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EFFECT OF HEXADECYLTRIMETHYLAMMONIUM BROMIDE MICELLES ON THE HYDROLYSIS OF SUBSTITUTED BENZOATE ESTERS

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The alkaline hydrolysis of nine *para*-substituted phenyl esters of *para*-substituted benzoates was studied in the presence and absence of hexadecyltrimethylammonium bromide (CTAB) micelles. The second-order rate constant for alkaline hydrolysis in CTAB micelles (k_{2m}) was calculated using a pseudo-phase ion-exchange model. the substituent effect on the second-order rate constant in the aqueous phase (k_{2w}) and on k_{2m} was analysed using Hammett's σp plots. The calculated ρ values in micelles were 0·8 unit larger than those in water. The effective low dielectric constant in the micellar surface may be responsible for the general effect of increasing the sensitivity of reactions to the electronic effect of substituents in micelles.

INTRODUCTION

Micelles can modify the rate of a number of chemical reactions.[1] Several models are now available which quantitatively simulate the effects of ionic micelles on reaction rate.[2] Using these models, the major contributions of micelles for catalysis or inhibition, particularly for bimolecular reactions in the ground state, became evident.[1,2] In general, the calculated second-order rate constants in the micelle and in water rarely differ by more than one order of magnitude.[2a] The rate changes arise from reagent concentration in the micelle, pK_a shifts and moderate differences in the rate constants in the two phases.[1,2a,3] However, in several reactions, micelles produce changes in reaction pathways, rate-limiting steps or reaction mechanisms.[4–6]

Few systematic studies of reaction mechanisms for bimolecular reactions in the micellar pseudo-phase have been made. Mechanistic studies on micellar effects on bimolecular reactions have been described for reactions such as the acid-catalysed hydrolysis of diethyl acetals from benzaldehyde[7a] and methyl *o*-benzoate,[7b] the OH$^-$-catalysed decomposition of substituted phenylpropyl halides,[8] the OH$^-$ attack on *p*-nitrophenyl phenylacetates,[9] ethyl *p*-benzoates,[10] diphenyl-*N*-methylamides,[11] phenyl carboxylates[12] and substituted sulphonates[13] and functional micellar catalysis on the hydrolysis of phenyl decanoate and benzoate esters.[14]

There are few documented cases in which the mechanistic proposal was derived from analysis of the second-order rate constants calculated for the reaction occurring in the micelles.[11,13] This calculation is crucial since, as stated above, observed rate constants for bimolecular reactions in the presence of micelles are mainly the result of reagent concentration rather than micellar effects on reactivity.

We have undertaken a systematic study of the effect of micelles on reaction mechanisms. Here we describe the effect of hexadecyltrimethylammonium bromide (CTAB) on OH$^-$ attack on substituted carboxylate esters. The second-order rate constants for OH$^-$ attack in the micelle were calculated using the pseudo-phase model with explicit consideration of ion- exchange (PPIE).[2a,b] In all cases the effect of substituents on the reaction in the micellar phase was larger than that in the aqueous phase. The rate-limiting step was unchanged on transferring the reaction from the bulk aqueous phase to the micelles.

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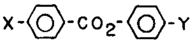
Table 1. Analytical data for the esters



No.	Compound	X	Y	Recryst solvent.	M.P. (°C) This work	M.P. (°C) Lit.
1	*p*-Nitrophenyl benzoate	H	NO_2	Methanol	142–143·5	142–143[17a]
2	*p*-Nitrophenyl *p*-nitrophenylbenzoate	NO_2	NO_2	Methanol–acetone	157–158·5	158–159[17a]
3	*p*-Nitophenyl *p*-methylbenzoate	CH_3	NO_2	Methanol	119–120	120–121[17a]
4	*p*-Nitrophenyl *p*-methoxybenzoate	CH_3O	NO_2	Methanol	164–165	167–168[15]
5	*p*-Nitrophenyl *p*-bromobenzoate	Br	NO_2	Dichloromethane	152–153	153–154[17b]
6	Phenyl benzoate	H	H	Methanol	69–70	69–70[15]
7	*p*-Cyanophenyl benzoate[a]	H	CN	Methanol	91–92	
8	*p*-Methylphenyl benzoate[a]	H	CH_3	Methanol	87–88	
9	*p*-Chlorophenyl benzoate	H	Cl	Methanol	88–90	88–89[17a]

[a] Elemental analyses and NMR spectral data (Instituto de Quimica, Central Analitica, Universidade de Sao Paulo) were in agreement with the proposed structure.

EXPERIMENTAL

CTAB (Merck) was purified by recrystallization from acetone–ethanol (80 : 20, v/v). Benzoic acids and substituted phenols (pure or specially pure grade)(Aldrich) were purified by standard procedures. All other reagents were of analytical-reagent grade and water was deionized and doubly glass distilled.

Esters of benzoic acids were prepared from the corresponding acid chlorides and phenols in the presence of pyridine.[15] *p-Nitrophenyl p*-nitrobenzoate was prepared by reacting *p*-nitrobenzoic acid with *p*-nitrophenol in the presence of $POCl_3$.[16] Analytical data for the esters are presented in Table 1.

The micelle–water distribution constants[18] for the esters (K_s) were determined as follows. To 2·00 ml of a 0·01 M NaCl solution thermostated at 30·0±0·1 °C containing the ester (6×10^{-6}–$3 \times 10^{-5} M$) successive aliquots of concentrated CTAB solution were added and the absorbance was recorded in a Beckman Model 25 spectrophotometer using the same concentration of CTAB as reference. The wavelengths used were 272, 265, 260, 265 and 260 nm for the esters **1**, **3**, **4**, **8** and **9**, respectively (see Table 1). K_s values were calculated from the equation[1a,3,18]

$$1/(\varepsilon_\psi - \varepsilon_w) = 1/(\varepsilon_m - \varepsilon_w) + \{1/[K_s(\varepsilon_m - \varepsilon_w)]\}(1/C_d) \qquad (1)$$

Where ε_w, ε_m and ε_ψ are the molar absorptivities of the ester in water, fully incorporated in the micelle and the solution containing detergent, respectively. The concentration of micellized detergent (C_d) was set equal to that of added detergent (C_t) minus the critical micelle concentration (CMC). The values of K_s were obtained from linear regressions of the data using equation (1). CMCs were determined by measurement of surface tension and were in agreement with literature values.[1a]

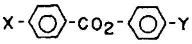
The reactions were initiated by adding a 5-μl aliquot of a concentrated ester solution in acetonitrile (except for **2**, in methanol) to 2·00 ml of a solution containing all other reagents. Data were obtained at 30±0·1 °C in a Beckman Model 25 spectrophotometer at 405 nm for esters **1**–**5** and 285, 290, 297 and 280 nm for esters **6**, **7**, **8** and **9** respectively. The apparent first-order rate constants for ester hydrolysis (k_ψ) were calculated from linearized absorbance versus time plots. Reactions followed first-order kinetics for at least four half-lives; the reported k_ψ values are the averages of at least two separate runs with a maximum deviation of 5%.

RESULTS

The second-order rate constant for the alkaline hydrolysis of esters **1**–**9** in aqueous solution (k_{2w}), determined from the (linear) plots relating the observed pseudo-first-order rate constants with $[OH^-]$ (Figure 1), are presented in Table 2. The k_{2w} value for ester **2** was obtained in borate buffers of different pH and extrapolated to zero buffer concentration (not shown). The values of k_{2w} are similar to those previously obtained for the same compounds in acetonitrile–water at higher ionic strength.[17a,19]

The distribution of the esters between water and micelles was determined using a spectrophotometric method which depends on the existence of a spectral change on incorporation of the substrate in the aggregate[18] (see Experimental). Within our spectral resolution (± 1 nm) no shift was observed in the wavelength of maximum absorption for the esters used here. However, the variation in the molar absorptivity for some of the esters on addition of CTAB (typical results are

Table 2. CTAB–water distribution and second-order rate constants for the alkaline hydrolysis of



Ester	X	Y	K_s ($l\,mol^{-1}$)	k_{2w}[a] ($l\,mol^{-1}s^{-1}$)	k_{2m}[b] ($l\,mol^{-1}s^{-1}$)	k_{2m}/k_{2w}
4	CH_3O	NO_2	800[b]	1·47	0·162	0·11
3	CH_3	NO_2	2000[a]	2·39	0·359	0·15
1	H	NO_2	1300[a]	5·29	0·979	0·18
5	Br	NO_2	1500[b]	9·68	3·87	0·40
2	NO_2	NO_2	1000[b]	143·00	100·00	0·70
8	H	CH_3	2550[a]	0·402	0·016	0·04
6	H	H	3550[a]	0·611	0·030	0·05
9	H	Cl	720[a]	0·989	0·088	0·09
7	H	CN	1500[b]	3·05	0·43	0·14

[a] Experimental value (see text).
[b] Best fit parameter of kinetic data analysis (see text).

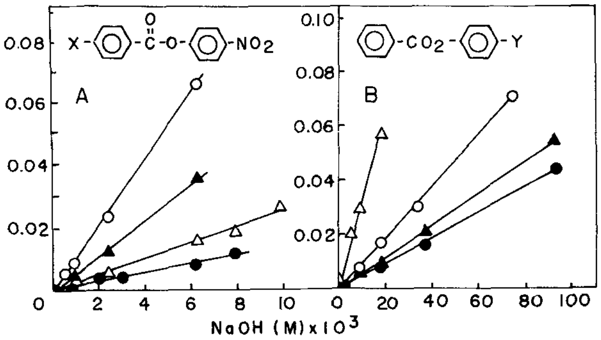


Figure 1. Determination of the second-order rate constants for the alkaline hydrolysis of substituted benzoate esters. (A) ○, ▲, △ and ● correspond to compounds **5**, **1**, **3** and **4**, respectively; (B) △, ○, ▲ and ● correspond to compounds **7**, **9**, **6** and **8** respectively

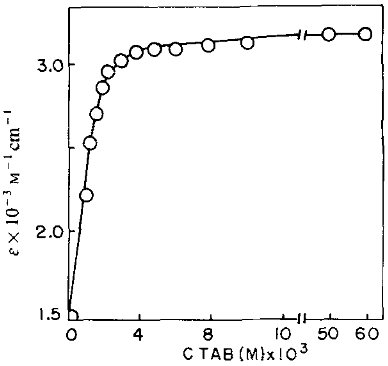


Figure 2. Effect of CTAB concentration on the molar absorptivity coefficient of compound **8** at 265 nm

shown in Figure 2) allowed the determination of K_s for esters **1**, **3**, **6**, **8** and **9** (Table 2).

The effect of CTAB on the alkaline hydrolysis of esters **1**–**5** was measured in buffered solutions under the following conditions: 0·02 M borate for **1** (pH = 10·0), **2** (pH = 8·3) and **5** (pH = 10·0) and triethylamine–HBr for **3** (pH = 11·2) and **4** (pH = 11·2)). The PPIE model was used to analyse quantitatively the data exemplified in Figure 3. It has been shown that the equation describing the reaction of OH^- with a neutral substrate in a CTAB micelle in the presence of an adequate buffer is[2b]

$$k_\psi = [OH_f]\,\frac{(k_{2m}/\bar{V})K_sK_{OH/Br}(Br_b/Br_f) + k_{2w}}{1 + K_sC_d} \qquad (2)$$

where $[OH_f]$ is the concentration of OH^- in the intermicellar aqueous phase calculated from the pH, $\bar{V}$ the partial molar volume of CTAB [0·37 $l\,mol^{-1}$ (Ref. 20)], $K_{OH/Br}$ the selectivity constant for the OH^-/Br^- ion exchange at the micelle surface (0·08[21]) and Br_b and Br_f the analytical concentrations of bound and free bromide, respectively. The procedure for the calculation of each of the terms in equation (2) has been described in detail.[22,23] This procedure requires the use of α, the degree of counter-ion dissociation from the micelle, which was taken as 0·2.[1a,2a,24] The CMCs were measured and corrected for ionic strength using a previously published procedure.[22] The fit of equation (2) to the experimental data was achieved using a least-squares multi-parametric program for a personal computer. This program permitted the use of either one or two parameters for data fit. In cases in which K_s had been independently determined (esters **1** and **3**, see above) the program fitted equation (2) to the data using only k_{2m} as an adjustable parameter. In the other cases the program gave the best fit values for K_s and k_{2m}. Representative data fits are presented in Figure 3(A and B). In all cases the fit of equation (2) to the data was excel-

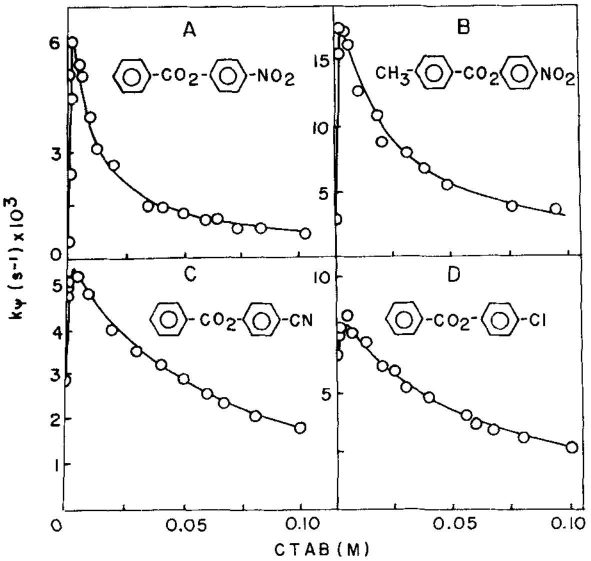


Figure 3. Effect of CTAB on the apparent first-order rate constant for alkaline hydrolysis of substituted benzoate esters. Curves are calculated (see text). (A) Compound **1** ($3{\cdot}0 \times 10^{-6}$ M), 0·02 M borate buffer, pH = 10·0; (B) compound **3** ($5{\cdot}0 \times 10^{-6}$ M), 0·02 M triethylamine–HBr buffer, pH = 11·2; (C) compound **7** (3×10^{-5} M), 0·01 M NaOH, 0·01 M NaBr; (D) compound **9** ($3{\cdot}0 \times 10^{-5}$ M), 0·01 M NaOH, 0·01 M NaBr

lent. The calculated values of $k_{2\mathrm{m}}$ and K_s and the ratios of second-order rate constants in the micelle and aqueous phase are given in Table 2.

The effect of CTAB on the rate of hydrolysis of esters **6**–**9** was studied, without buffer, in 0·01 *M* NaOH. The equation used to analyse the data in the absence of buffer was[2b]

$$k_\psi = [\mathrm{OH_t}] \frac{(k_{2\mathrm{m}}/\bar{V})K_\mathrm{s}K_{\mathrm{OH/Br}}(\mathrm{Br_b}/\mathrm{Br_f}) + k_{2\mathrm{w}}}{(1 + K_\mathrm{s}C_\mathrm{d})[1 + K_{\mathrm{OH/Br}}(\mathrm{Br_b}/\mathrm{Br_f})]} \qquad (3)$$

where $[\mathrm{OH_t}]$ is the total added NaOH. All other parameters and procedures were as described for the fit of equation (2). Representative data are presented in Figure 3 (C and D). The fit of the experimental data to the corresponding equation was within experimental error. The best fit values of $k_{2\mathrm{m}}$ and K_s are presented in Table 2.

DISCUSSION

Several micellar-modified bimolecular reactions between a hydrophilic ion whose charge is opposite to that of the micelle and a neutral substrate have been quantitatively analysed using the PPIE model.[1–3] It is becoming increasingly clear that this model cannot explain several features of micelle-modified kinetics, especially at high electrolyte concentrations or when using a micelle with a high fractional coverage of very hydrated counter ions, such as $\mathrm{OH^-}$.[25] Even in some of these cases the failure of the PPIE model can be ascribed to significant changes in the activity coefficient of the intervening ions in the aqueous phase rather than to a failure of the pseudo-phase concept itself.[26] The conditions used here, low $\mathrm{OH^-}$ coverage of the CTAB micelle and low salt concentration, are precisely those in which most of the more encompassing models reduce to the PPIE model,[27] and hence are those most amenable to quantitative treatment by the simple model. The excellent fit of the experimental data to the model for a series of esters is a clear demonstration of this fact. This is especially relevant for those cases in which the only variable parameter in the computer fit was the second-order rate constant in the micellar phase.

A major problem in analysing the effect of the micellar reaction medium on bimolecular reactions is to define the appropriate concentration units because second-order rate constants are expressed in units of reciprocal time and concentration. In order to compare $k_{2\mathrm{m}}$ with $k_{2\mathrm{w}}$, a reaction volume in the micelle has to be defined.[1b,2a] We have taken total partial molar volume of the micellized detergent as a reasonable approximation of the reaction volume.[3,22] Other workers have chosen to consider different reaction volume elements, differing from $\bar{V}$ by not more than a a factor of 2–3.[1b]

When comparing $k_{2\mathrm{m}}$ values for related compounds, the choice of a single value for the reaction volume implies that the reaction site is similar for all substrates. There is evidence showing that, at low substrate/micelle ratios, compounds with single phenyl rings (unsubstituted by long alkyl chains) lie at the interface of a positively charged micelle.[1,28] Since the structural variations in the ester series used here are not extensive, it is safe to assume that there are no major solubilization site differences within the series. Moreover, the values of K_s differ, by, at most a factor of 4·4. (Table 2), a value which corresponds to a difference in transfer energy of 900 cal (1 cal = 4·184 J). This value is equivalent to the increase in the chemical potential difference for water–micelle transfer resulting from the addition of one[29] or at the most two[30] methylene groups to an organic molecule. It should also be noted that even though the $k_{2\mathrm{m}}$ values for one of the series (esters **1** and **6**–**9**) were significantly lower than the corresponding $k_{2\mathrm{w}}$ values, there was no relationship between the values of K_s and $k_{2\mathrm{m}}$. Therefore, we concluded that the differences observed in the $k_{2\mathrm{m}}$ reflect substituent effects of the reaction in the micelles rather than differences in the solubilization sites[31] of the substrates in the micelle.

The calculated second-order rate constants for $\mathrm{OH^-}$ attack on benzoate esters in micelles were lower than those in the aqueous phase (Table 2). In several other cases, where $k_{2\mathrm{m}}$ values for alkaline ester hydrolysis on positively charged micelles have been calculated,

$k_{2m} < k_{2w}$.[32] Even considering the uncertainties regarding the reaction volume estimate (see above), there was an increase in the apparent activation energy for the reaction with micelle-solubilized reagents. This difference was more evident with the less reactive esters (Table 2). The data obtained here do not permit a detailed analysis leading to the understanding of the factors involved in this reactivity decrease. Several factors will contribute to the observed results. OH^- binds weakly to CTA micelles, as demonstrated by the (low) values of ion-exchange constants with other counter ions such as Br^- or Cl^-.[21] Further the properties of both CTAOH micelles and dioctadecyldimethylammonium hydroxide bilayers at moderate ionic strengths have been rationalized in terms of an approach of OH^- ion to the interface not exceeding 2·5 Å.[33] Thus, the OH^- distribution function should be centred at a certain distance from the interface. The data available[1,28] allow one to consider that the distribution function for the ester will be centred at the interface. Thus both reagents occupy, on average, different sites in the aggregate. Moreover, the high effective ionic strength at the micellar surface[1] will affect the activity coefficients of both reagents and transition state. Since OH^- is the most hydrated species, the largest effect of local ionic strength is likely to be on the activity coefficient for this ion.[34]

The effect of substituents on the reaction was analysed using Hammett plots (Figure 4). There was a strict linear relationship (correlation coefficients better than 0·999) between log k_2 values and the substituents' σ values[17a,35] for reaction in water and in micelles. In water the value of ρ for esters **1**–**5**(ρ_w^X) was 1·86 and the value of ρ_w^Y was 1·06 (esters **1**, **6**–**9**). In micelles the corresponding values of ρ_m^X and ρ_m^Y were 2·65 and 1·83, respectively.

The rate-determining step for (alkaline) ester hydrolysis has been unequivocally shown to be OH^- attack for simple carboxylic esters ranging from *p*-nitrophenyl acetate to methyl *o*-benzoate.[17a,19,36] Maintaining a rate-limiting step over a range of leaving group p*K*s values of 9 units makes a micellar-induced change in the rate-determining step for this reaction unlikely. As expected for a rate-limited OH^- attack,[17a,19] the ρ_w and ρ_m values were higher for substituents in the benzoic acid moiety (Figure 4). The values of ρ_w were similar to those previously reported for the hydrolysis of *p*-nitrophenyl benzoates[17a] (2·04) and substituted phenyl benzoates[19] (1·27) in 33% acetonitrile. ρ_m^X was also higher than ρ_m^Y and the difference in ρ (between substitution in the benzoate and phenyl moieties) was identical in water and micelles. In this case micelles did not affect the rate-limiting step.

The reaction in micelles was more sensitive to substituent effects (Figure 4). The $\Delta\rho_{mw}$ value ($\rho_{micelle} - \rho_{water}$) in both cases approached 0·8. An increase in the Hammett ρ value on transfer of the reaction from water to a micelle was first noted in the acid-catalysed hydrolysis of methyl *o*-benzoates by Dunlap and Cordes.[7b] In several cases $\Delta\rho_{mw}$ is remarkably similar,[7–13] ρ_m always being greater than ρ_w. In the case of amide hydrolysis the increase in ρ has been attributed to the occurrence of a more product-like transition state in the micelle.[37] Part of the solvent effect on ρ can be attributed to a change in the interaction between the reaction centre and the substituent as the dielectric constant of the solvent changes. Hence the electrostatic interactions should increase as the dielectric constant of the solvent decreases.[38] This is illustrated by a $\Delta\rho$ value of 0·96 resulting from a water–ethanol change in the dissociation of benzoic acids.[38] The effective dielectric constant in the CTAB micelle interface has been estimated by several methods to be 30,[1a] a value consistent with an effect on ρ of a solvent of lower dielectic constant than water for this particular reaction.

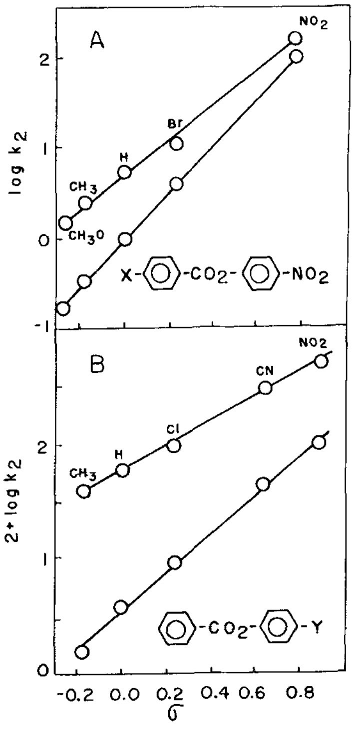


Figure 4. Effect of substituents on the second-order rate constants for the alkaline hydrolysis of substituted benzoates in (○) water and (•) micelles. (A) *p*-Nitrophenyl *p*-X-benzoates; (B) *p*-Y phenylbenzoates.

In conclusion, we have studied the effect of micelles on the alkaline hydrolysis of esters. The data were analysed quantitatively and second-order rate constants in the micellar pseudo-phase were calculated. Evaluation of substituent effects using Hammett plots demonstrated that micelles do not affect the rate-limiting step in this reaction and that the reaction in micelles is more sensitive to the effect of substituents. This effect may be general and may reflect the increase in the electronic contribution of the substituent on the reaction centre due to the low effective dielectric constant at the micellar surface.

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