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Effects of a Cationic Surfactant on the Rate of Alkaline Hydrolysis of *p*-Substituted Benzenesulfonyl Fluorides

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The effect of a cationic surfactant, cetyltrimethyl ammonium bromide (CTAB), on the rate of alkaline hydrolysis of four *p*-substituted benzene sulfonyl fluoride derivatives was investigated. The *p*-substituents were classified into electron-withdrawing (p-NO_2) and electron-donating (p-NH_2, p-CH_3CONH and p-CH_3) groups. These different groups produced opposite effects on the rate of alkaline hydrolysis of the corresponding esters in the presence of CTAB. Our investigation on the alkaline hydrolysis of various *p*-substituted benzene sulfonyl fluorides indicated an inhibitory effect of CTAB in all cases irrespective of the nature of the *p*-substituent. Solubility studies and multiplot analysis of the kinetic data clearly indicated that the various substituents were appreciably partitioned into the micellar phase. The solubility studies further indicated complexation between the substrate and surfactant. It may be concluded that in sulfonyl fluoride–CTAB systems, the extent of interaction between the substrate and surfactant may be the primary factor determining the type of effects observed instead of the electron activity of the *p*-substituent. The substrate solubilization in the submicellar region may also play a secondary role.

Keywords——micellar system alkaline hydrolysis; *p*-substituent effect; CTAB net inhibitory effect; solubilization; surfactant–substrate interaction

Introduction

Solubilization of pharmaceuticals in micelles results in a change of environment, which can lead to enhanced or decreased stability, or no effect.[1] The inhibitory effects of micelles on the rates of chemical reactions have profound implications in relation to the stabilization of chemically unstable and potentially useful drugs in aqueous pharmaceutical formulations.

Much of the published work on micellar catalysis and inhibition has been on esters, and in most cases, the effects have been attributed to electrostatic and/or hydrophobic interactions between the substrate and surfactant aggregates.[2] Winterborn *et al.*[3,4] reported that the type of *p*-substituent group (either electron-donating or electron-withdrawing determines whether the effect of cetyltrimethyl ammonium bromide (CTAB) on the rate of base-catalyzed hydrolysis of acetate and benzoic acid esters in one of enhanced or decreased stability. The differences in the nature of rate modifications were postulated to be dependent upon the net charge of the *p*-substituent[3] or upon the low dielectric constant at the micellar surface combined with increased hydroxide ion concentration in accordance with the electrostatic theory.[4] In a recent investigation, it was found[5] that the base-catalyzed hydrolysis of sulfanilyl fluoride did not follow the electrostatic model, as inhibition was observed in anionic, cationic and nonionic surfactant systems.

In this study, the effect of different *p*-substituents—electron-withdrawing and donating—on the rates of alkaline hydrolysis of various benzene sulfonyl fluorides in the presence of CTAB was investigated. Benzene sulfonyl fluoride derivatives are very suitable for this investigation since they: a) Are highly solubilized by surfactants, and thus one would expect their reaction rates to be affected; b) Undergo rapid hydrolysis which should minimize any long-term instability induced by surfactants; c) React *via* a relatively uncomplicated alkaline hydrolysis pathway[6] as compared to an ester which potentially can undergo a multi-pathway reaction;[7] d) Can be easily and accurately monitored by using ultraviolet (UV) spectrophotometry, as a definite change in the spectrum occurs on hydrolysis.

Experimental

Materials——The following benzene sulfonyl fluoride derivatives were used; *p*-aminobenzenesulfonyl fluoride, *p*-toluenesulfonyl fluoride, *p*-acetamidobenzene sulfonyl fluoride (Aldrich Chemical Co., Inc., Milwaukee, Wis.). Analar grade of cetyltrimethyl ammonium bromide was further purified according to the method reported by Casilio *et al.*[8]

Preparation of Solutions——The sulfonyl fluoride derivatives are poorly soluble in water so stock solutions were prepared in isopropanol–water mixture. The amount of isopropanol added to the reaction mixture is limited, but a sufficient quantity of the compound can be dispersed in the aqueous system. Delory and King's carbonate–bicarbonate buffer was used to maintain a pH of 10 in the reaction system. Sodium chloride was added to all solutions to maintain an ionic strength of 0.5. A constant-temperature bath was used for all studies. All the kinetic studies were conducted at 28 °C, and the surfactant concentrations used were above the cmc value of 9.2×10^{-4} M or 0.034% (w/v) at 25 °C for CTAB.[3]

Kinetic Studies——UV absorbance measurements were used to monitor the hydrolysis of the various derivatives. Before the addition of aliquots of sulfonyl fluoride to the reaction solution, the pH was determined and the reaction system pre-equilibrated to the desired temperature. Samples were withdrawn periodically, chilled and analyzed spectrophotometrically. The resultant data yielded typical first-order plots.

Theoretical

In a recent report,[9] models used to describe micellar inhibition of bimolecular pseudo-first-order reactions were discussed and a preferred model was proposed. The overall rate expression can be presented thus:

$$k_{\mathrm{obs}} = \frac{k_{\mathrm{w}} + k_{\mathrm{m}} \acute{P} \%_{\mathrm{m}}}{1 + \acute{P} \%_{\mathrm{m}}} \qquad (1)$$

Where k_{obs} = the observed rate constant

k_{w} = aqueous reaction rate constant

k_{m} = micellar reaction rate constant

$\%_{\mathrm{m}} = (\%_{\mathrm{T}} - \%_{\mathrm{cmc}})$ *i.e.*, the concentration of surfactant which exists in the form of micelles expressed as % (w/w)

$\%_{\mathrm{T}}$ = total concentration of surfactant expressed as % (w/w)

$\%_{\mathrm{cmc}}$ = concentration of surfactant at the cmc expressed as % (w/w)

$\acute{P}$ = the partition factor

It is important to note that the partition factor, $\acute{P}$, replaces the simple partition coefficient, P. The two are related as shown in Eq. 2 below:[9]

$$\acute{P} = P d_{\mathrm{m}} / 100 d_{\mathrm{w}} \qquad (2)$$

where d_{w} = density of aqueous phase

d_{m} = density of micellar phase

Since the density of micelles, d_{m}, is approximately equal to the density of the aqueous solution, $\acute{P}$ will be approximately equal to $P/100$.

$$\therefore \quad P = 100 \acute{P} \qquad (3)$$

Rearrangement of Eq. 1 yields several plot types which were utilized to analyze the rate constant-surfactant concentration data. The plot types applied are discussed as cases 1 to 3.[5]

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Case 1 Type I Plot

A rearrangement of Eq. 1 yields Eq. 4:

$$\frac{k_w - k_{obs}}{k_{obs}} = \left(1 - \frac{k_m}{k_{obs}}\right)\acute{P}(\%_{oT} - \%_{ocmc}) \tag{4}$$

At low surfactant concentrations, the ratio k_m/k_{obs} is insignificant compared to Eq. 1 and Eq. 4 reduces to

$$\frac{k_w - k_{obs}}{k_{obs}} = \acute{P}(\%_{oT} - \%_{ocmc}) \tag{5}$$

The assumption of $1 > k_m/k_{obs}$ was established in all cases since inhibitory effects were observed for all the compounds in the presence of the surfactant. The above equation predicts that a plot of $(k_w - k_{obs})/k_{obs}$ *vs.* $\%_T$ will exhibit a linear segment in the range of low surfactant concentration where k_m is sufficiently small compared to k_{obs}.

The analysis of the plots and the extraction of parameters were therefore limited to the linear segment where $k_m/k_{obs} \ll 1$. Further analysis and rearrangements of Eq. 1 yielded types II and III plots. A summary of the plot types and the kinetic parameters extractable from them are summarized in Table 1.

The analysis of the kinetic data was conducted individually for each sulfonyl fluoride derivative–CTAB system, using the multiplot approach.[5]

Results and Discussion

Benzenesulfonyl Fluoride–CTAB System

The functions needed for types I, II and III plots (summarized in Table I) were calculated and are listed in Table II. The corresponding plots are shown in Figs. 1—3. The slopes of these linear plots yielded apparent kinetic partition factors ($\acute{P}$) of 1.78, 1.82 and 1.79, respectively. All the kinetic parameters extracted are listed in Table III. The high values of partition factor, P ($P = 100\acute{P}$),[9] obtained is an indication that the substrate may well be partitioned or incorporated into the micelles.

p-Toluenesulfonyl Fluoride–CTAB System

The analysis of data was carried out as described above and all the calculated parameters are listed in Table III. Although the $\acute{P}$ values obtained here are not as large as those obtained in the benzenesulfonyl fluoride system, they are still indicative of a considerable incorporation of the substrate into the micellar phase.

p-Aminobenzenesulfonyl Fluoride–CTAB System

The data were analyzed as above. All the calculated parameters are listed in Table III.

TABLE I. Summary of Plots and Kinetic Parameters Extractable from Them[a)]

Type plot No.	Type of plot	Y intercept	X intercept	Slope
I	$(k_w - k_{obs})/k_{obs}$ *vs.* $\%_{oT}$	$-P^1\%_{ocmc}$	$\%_{ocmc}$	P^1
II	k_w/k_{obs} *vs.* $\%_{oT}$	$(1 - P^1\%_{ocmc})$	At $k_w/k_{obs} = 1$ $\%_{oT} = \%_{ocmc}$	P^1
III	$1/k_{obs}$ *vs.* $\%_{oT}$	$\frac{(1 - P^1\%_{ocmc})}{k_w}$	At $1/k_{obs} = 1/k_w$ $\%_{oT} = \%_{ocmc}$	P^1/k_w

a) N.D. Ifudu, Ph. D. Thesis, (1979). University of Connecticut, U.S.A. (ref. 5).

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TABLE II. Observed Pseudo-First-Order Rate Constants, k_{obs}, at 28 °C for Alkaline Hydrolysis of Benzenesulfonyl Fluoride as a Function of CTAB Concentration, and the Functions Calculated for Types I to III Plots

Total surfactant conc. ($\%_T$ (w/v))	$k_w \times 10^2$ (min^{-1})	$k_{obs} \times 10^2$ (min^{-1})	$k_w - k_{obs}$ (min^{-1})	$\frac{(k_w - k_{obs})}{k_{obs}}$	k_w/k_{obs}	$1/k_{obs}$ (min)
0.00	4.265					
0.05		3.554	0.711	0.200	1.200	28.137
0.08		3.380	0.885	0.262	1.262	29.586
0.10		3.186	1.079	0.339	1.340	31.387
0.15		3.094	1.171	0.378	1.378	32.320
0.20		2.920	1.345	0.461	1.461	34.247
0.25		2.743	1.522	0.555	1.555	36.450

Substrate concentration was 8.7×10^{-4} M.

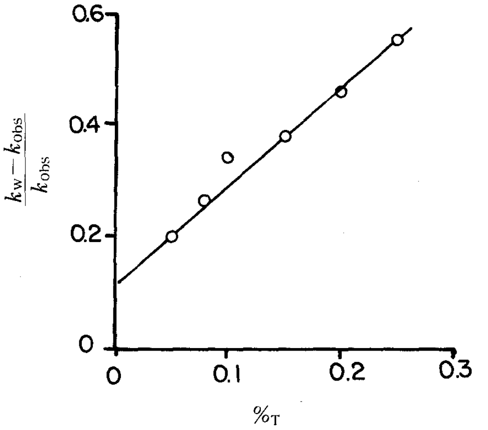

Fig. 1. Plot of $(k_w - k_{obs})/k_{obs}$ vs. $\%_T$ for the Alkaline Hydrolysis of Benzenesulfonyl Fluoride as a Function of Cetyltrimethyl Ammonium Bromide Concentration at 28 °C

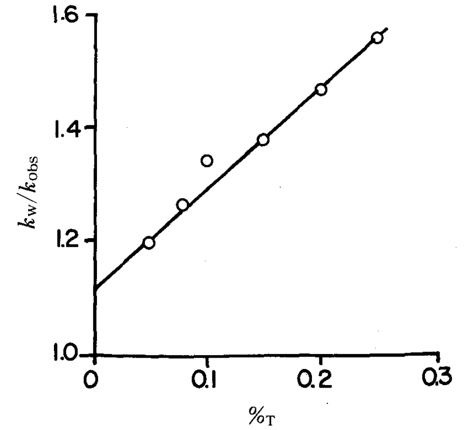

Fig. 2. Plot of (k_w/k_{obs}) vs. $\%_T$ for the Alkaline Hydrolysis of Benzenesulfonyl Fluoride as a Function of Cetyltrimethyl Ammonium Bromide Concentration at 28 °C

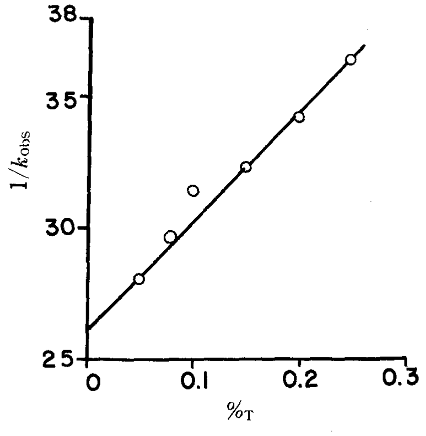

Fig. 3. Plot of $1/k_{obs}$ vs. $\%_T$ for the Alkaline Hydrolysis of Benzenesulfonyl Fluoride as a Function of Cetyltrimethyl Ammonium Bromide Concentration at 28 °C

The high value of 5.44 for $\acute{P}$ could be indicative of enhanced partitioning of the substrate into the micellar environment.

p-Acetamidobenzenesulfonyl Fluoride–CTAB System

A $\acute{P}$ value of about 2.08 was obtained from all the types I to III plots. All the other kinetic

Table III. Summary of the Partition Factors ($\acute{P}$) Calculated for *p*-Substituted Benzenesulfonyl Fluoride Derivatives and Benzenesulfonyl Fluoride (the Parent Compound)

Plot types	Partition factors (from linear regression analysis)				
	p-Nitro	*p*-Acetamide	*p*-Amino	*p*-Toluene	Parent compound
$\frac{(k_w - k_{obs})}{k_{obs}}$ *vs.* $\%_T$	1.923	2.083	5.791	0.434	1.792
k_w/k_{obs} *vs.* $\%_T$	1.926	2.083	5.442	0.434	1.796
$1/k_{obs}$ *vs.* $\%_T$	1.931	2.098	5.442	0.436	1.792

Table IV. Stabilization Factor Calculated as a Function of Substrate Type and CTAB Concentration

Surfactant conc. ($\%_T$ (w/v))	Stabilization factor$=k_w/k_{obs}$ calculated for each *p*-substituted benzenesulfonyl fluoride derivative				
	p-CH_3CONH	*p*-NH_2	*p*-CH_3	H	*p*-NO_2
0.05	1.19	1.37	1.078	1.200	1.237
0.08	1.25	1.55	—	1.262	1.291
0.10	1.29	1.63	1.098	1.340	1.358
0.15	1.39	2.02	1.109	1.378	1.407
0.20	1.50	2.15	1.122	1.461	1.526
0.25	1.60	2.39	1.141	1.555	1.621

parameters obtained are listed in Table III. This substrate also showed considerable micellar partitioning.

p-Nitrobenzenesulfonyl Fluoride–CTAB System

Table III shows all the parameters extracted from the types I to III plots. A $\acute{P}$ value of about 1.90 is indicative of substrate partitioning comparable to that in the above cases.

Plots of pseudo-first-order rate constants as a function of CTAB concentration for the degradation of the *p*-substituted benzenesulfonyl fluorides are shown in Fig. 4. The results clearly show that the hydrolysis of all the substrates was inhibited in the presence of CTAB. Three of the substituents of the compounds studied were electron-donating, the order of electron activity being *p*-NH_2>*p*-CH_3CONH>*p*-CH_3 while the *p*-NO_2 group is electron-attracting.[10] In the studies reported by Winterborn *et al.*[3,4] the observed effect of inhibition or catalysis was explained on the basis of the substituent group effect.

The results obtained in the sulfonyl fluoride–CTAB systems showed that the nature of the *p*-substituent did not determine the reaction type. Analysis of the results indicated appreciable stabilization in all cases as shown in Fig. 5. The stabilization effects of the various substituents did not follow any particular pattern. One would have expected that the stabilization effects due to the electron-donating groups would be greater than that exhibited by the unsubstituted compound or the electron-withdrawing group, if the Winterborn hypothesis[3,4] is applicable to the sulfonyl fluoride–CTAB systems. The degree of stabilization is in the order $NH_2 > NO_2 > CH_3CONH > H > CH_3$. It was expected that even if the *p*-NO_2 derivative showed any stabilization, it would be the least stable. Surprisingly, this was not the case. The order of the partition factors shows a good correlation with the stabilization factors. Thus the *p*-NH_2 and *p*-CH_3 derivatives with the highest and lowest partition factors exhibited

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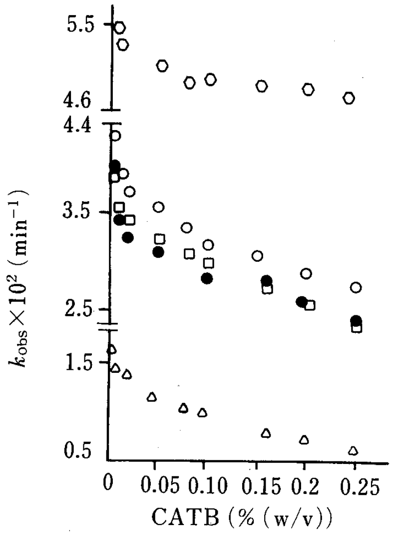

Fig. 4. Comparison of the Inhibitory Effects of Cetyltrimethyl Ammonium Bromide on the Rate of Alkaline Hydrolysis of Various *p*-Substituted Benzenesulfonyl Fluorides

△, NH_2; ●, NO_2; □, CH_3CONH; ○, H; ○, CH_3.

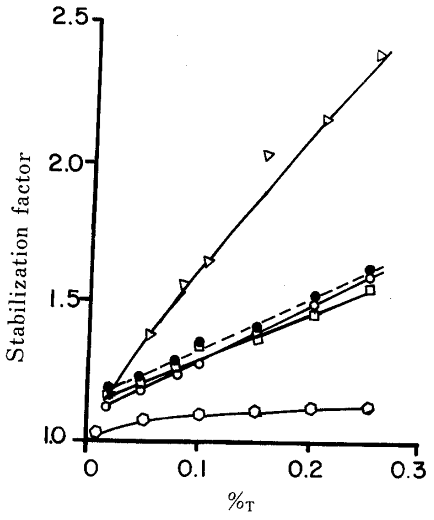

Fig. 5. Plot of the Stabilization Factors for Various Benzenesulfonyl Fluoride Derivatives as a Function of Cetyltrimethyl Ammonium Bromide Concentrations

△, NH_2; ●, NO_2; □, CH_3CONH; ○, H; ○, CH_3.

the highest and lowest stabilization factors, respectively. The effects can be explained on the basis of the substrate solubilization and also the strong interaction between the benzenesulfonyl fluoride moiety and CTAB. UV spectral studies indicated that the sulfonyl fluoride moiety is solubilized in the submicellular surface. In this region, the substrates, irrespective of the *p*-substituent group, are subjected to decreased hydroxide ion activity and a dielectric constant that can be significantly different from that of the bulk aqueous phase. These systems were further investigated by conducting solubility studies of sulfonyl fluoride as a function of surfactant concentration, to determine whether the compounds were incorporated into the micelles and, if incorporated, whether the distribution coefficient is constant. Interestingly, three phases rather than the conventional two-phase system were obtained in the solubility study; a supernatant upper layer, an intermediate oily layer and a solid bottom layer. Analysis of the phases showed that the oily layer was a complex of the surfactant and substrate and that the solid bottom layer did not contain surfactant but was pure substrate. The results suggest that the inhibitory effect observed with all the *p*-substituted derivatives tested is explicable not only in terms of micellar solubilization but also the degree of interaction between the substrate and surfactant. Analysis of the oily phase and supernatant layer clearly indicated an apparent increase in the solubility of the derivatives as a function of CTAB concentration, but interpretation of the data was difficult because of the oily layer formation.

In conclusion, the alkaline hydrolysis of *p*-substituted benzenesulfonyl fluoride derivatives (with either electron-donating or withdrawing *p*-substituents) in the presence of CTAB is not determined by the electron activity of the substituent group, although it is possible that this could influence the magnitude of the observed effects. Inhibition of hydrolysis was observed for all derivatives as a function of CTAB concentration. The inhibitory effect arises from a combination of submicellar substrate solubilization and interaction between the surfactant and sulfonyl fluoride derivatives. The kinetic partition coefficients were calculated from the reaction rate constant-surfactant concentration data by using rearranged forms of Eq. 1.[9] Ordinarily the partition or distribution coefficient would be obtained from independent experiments such as equilibrium solubility and gel filtration studies.[2,3] A literature review suggested that the results of such experiments may not be applicable to kinetic systems[2,4,11] and its use even for simple comparisons may lead to erroneous conclusions.

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