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Micellar Catalysis of Organic Reactions. 23. Effect of Micellar Orientation of the Substrate on the Magnitude of Micellar Catalysis

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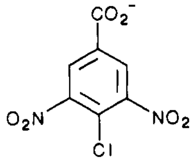
The orientation of sodium 4-chloro-3,5-dinitrobenzoate (1), sodium 2-chloro-3,5-dinitrobenzoate (2), sodium 4-fluoro-3-nitrobenzoate (3), and sodium 2-fluoro-5-nitrobenzoate (4) in micelles of cetyltrimethylammonium bromide (CTAB) has been determined by ^{1}H and ^{19}F NMR studies. Rate constants for the hydroxydehalogenation of compounds 1–4 in water and in CTAB (0.1–40 mM) have been determined. The observed rate constants over this range of CTAB concentration have been treated by a computer program to determine the best values for the rate constant for reaction in the micellar pseudophase (k_2^{m}), the binding constant (K_{s}), and the exchange constant of nucleophile and micellar counterion ($K_{\mathrm{Br}}{}^{\mathrm{OH}}$). In all cases, the rate constant within the micelle (k_2^{m}) is less than in water (k_2^{w}). For compounds 2 and 4, where the reaction center is close to the micelle–water interface, k_2^{m} is a higher percentage of k_2^{w} than for compounds 1 and 3, where the reaction center is buried deeper inside the micelle. Significant catalysis was observed at CTAB concentrations below the normally accepted critical micelle concentration (cmc) of CTAB. Plots of rate versus CTA concentration between 0.1 and 1 mM indicate that, under these reaction conditions, the cmc of CTAB is 3×10^{-4} M. After allowing for the different activation provided by the nitro groups of compounds 1 and 2, the para/ortho rate ratio for the carboxylate group was calculated to be 34 (in water) and 18.5 (in CTAB). Similarly, for compounds 3 and 4, the para/ortho rate ratio for CO_2^- was found to be 600 (in water) and 348 (in CTAB).

Introduction

According to the pseudophase ion-exchange model of micellar catalysis,[1-3] the magnitude of the observed catalysis of a bimolecular reaction depends on the relative rates of reaction in the aqueous pseudophase (k_2^{w}) and in the micellar pseudophase (k_2^{m}), on the binding constant of the substrate to the micelle (K_{s}), and on the competition between the nucleophile and micellar counterion for the available sites on the micelle (e.g., $K_{\mathrm{Br}}{}^{\mathrm{OH}}$ for basic hydrolysis in a bromide micelle like cetyltrimethylammonium bromide (CTAB)). It seems reasonable to expect that a factor of importance to the relative rates in the aqueous and micellar pseudophase would be the orientation of the substrate molecule in the surfactant aggregate. In most cases reported in the literature, this orientation is not known with any certainty.

Recently,[4] NMR studies have been used to probe substrate orientation in micelles with a view to explaining the phenomenon of viscoelasticity observed for some substrates when dissolved in micellar solutions.[5] We have studied the hydroxydehalogenation of a number of aromatic substrates (1–4) in the presence of micelles of CTAB. Two of these reactions (compounds 1 and 4) have been studied previously[6] over a limited CTAB concentration range. We now report kinetic data for these reactions between 0.1 and 40 mM CTAB (Table S1, Supplementary Material). These substrates have been chosen because they all contain a carboxylic acid group which is ionized in the basic conditions used. It seems reasonable to assume that this charged group would be present at the micelle–water interface, allowing better solvation in the aqueous pseudophase than in the less polar micellar pseudophase. Indeed, previous ^{1}H NMR studies for sodium salicylate and for sodium *m*-hydroxybenzoate[4] have indicated that this is a reasonable conclusion. Furthermore, it is expected that the hydrophobic nitro group which reduces water solubility of organic compounds would be more deeply solubilized into the micelle. These two factors are probably the major criteria controlling the orientations of substrates 1–4 in micelles of CTAB.



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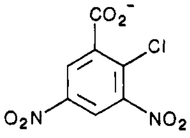

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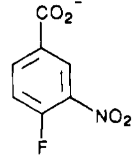

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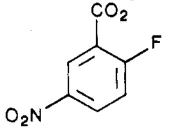

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For two of our substrates (2 and 4), the halogen leaving group is ortho to the carboxylate group and hence should be aligned close to the micelle–water interface. For the other substrates (1 and 3), the halogen leaving group is para to the carboxylate group and hence should be more deeply buried into the micellar pseudophase. We now report ^{1}H NMR and ^{19}F NMR studies to confirm the orientation of these substrates in micelles of CTAB.

Results and Discussion

NMR spectra for compounds 1–4 were determined in D_2O solution in the absence and in the presence of micelles of CTAB. The chemical shifts of the fluorine and proton nuclei are in Table I. The chemical shifts are reported relative to $FCCl_3$ and TMS for fluorine and protons, respectively. External reference samples of CF_3COOH and CH_3CN were used for fluorine and proton spectra, respectively. The reference compounds were contained in sealed tubes immersed in the aqueous solution in the NMR tube. This avoided the possibility of the reference compound being solubilized within the micelles and leading to a change in chemical shift compared to that in water.

It has been reported[4] that protons oriented within the micelle experience an upfield change in chemical shift and

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(1) Menger, F. M.; Portnoy, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 4698.

(2) Bunton, C. A. *Catal. Rev.-Sci. Eng.* **1979**, *20*, 1.

(3) Rodenas, E.; Vera, S. *J. Phys. Chem.* **1985**, *89*, 513.

(4) Manohar, C.; Rao, U. R. K.; Valaulikar, B. S.; Iyer, R. M. *J. Chem. Soc., Chem. Commun.* **1986**, 379.

(5) Rao, U. R. K.; Manohar, C.; Valaulikar, B. S.; Iyer, R. M. *J. Phys. Chem.* **1987**, *91*, 3286.

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Table I. NMR Chemical Shifts Observed for Compounds 1-4 in D_2O and in CTAB (20 mM)

no.		F^a	$H_2{}^b$	$H_3{}^b$	$H_4{}^b$	$H_5{}^b$	$H_6{}^b$
1	D_2O		8.4593				8.4593
	CTAB		8.4434				8.4434
	Δ^c		-0.0159				-0.0159
2	D_2O				8.6930		8.3810
	CTAB				8.4079		8.3064
	Δ^c				-0.2851		-0.0746
3	D_2O	-61.67	8.4519			7.3370	8.0784
	CTAB	-63.98	8.4619			7.1920	8.1243
	Δ^c	-2.31	+0.010			-0.1450	+0.0459
4	D_2O	-50.47		7.2563	8.2068		8.3757
	CTAB	-49.80		7.1498	8.0307		8.4748
	Δ^c	+0.67		-0.1065	-0.1761		+0.0991

[a] Chemical shift relative to $CFCl_3$ (0 ppm). External reference CF_3COOH (-77.0 ppm). [b] Chemical shift relative to TMS (0 ppm). External reference CH_3CN (1.93 ppm). [c] Change of chemical shift on transfer from D_2O to CTAB. Negative values indicate an upfield shift; the probe nucleus is in a nonpolar region of the micelle. References 4, 5.

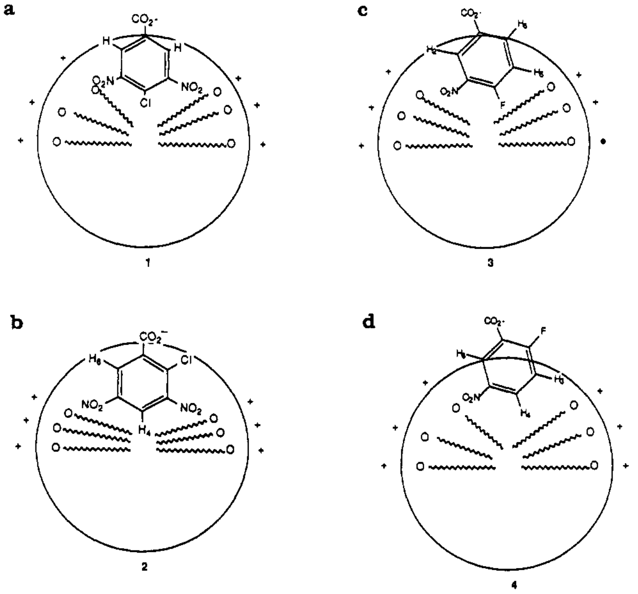

Figure 1. Schematic representation of the orientation of (a) substrate 1, (b) substrate 2, (c) substrate 3 and (d) substrate 4 solubilized by a CTAB micelle.

the results were interpreted on this basis. The orientation of compound 1 in the micelle is shown in Figure 1a. The very small change in chemical shift of protons 2 and 6 in this molecule is taken to indicate that they are present at the interface. For compound 2, both H-4 and H-6 experienced large upfield changes of chemical shift on transfer from D_2O to micelles. This indicated that they were buried inside the micelle. The orientation of compound 2 is shown in Figure 1b. For compound 3, both the fluorine and H-5 experienced upfield changes of chemical shift, indicating that they were buried inside the micelle. However, for H-2 and H-6, a very slight downfield movement of chemical shift was observed, indicating that they were at the micelle–water interface. This orientation is depicted in Figure 1c. For compound 4, H-3 and H-4 experienced an upfield change of chemical shift and are thus buried inside the micelle. However, the fluorine and H-6 show downfield changes of chemical shift, indicating that they are at the interface. The orientation of compound 4 is shown in Figure 1d. Thus, the NMR results suggest that the halogen nucleofuge of compounds 2 and 4 is better situated for substitution by a hydroxide ion, located either in the aqueous intermicellar pseudophase or at the interface, than those of compounds 1 and 3.

Second-order rate constants for the hydroxydehalogenation of compounds 1-4 are in Table S1. The first point that is obvious is that catalysis is observed below the generally accepted cmc of CTAB, of 9×10^{-4} M.[3,7] A plot of rate versus [CTA] between 0.1 and 1.0 mM CTAB is shown in Figure 2 for all compounds. It is clear from this figure that the cmc of CTAB under reaction conditions, i.e., in the presence of NaOH and the substrate molecule, is in fact 3×10^{-4} M. This constitutes an alternative method to determine the cmc under reaction conditions. The conventional methods, i.e., conductivity or surface tension measurements as a function of [CTA] are not readily applicable to actual reaction solutions. Bunton has previously reported that the cmc of CTAB is reduced in the presence of added NaOH.[8,9] Fendler[10] has also noted that, for ionic surfactants, the cmc decreases significantly with increasing ionic strength and changes somewhat unpredictably with temperature. We concur on this point and suggest that for studies of basic hydrolysis

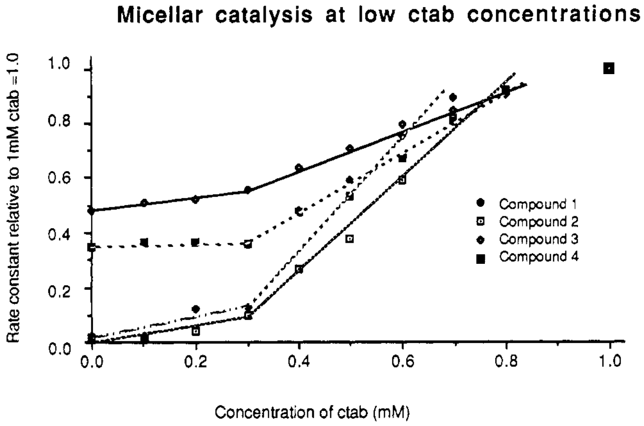

Figure 2. Variation of second-order rate constant k_2 (relative to 1 mM CTAB) with CTA concentration between 0.1 and 1.0 mM CTAB.

Table II. Estimated Micellar Parameters for the Hydroxydehalogenation of Compounds 1-4[a]

no.	catalysis[b]	$10^5k_2{}^w$, $M^{-1}\ s^{-1}$	$10^5k_2{}^m$, $M^{-1}\ s^{-1}$	K_s, M^{-1}
1	48	96.5	34.3 (0.35)[c]	2750
2	70.4	6.35	3.94 (0.62)[c]	1225
3	2.6	250	26.6 (0.11)[c]	731
4	5.3	10.3	2.05 (0.20)[c]	346

[a] Using $K_{Br}{}^{OH} = 10$; cmc = 3×10^{-4} M; $\beta = 0.8$. [b] Ratio of maximum observed rate in CTAB to rate in water. [c] Value in parenthesis is $k_2{}^m/k_2{}^w$.

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(7) Rodenas, E.; Vera, S. *Tetrahedron* **1986**, *42*, 143.

(8) Bunton, C. A.; Robinson, L. *J. Am. Chem. Soc.* **1968**, *90*, 5972.

(9) Cipiciani, A.; Linda, P.; Savelli, G.; Bunton, C. A. *J. Phys. Chem.* **1983**, *87*, 5262.

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in micelles of CTAB, a value of 3×10^{-4} M be used in future work, especially for substrates containing the CO_2^- group.

The kinetic data for these reactions was subjected to a computer simulation, based on the model of Rodenas and Vera[3,7] to determine the best values of K_s, K_{Br}^{OH}, and k_2^m. These results are in Table II.

$[X]_w$ and $[X]_m$ refer to the concentrations of the ion X^- in the aqueous phase and in the micellar pseudophase, respectively, relative to the total volume of solution, so that $[X] = [X]_m + [X]_w$. m_x is the fraction of X^- counterions relative to the total number of micellar cta^+ ions. Since, if the surfactant concentration is sufficient for micelles to form, $[cta]_w = cmc$, $[cta]_m = [cta] - cmc$, and $[X]_m = m_x[cta]m$. In the ctab systems

$$k_2 = \frac{k_w + (k_m K_s - k_w) m_{OH}[cta]_m/[OH]}{1 + K_s[cta]_m} \qquad [1]$$

where m_{OH} can be obtained from

$$m_{OH}^2 (K_{Br}^{OH} - 1)[cta]_m + m_{OH}\{[OH] + K_{Br}^{OH}[Br] - \beta(K_{Br}^{OH} - 1)[cta]_m\} - \beta\,[OH] = 0 \qquad [2]$$

$K_{Br}^{OH} = [Br]_w[OH]_m/[OH]_w[Br]_m$ is the phase distribution equilibrium constant, $K_s = [S]_m/[S]_w[cta]_m$ is the substrate–micelle binding constant, k_w is the second-order rate constant for the reaction in the aqueous phase, and k_m is the rate constant for the reaction in the micellar phase, given by

$$rate_m = k_m \frac{[s]_m[OH]_m}{[cta]_m}$$

The term $[OH]_m$ refers to the molar concentration of OH^- related to the total volume of solution. To obtain a second-order rate constant characteristic of the micellar phase suitable for direct comparison with k_w, the hydroxyl concentration should rather be related to the volume of the Stern layer.[3]

k_2^m is defined by $rate_m = k_2^m[OH]_m^{true}[S]_m$ and obtained from $k_2^m = k_m V_{cta}$, since $[OH]_m^{true} = [OH]_m/[cta]_m V_{cta}$, where V_{cta} is the molar volume of the Stern layer, taken as 0.14 $dm^3\ mol^{-1}$.

The variation of observed rate with detergent concentration for compounds **1**–**4** is shown in Figure 3a–d. The solid lines represent calculated values of k_2 obtained from the parameters listed in Table II and eq 1 and 2. In line with previous reported results,[11] a unique set of parameters was not achieved, since the values of K_{Br}^{OH} and k_2^m are compensatory and a good fit could be obtained with a number of combinations of these parameters.

We have found that $K_{Br}^{OH} = 10$ gave an excellent fit of experimental to calculated data for all compounds and this is within the range 10–20, which is commonly used.[9] As mentioned above, we have used 3×10^{-4} M for the cmc of CTAB. The rate constant for reaction within the micelle, k_2^m, was insensitive to the cmc, but the binding constant was greatly affected and the fit of experimental to calculated data was much better for cmc = 3×10^{-4} M than 9×10^{-4} M since considerable catalysis was detected between 0.3 and 0.9 mM CTAB.

In all cases, the rate constant for reaction in the micelle k_2^m was less than for reaction in water k_2^w. This is surprising Bunton[12] has reported that for hydroxydechlorination of 1-chloro-2,4-dinitrobenzene k_2^m/k_2^w = 3.5 in micelles of CTAB. However, the difference can be explained when one considers that the hydrolysis of compounds **1**–**4** involves reactions between anions resulting in the concentration of charge, a reaction which is sensitive to the polarity of the environment. Since the polarity of micelles, even in the Stern layer, is less than that of water,[13] a reduction of rate on transfer from H_2O to micelles is expected in terms of the Hughes–Ingold solvent theory.[14]

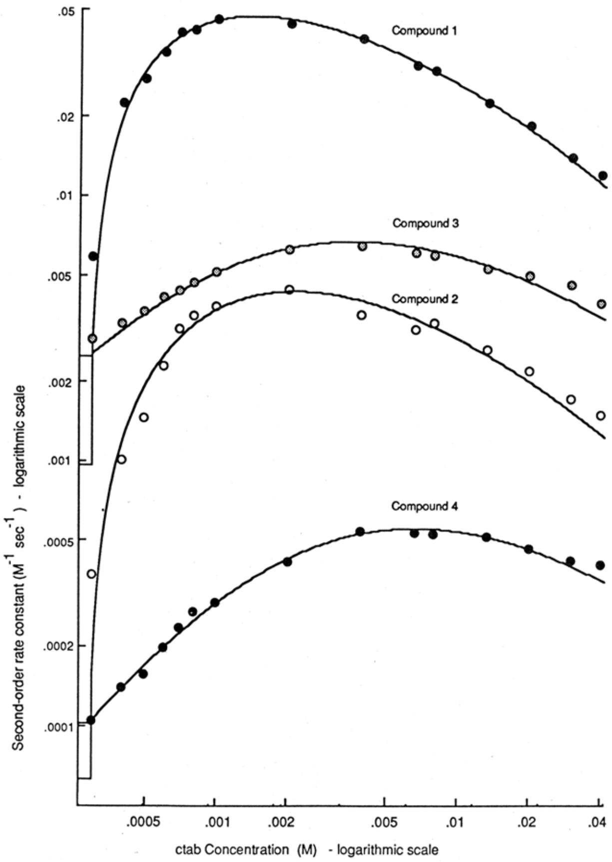

Figure 3. Variation of the second-order rate constant k_2 with CTA concentration for substrates **1**–**4**. The curves are predicted from the parameters in Table II and eq 1 and 2.

The k_2^m/k_2^w ratios are larger for the dinitro compounds than for the mononitro compounds. This is explained by the better delocalization of the double negative charge in the transition state of the dinitro compounds, thus rendering the decrease in polarity on transfer from water to CTAB a less serious problem.

On looking more closely at the k_2^m values, we notice that for compounds **2** and **4**, where the halogen is close to the micelle–water interface, the calculated k_2^m value is a higher percentage of the rate in water than for compounds **1** and **3**, respectively, where the halogen is buried inside the micelle. Thus, the orientation of the substrate molecule in the micelle plays an important role in determining the ratio k_2^m/k_2^w and hence the overall catalysis observed.

It is also of interest to note the larger K_s values of the dinitro compounds **1** and **2** than for the mononitro compounds **3** and **4**. It is well known that nitro groups reduced water solubility of organic compounds so larger binding constants for compounds containing two such groups is not unexpected.

Para/Ortho Rate Ratios for CO_2^-. Before comparing the rate of hydroxydehalogenation of compounds **1** and **2**

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or compounds **3** and **4** to determine the para/ortho rate ratio for the CO_2^- group, it is necessary to allow for the different activation provided by the nitro groups in each compound. For example, compounds **3** and **4** have activation provided by an ortho and a para nitro group, respectively. Miller[15b] has reported that, for methoxydefluorination in methanol at 50 °C, *p*-fluoronitrobenzene reacts some 1.4 times faster than the ortho isomer. However, for compounds **3** and **4** hydroxydefluorination occurs faster for compound **3** despite activation by an *o*-nitro group both in water (24-fold) and in CTAB (13-fold). Thus, the differential Coulombic repulsion between the attacking nucleophile and a CO_2^- group ortho to the reaction center (**4**) or para to the reaction center (**3**) is more important than differences in activation provided by the nitro groups in these compounds and this leads to para/ortho rate ratios 34 (H_2O) and 18.5 (CTAB) for the CO_2^- group.

Similarly for compounds **1** and **2**, activation is provided by two nitro groups at the 2- and 6-positions for **1** but at the 2- and 4-positions for **2**. Miller[15a] has reported that, for methoxydechlorination in methanol at 0 °C, 1-chloro-2,4-dinitrobenzene reacts some 40 times faster than the 2,6-dinitro isomer. However, for compounds **1** and **2**, hydroxydechlorination occurs faster for compound **1** despite activation by 2,6-dinitro groups both in water (15-fold) and in CTAB (8.7-fold). Thus, the unfavorable Coulombic repulsion between an attacking nucleophile and the CO_2^- group ortho to the reaction center is strong enough to reverse a 40-fold difference in activation provided by the nitro groups and this leads to para/ortho rate ratios 600 (H_2O) and 348 (CTAB) for the CO_2^- group.

In both series, the para/ortho rate ratio for the CO_2^- group is smaller in micelles of CTAB than in water. This smaller ratio reflects the smaller k_2^m value for the compound with the CO_2^- group para to the reaction center (compounds **1** and **3**) rather than increased values of k_2^m for the compounds with the CO_2^- group ortho to the reaction center (compounds **2** and **4**). Thus, the important factor underlying this difference is orientation of the substrates within the micelle (unfavorable for **1** and **3**) rather than a reduction in the Coulombic repulsion between the nucleophile and CO_2^- group (for **2** and **4**) by the positively charged surface of the micelle.

Experimental Section

Materials. 2-Fluoro-5-nitrobenzoic acid was available from previous work.[6] 4-Fluoro-3-nitrobenzoic acid (Sigma), 2-chloro-3,5-dinitrobenzoic acid (Fluka), and 4-chloro-3,5-dinitrobenzoic acid (Aldrich) were commercially available. CTAB was purified by the method Mukerjee and Mysels.[16] Distilled water was further purified with a Millipore system to achieve a resistivity of 16 MΩ cm.

Kinetics. Stock solutions of the substrates **1**–**4** (0.01 M in A.R. acetonitrile), CTAB (0.06 or 0.02 M in water), and sodium hydroxide (0.3 M in water) were prepared. The sodium hydroxide was standardized by titration against hydrochloric acid with bromocresol green as indicator. The required amount of CTAB solution was pipetted into a cuvette and the substrate (18 μL) was added by microsyringe. The solution was allowed to reach thermal equilibrium, and the reaction was initiated by the addition of sodium hydroxide solution. The mixture was then stirred vigorously and product formation was monitored at 442 nm (compound **1**), 373 nm (compound **2**), 416 nm (compound **3**), and 414 nm (compound **4**), on either a Varian Associates DMS70 or a 635 UV-vis spectrophotometer. The reactions were followed for 10 half-lives if practical. For slow reactions, data were collected over at least 2 half-lives. A computer program designed to give the best straight-line fit was used to provide an infinity value. Good agreement was obtained between rate constants obtained by the two methods. Reactions were carried out in the cuvette maintained at constant temperature in the jacketed cell holder of the spectrophotometer. The temperature within the cell was determined with a Jenco thermistor thermometer: for compounds **1** and **2**, reaction in 0.02 M NaOH at 30.3 °C and for compounds **3** and **4**, reaction in 0.1 M NaOH at 56 °C.

NMR Spectra. NMR spectra were obtained on a JEOL 200-MHz spectrometer, either in D_2O solution (10 mM) or in 20 mM CTAB dissolved in D_2O. External standards of trifluoroacetic acid or acetonitrile in sealed capillaries were used in ^{19}F and ^{1}H spectra, respectively.

Acknowledgment. We are pleased to acknowledge the assistance of S. Pengprecha in obtaining the NMR spectra.

Registry No. **1**, 69644-63-9; **2**, 20627-91-2; **3**, 114396-94-0; **4**, 2926-39-8; CTAB, 57-09-0.

Supplementary Material Available: Observed second-order rate constants for the hydrolysis of compounds 1–4 in water and in the presence of CTAB (0.1–40 mM) (Table S1) (1 page). Ordering information is given on any current masthead page.

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[15] Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968; (a) p 104, (b) pp 142, 165.

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