concentration. Since this estimate of  $K_p$  is determined from its influence on the observed rate of reaction, its value should be more appropriate to this discussion.

At low surfactant concentration,  $V$  is small and  $(1-V)$  approaches unity. A plot of  $k_{obs}$  against  $(k_w - k_{obs})/V$  should be linear with a slope of  $1/K_p$  and intercept  $k_m$ . The only data available for a plot of this form are those presented previously for the effect of surfactant concentration on the hydrolysis of ethyl *p*-aminobenzoate in glycine buffer of pH 10.39 at 50° (7). Figure 2 shows data plotted according to Eq. 4. The linear relationship is reasonable with a slope of  $1.047 \times 10^{-3}$  and an associated standard error of  $1.26 \times 10^{-4}$ , giving a  $K_p$  value of 956 compared with a value of 381 obtained by gel filtration at 50°. Since the  $K_p$  value obtained from the kinetic data differs markedly from that obtained by gel filtration, it appears that the latter does not reflect the binding that occurs during hydrolysis. In the absence of relevant kinetic data to calculate the partition coefficients at 25°, it was assumed that the value at 25° determined by gel filtration has the same "error" as that determined at 50° (i.e., a factor of 2.5 too low), which gives a "corrected" value,  $K_p'$ , for the *p*-amino substituent of 1715, giving a corrected micellar rate,  $k_m'$ , of  $3.81 \times 10^{-7} \text{ min}^{-1}$ . If it is further assumed that all of the partition coefficients determined by gel filtration have this same error and the micellar rate constants are recalculated, the values given in



**Figure 5**—Diagrammatic representation of data plotted according to the Hammett relationship to show the effect of decreased dielectric constant and increased pH on the base-catalyzed hydrolysis of *p*-substituted ethyl benzoates.

Table II are obtained. Figure 3 shows a plot of these corrected  $k_m'$  values together with  $k_w$  on a log scale against the substituent constant; also shown is a plot for the  $k_m$  values calculated using the  $K_p$  values from gel filtration, ignoring the negative values. The Hammett reaction constants,  $\rho$ 's, for  $k_m$  and  $k_m'$  obtained from the slopes of these lines were 2.50 and 2.25, respectively.

It is apparent that the nature and magnitude of the modifying effect of I on the base-catalyzed hydrolysis of *p*-substituted ethyl benzoates are dependent upon the  $\sigma$  value of the *p*-substituent and, therefore, on the electron distribution in the ester as a result of the combined inductive and mesomeric effects of the substituent. Previously it was suggested that the electron distribution exerts this influence by governing the site and/or orientation of the ester with respect to the micellar surface (7). The present results favor an alternative mechanism to account for the observed rate modifications based on the values of the Hammett reaction constants.

The value of the Hammett reaction constant,  $\rho$ , is known to vary with the dielectric constant of the medium (15). For the hydroxyl-ion-catalyzed hydrolysis of *p*-substituted ethyl benzoates in various aqueous organic solvent mixtures,  $\rho$  increases with a decrease in the dielectric constant (14-16),  $\rho$  values in the region of 2.0-2.5 being reported for solvents with dielectric constants lying between 30 and 55. The increased values of the reaction constant of 1.98, 2.25, and 2.50 for  $k_{obs}$  in the presence of surfactant,  $k_m'$ , and  $k_m$ , respectively, over that of 1.49 for the aqueous reaction in the absence of surfactant micelles could therefore be associated with a decrease in dielectric constant at the micellar surface.

Although no values are presently available for this surfactant (I) system, Mukerjee and Ray (17) estimated the dielectric constant at the surface of dodecylpyridinium micelles to be approximately 36 by examination of charge transfer spectra. Values of this order are not inconsistent with those postulated in the Bockris-Devanathan-Müller model of the electrical double layer, where values of 6-12 and approximately 30 were calculated for the inner and outer Helmholtz layers, respectively (18, 19), the latter being the supposed site for charge transfer reactions (20). This leads to the postulation that in these systems the ester molecules are not penetrating the micelle but are adsorbed close to the micellar surface in the region of the outer Helmholtz plane.

From theoretical considerations, the rate of base-catalyzed hydrolysis of *p*-substituted ethyl benzoates should decrease when the dielectric constant of the medium is decreased (21). This was confirmed by the work of Tommila and coworkers (22-24). Thus, data for the base-catalyzed hydrolysis of *p*-substituted ethyl benzoates in water and a medium of lower dielectric constant, plotted according to the Hammett relationship, will be as shown diagrammatically in Fig. 4. The rates of hydrolysis of all of the esters are decreased in the lower dielectric constant system, the magnitude of the effect increasing with the decreasing Hammett  $\sigma$  value. A decrease in dielectric constant cannot, therefore, account for the increase in rate observed for the *p*-nitro and *p*-cyano substituents. If the pH of the lower dielectric constant system is increased, i.e., if there is a greater hydroxyl-ion concentration in the region immediately adjacent to the micellar surface than that of the aqueous system, the pattern of results shown in Fig. 5

<sup>3</sup> For derivation of this equation, see the Appendix.

could be obtained. This is similar to the experimental findings shown in Fig. 3.

From a knowledge of the micellar  $\zeta$ -potential, the increased pH at the shear plane of the micelle over that in the bulk solution may be calculated by application of the Boltzmann distribution theory (25). The  $\zeta$ -potential values for I are not available in the literature but, in general, values of  $\zeta$  for ionic surfactants are found to be between 50 and 120 mv; e.g., sodium lauryl sulfate = -101 mv in the absence of added salt and = -68 mv in the presence of 0.1 M sodium chloride (26) and the values for decyl-, dodecyl-, and tetradecyltrimethylammonium chlorides in the absence of added salt are 57, 75, and 118 mv, respectively (27). If a value of 50 mv for the  $\zeta$ -potential of I as micelles is assumed, then the increased pH at the shear plane over that in the bulk phase will be 0.84 of a pH unit. Assuming ideal kinetic behavior, i.e., the slope of a log  $k_{\text{obs}}$  versus pH plot is unity, the pH increase required to produce the corrected micellar rate constant of  $8.88 \times 10^{-4} \text{ min}^{-1}$  for the *p*-nitro compound compared to the aqueous rate constant of  $6.0 \times 10^{-4} \text{ min}^{-1}$  is 0.3 of a pH unit, leaving 0.54 of a pH unit to compensate for the reduced rate due to the lower dielectric constant at the micellar surface.

Thus, a mechanism to account for the observed effect of I on the base-catalyzed hydrolysis of *p*-substituted ethyl benzoates based on a low dielectric constant at the micellar surface combined with an increased hydroxyl-ion concentration in accordance with electrostatic theory is feasible. Although this hypothesis is founded on estimated micellar rate constants, due to the lack of accurate partition coefficients, we consider that the results available are sufficient to warrant the interpretation presented.

Further work to validate these hypotheses is now proceeding in these laboratories.

#### APPENDIX: DERIVATION OF EQ. 3

From Eq. 1:

$$k_{\text{obs}} = k_w F_w + k_m F_m \quad (\text{Eq. A1})$$

$$\therefore k_{\text{obs}} = k_w F_w + k_m(1 - F_w) \quad (\text{Eq. A2})$$

The partition coefficient,  $K_p$ , for the esters between cetrimonium micelles and the aqueous phase may be represented by Eq. A3:

$$K_p = \frac{C_m}{C_w} = \frac{N_m}{N_w} \cdot \frac{1-V}{V} \quad (\text{Eq. A3})$$

where  $C_m$  and  $C_w$  are the concentrations of the ester in the micellar and aqueous phases, respectively;  $N_m$  and  $N_w$  are the moles of substrate in the micellar and aqueous phases, respectively, for unit volume of system; and  $V$  is the volume fraction of the micellar phase.

By definition, Eq. A4 may be written:

$$F_w = \frac{1}{1 + \frac{N_m}{N_w}} \quad (\text{Eq. A4})$$

By combining Eqs. A3 and A4, one obtains:

$$F_w = \frac{1}{1 + K_p V} = \frac{(1-V)}{(1-V) + K_p V} \quad (\text{Eq. A5})$$

Substituting for  $F_w$  in Eq. A2 gives:

$$k_{\text{obs}} = k_w \frac{(1-V)}{(1-V) + K_p V} + k_m \left( 1 - \frac{(1-V)}{(1-V) + K_p V} \right) \quad (\text{Eq. A6})$$

$V$  is calculated from the concentration of micelles in  $\text{g ml}^{-1}$  and the partial specific volume of the surfactant in micellar form. The latter is obtained from density measurements (9).

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