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Specificity in the Micellar Catalysis of a Hofmann Elimination[1,2]

M. J. Minch,* Shin-Shin Chen, and Richard Peters

Department of Chemistry, University of the Pacific, Stockton, California 95211

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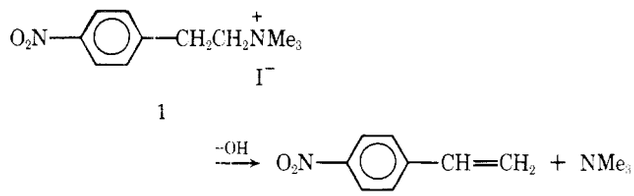
The E2 elimination of trimethylamine from *p*-nitrophenethyltrimethylammonium iodide in 0.1 M NaOH is inhibited by anionic micelles of sodium dodecyl sulfate. Cationic micelles of hexadecyltrimethylammonium bromide and zwitterionic micelles of *N*,*N*-dimethyl-*N*-dodecylglycine have little effect on the reaction rate. However, micelles of *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(2-hydroxethyl)ammonium bromide and *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide are catalytic at high alkali concentrations (pH >12.0), where the surfactants are converted into proteophilic zwitterions which participate as bases in the elimination. This is a significant exception to the general observation that all surfactants of the same charge type cause the same type of reactivity change.

Surfactants affect the reactivity of molecules hydrophobic enough to be taken into micelles and, in the last few years, considerable attention has been directed to the catalysis observed in many cases.[3-5] We recently reported that cationic micelles of hexadecyltrimethylammonium bromide (CTABr) markedly increase the acidity of carbon acids.[6] We have since examined the catalytic effectiveness of CTABr and other surfactants toward the hydroxide-catalyzed elimination reaction of 4-nitrophenethyltrimethylammonium iodide (1).



This reaction received some attention by Hughes and Ingold[7] and more recently by Hodnett[8] but this is the first reported examination of the rate of 4-nitrostyrene formation as a function of pH, temperature, and surfactant concentration. This is the first reported study of the effect of micelles on the synthetically important Hofmann elimination reaction.

Experimental Section

Materials. Sodium dodecyl sulfate (Aldrich) and CTABr (Matheson) were purified by the methods of Grunwald.[9] *N*,*N*-Dimethyl-*N*-hexadecyl-*N*-(2-hydroxethyl)ammonium bromide (**2**) was prepared by quaternizing *N*,*N*-dimethylethanolamine (Aldrich) with 1-bromohexadecane (Eastman) in refluxing 2-propanol and was purified by recrystallization from EtOH: mp 194–204 °C (lit.[10] 208–210 °C); NMR (D_2O) δ 3.10 (s, NCH_3), 1.26 [s, $C(CH_2)_n$], 0.86 (t, CCH_3). *N*,*N*-Dimethyl-*N*-dodecylglycine[11] (**3**) was prepared by quaternizing *N*,*N*-dimethylglycine with 1-bromododecane (Aldrich) in 2-propanol and was purified by recrystallization from EtOH–Et_2O: mp 200–205 °C (lit.[11] 183 °C); NMR (D_2O) δ 3.29 (s, NCH_3), 1.31 1s, $C(CH_2)_n$], 0.85 (t, CCH_3). The *N*,*N*-dimethylglycine was prepared by reductive methylation[12] and was purified by recrystallization from EtOH–Et_2O. *N*,*N*-Dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide (**4**) was prepared by quaternizing *N*,*N*-dimethylpropylamine (Aldrich) with 1-bromohexadecane (Eastman) in refluxing 2-propanol and was purified by recrystallization from EtOH: mp 84–89 °C; NMR (D_2O) δ 3.12 (s, NCH_3), 1.32 [s, $C(CH_2)_n$], 0.89 (t, CCH_3). *n*-Octylamine was distilled under reduced pressure and stored over NaOH.

4-Nitrophenethyltrimethylammonium Iodide (1). Phenethylamine (22 g, 0.18 mol) was slowly added to 100 mL of rapidly stirred red fuming nitric acid at 5 °C. After 3 h the reaction mixture was poured onto ice and made alkaline with NaOH solution. The product was extracted with ether; the extract was dried (Na_2SO_4) and evaporated to dryness. The crude 4-nitrophenethylamine (22 g, 0.13 mol) was combined with 100 mL of 2-propanol, 16 g of K_2CO_3, and 137 g (60 mL, 0.91 mol) of iodomethane and heated at reflux for 60 h. When cool the reaction mixture solidified. Part of the solid was soluble in hot EtOH, and this solution yielded yellow crystals of product which were recrystallized twice: mp 195–196 °C (lit.[7] 199 °C); NMR (Me_2SO-d_6) δ 3.40 (s, NCH_3), 3.53 (s, NCH_2), 3.84 (m, $ArCH_2$), 8.00 and 8.55 (AA'BB' pattern, ArH). Anal. Calcd for $C_{11}H_{17}N_2O_2I$: C, 39.30; H, 5.10; N, 8.33; I, 37.75. Found: C, 39.27; H, 5.17; N, 8.49; I, 37.82.

Kinetics. The reactions were followed spectrophotometrically at 320 nm using a Beckman Model DB spectrophotometer with a water-jacketed cell compartment. The temperature was maintained within 0.1 °C by a Lauda K2/R constant temperature water circulator. All surfactant solutions were prepared on the day of use from carbonate-free NaOH solution and stored in tightly stoppered flasks. The NaOH stock solutions were prepared from freshly boiled, N_2 satu-

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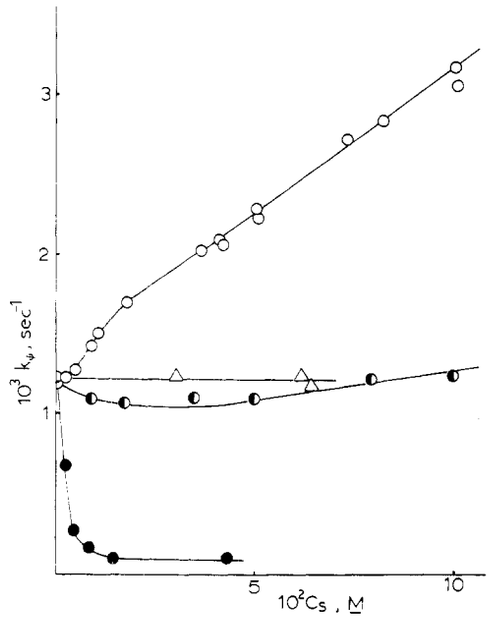

Figure 1. The observed first-order rate constant k_ψ for 4-nitrostyrene formation from **1** in 0.1 M NaOH at 39 °C as a function of surfactant concentration. The surfactants are (○) **2**, (△) **3**, (◐) CTABr, and (●) NaLS.

rated, glass-distilled water and standardized by titration with potassium acid phthalate (phenolphthalein). The pH of the 0.10 M NaOH stock solutions was always found to be 12.93 ± 0.06 whenever aliquots were removed (vs. pH 12.0 standard buffer). All kinetic runs were initiated by injecting 50 μL of an aqueous substrate stock solution into a cuvette of the appropriate buffer or NaOH solution in the spectrophotometer cell compartment. The first-order rate constants, k_ψ, were evaluated from plots of log $(A_\infty - A_t)$ vs. time (seconds) where A_t and A_∞ are the absorbances at time t and after 10 half-lives, respectively. The A_∞ values were stable except in the presence of *n*-octylamine, at low pH (<12) or with higher concentrations of **2** than described here. The rate constants for *n*-octylamine runs were evaluated by the method of Guggenheim. All rate constants used to evaluate activation parameters were taken from lines with least-squares correlation coefficients greater than 0.998. The second-order rate constants, k_{II}, were calculated using the stoichiometric NaOH concentrations.

Results and Discussion

In the absence of surfactant the values of 10^4k_ψ, the first-order rate constant, are 12.2, 9.8, 6.4, 3.0, and 1.1 s^{-1} for 0.10, 0.08, 0.05, 0.02, and 0.01 M NaOH, respectively, at 39 °C. The ionic strength was maintained at 0.10 M with NaCl. A plot of k_ψ vs. hydroxide ion concentration is linear indicating an E2 mechanism. The second-order rate constant is 1.16×10^{-2} M^{-1} s^{-1} at 39 °C. The observed 10^4k values for the reaction in 0.10 M NaOH at 25.0, 35.0, 39.0, 45.0, and 49.7 °C are 4.0, 8.9, 12.0, 22, and 30, respectively, corresponding to $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values of 15.2 kcal/mol and −23 eu. The large negative entropy is consistent with a bimolecular (E2) process. The solvent-isotope effect is also consistent with an E2 mechanism. The first-order rate constant in 0.0135 M NaOD–D_2O at 39 °C is 2.97×10^{-4} s^{-1}. This corresponds to a solvent-isotope effect, k_{HO^-}/k_{DO^-}, of 0.53 which compares very favorably with the values of 0.56 and 0.58 reported by Thornton[13] for $PhCH_2CH_2N^+Me_3Br^-$ and *p*-$ClPhCH_2CH_2N^+Me_3Br^-$, respectively, at 80.5 °C.

The reaction is inhibited by NaCl and $Me_3N^+CH_2CH_2O$-HI^- in 0.10 M NaOH. The values of 10^4k_ψ are 6.08, 4.6, and 3.3 s^{-1} for 0.488, 1.29, and 3.41 M NaCl, respectively, and 7.24 and 6.8 s^{-1} for 0.313 and 1.87 M $Me_3N^+CH_2CH_2OHI^-$ at 39 °C. Inhibition by added electrolytes is the expected situation for the reaction of an anion with a cation.[14]

Surfactant Effects. The effect of sodium dodecyl sulfate (NaLS), CTABr, **2**, and **3** on k_ψ for 0.10 M NaOH at 39 °C is given in Figure 1; in this figure C_s represents the concentration of surfactant. The effect of higher CTABr concentrations and the effect of added solutes at high CTABr concentrations are given in Table I.

Table I. Effect of CTABr and Additional Solutes

C_{CTABr}, M	Solute	C_{solute}, M	10^3k_ψ,[a] s^{-1}
			1.16
0.106			1.39
0.178			1.4
0.205			1.52
0.006	Igepal[b]	0.023	1.08
0.027	Igepal[b]	0.023	1.30
0.149	Igepal[b]	0.023	1.44
0.100	*n*-Octylamine	0.062	1.5
0.100	*n*-Octylamine	0.103	1.5

[a] First-order rate constant at 39 °C. [b] Igepal CO-630: nonylphenoxypoly(ethyleneoxy)ethanol (General Aniline and Film Corp.).

Anionic micelles of NaLS retard the elimination by incorporating substrate, protecting it from hydroxide ions. Ester saponification is inhibited by anionic micelles for the same reason.[15] Anionic micelles may also retard elimination because the stabilizing interactions between the anionic micelle and cationic substrate are reduced upon transition state formation. Low concentrations (<0.1 M) of CTABr are not catalytic probably because little or no substrate is taken into the cationic micelle. The limited incorporation of cationic substrate into cationic micelles is consistent with our finding that the aromatic ^1H NMR signals of **1** in D_2O do not shift upfield upon the addition of enough CTABr to produce a 0.1 M solution. Upfield shifts are observed when aromatic solubilisates are incorporated into CTABr micelles.[16] Concentrations of CTABr high enough to incorporate substrate cause only a slight rate increase because the number of hydroxide ions per micelle is small at such CTABr concentrations. Mixtures of CTABr and the nonionic surfactant Igepal CO-630[17] are inhibitory at low CTABr/Igepal ratios and no more catalytic than CTABr alone at high ratios. Added *n*-octylamine does not appreciably increase the catalytic effectiveness of CTABr. There is a slow decline in the final absorbance reading (A_∞) in the presence of amines, probably because of the amine attack on the styrene. Micelles of the zwitterionic surfactant **3** are not catalytic.

Micelles of **2** are catalytic and, as Table II indicates, the extent of catalysis varies with the concentration of **2** in a complicated manner depending on the concentration of NaOH. The rate constant increases most steeply with the concentration of **2** when the hydroxide ion concentration is around 0.186 M. At hydroxide ion concentrations well above and below this value, the rate constant increases less steeply. We believe that a significant portion of the surfactant molecules is converted into the alkoxide (zwitterion) form at these NaOH concentrations and that **2** is catalytic because the proteophilic zwitterion acts as a base in the elimination. Another explanation is that the alkoxy form of the surfactant can act as an indirect general base which abstracts a proton from water, forming a hydroxide ion which then reacts with substrate. Such a reaction is kinetically indistinguishable from direct proton abstraction from the substrate by the alkoxide form of the surfactant.

$$HO^- + RN^+Me_2CH_2CH_2OH \rightleftharpoons H_2O + RN^+Me_2CH_2CH_2O^-$$

The catalysis is not just due to an electrostatic effect because the nonnucleophilic zwitterion **3** is not a catalyst.

Table II. Catalysis by 2 in NaOH Solution[a]

C_{NaOH}, M	10^2C_s,[b] M	10^3k_ψ,[c] s^{-1}	$k_{\psi cat.}$[d]/$k_{\psi 0}$
0.010[e]		1.1	
0.010[e]	2.6	1.90	1.7
0.010[e]	8.3	3.25	3.0
0.010[e]	12.4	3.40	3.1
0.10		1.16	
0.10	0.50	1.29	1.11
0.10	0.91	1.43	1.23
0.10	1.05	1.52	1.31
0.10	1.81	1.72	1.48
0.10	3.63	2.04	1.76
0.10	4.10	2.11	1.82
0.10	4.20	2.06	1.78
0.10	4.78	2.06	1.78
0.10	5.03	2.24	1.93
0.10	7.26	2.74	2.36
0.10	8.20	2.85	2.45
0.10	10.6	3.21	2.77
0.186		2.26	
0.186	2.6	4.02	1.78
0.186	4.9	4.78	2.12
0.186	7.5	5.89	2.61
0.186	9.9	6.86	3.04
0.504		5.07	
0.504	1.5	6.53	1.29
0.504	2.9	8.69	1.71
0.504	6.2	11.4	2.25

[a] Rate constants measured at 39 °C. [b] Concentration of *N,N*-dimethyl-*N*-hexadecyl-*N*-(2-hydroxyethyl)ammonium bromide. [c] Observed first-order rate constant. [d] Ratio of the observed first-order rate constant to that observed at the same NaOH concentration without added surfactant. [e] Ionic strength maintained at 0.1 with 0.09 M NaCl.

Table III. Catalysis by 4 in NaOH Solution[a]

C_{NaOH}, M	10^2C_s,[b] M	10^4k_ψ,[c] s^{-1}	$k_{\psi cat.}$[d]/$k_{\psi 0}$
0.0154		2.43	
0.0154	1.6	2.60	1.07
0.0154	8.1	3.55	1.44
0.0154	13.1	4.40	1.81
0.0964		11.2	
0.0964	2.1	15.7	1.40
0.0964	4.5	19.5	1.74
0.0964	7.5	25.7	2.29
0.0964	14.2	33.1	2.96
0.0624		56.1	
0.624	2.0	79.7	1.42
0.624	4.5	106	1.88
0.624	11.7	168	2.99

[a] Rate constants measured at 39 °C. [b] Concentration of *N,N*-dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide. [c] Observed first-order rate constant. [d] Ratio of the observed first-order rate constant to that observed at the same NaOH concentration without added surfactant.

Moreover, we have found that nonmicellar electrolytes retard the reaction.

The presence of an ionizable OH group is essential for catalysis. We found that micelles of **4** are catalytic and the extent of catalysis depends upon the NaOH concentration. The data in Table III indicate that $k_{\psi cat.}/k_{\psi 0}$ (the ratio of rate constants in the presence and absence of **4**) increases more steeply with surfactant concentration in 0.624 M NaOH than in 0.0154 M NaOH. The surfactant **4** does not form as much zwitterion at the lower NaOH concentration.

Bunton and co-workers[18] have recently shown that micelles of **2** are catalytic bases in the transformation of the 3-bromo-3-phenylpropionate ion to the *trans*-cinnamate ion in dilute alkali. They estimated[10,18] a pK_a of 12.4 for **2** but found, as we did, that the extent of catalysis is not directly proportional to the base concentration. The fraction of surfactants converted into zwitterions is not directly proportional to the NaOH concentration because, unlike a monomeric species, a micellar acid does not have a constant K_a but one that depends on the net charge of the micelle[19] which reflects the extent of ionization and counterion binding. Moreover, the catalytic effectiveness of zwitterions may be higher when few are formed because the cationic substrate initial state would be destabilized relative to the transition state by the largely cationic micelle. Catalysis by **2** is inhibited by added NaCl; the 10^3k_ψ values (s^{-1}, 39 °C) observed for 0.10 M NaOH with 0.050 M **2** decreased from 2.24 to 1.44 and 1.38 with 0.88 and 1.16 M NaCl, respectively. Added NaCl increases the viscosity of alkaline solutions of **2**; a 0.050 M solution of **2** in 0.10 M NaOH with 3.5 M NaCl is opalescent and almost too viscous to pour. We were not able to examine the catalytic effectiveness of concentrations of **2** greater than 0.10 M in 0.10 M NaOH because these solutions were too viscous for uniform mixing. Also we could not directly verify the lack of catalysis by **2** at pH values significantly below the pK_a of **2** because product decomposition precluded stable infinities over such long reaction times.

We have found a significant exception to the general observation that all surfactants of the same charge type cause the same type of reactivity change and we are currently investigating the catalytic effectiveness of other β-hydroxy quaternary ammonium surfactants on the Hofmann elimination reactions of chiral compounds.

Registry No.—**1**, 7101-10-2; **2**, 20317-32-2; **3**, 683-10-3; **4**, 63989-29-7; *N,N*-dimethylethanolamine, 108-01-0; 1-bromohexadecane, 112-82-3; *N,N*-dimethylglycine, 1118-68-9; 1-bromododecane, 143-15-7; *N,N*-dimethylpropylamine, 926-63-6; phenethylamine, 64-04-0; 4-nitrophenethylamine, 24954-67-4; iodomethane, 74-88-4; CTABr, 57-09-0.

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