Micellar-Catalyzed Reaction of Hydroxamic Acids

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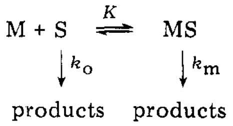
Micellar catalysis has attracted considerable interest[1-4] with regard to fundamental studies of catalysis and mechanism and for its relationship to enzymatic processes. The hydrolysis of amide-like substances is of interest because of their relationship to peptides. There seems to be only one report[5] of micellar catalysis of amide hydrolysis and that is only a very small catalysis in the base-catalyzed hydrolysis of N-methyl-p-nitroacetanilide by cationic micelles; the corresponding p-H and p-methoxy anilide reaction rates were slightly decreased by the surfactant.

Considerable modification of the leaving group in the hydrolysis reaction results from substitution of a hydroxamic acid for an amide. The electronegative hydroxyl in place of hydrogen will result in a better leaving group, i.e., the expelled species is a weaker base. Such substitution might lead to a significant change in reactivity in a micellar system. The data reported here demonstrate that respectable anionic micellar catalysis for the acid-catalyzed hydrolysis of octanohydroxamic acid does occur. (Mechanistic studies of the acidic hydrolysis of hydroxamic acids have been reported.[6]) The kinetic measurements are summarized in Table I. Examination of the effect of hydrochloric acid concentration[7] and of the temperature and sodium chloride concentration[8] on the critical micelle concentration (cmc) of sodium dodecyl sulfate suggests a cmc of 10^{-3} M for the conditions listed in Table I. Rate increases should occur near and above, but not below, the cmc for micellar catalysis. This is shown in Table I for sodium dodecyl sulfate. In addition, rate data for reaction in the presence of the simple salts sodium chloride and sodium p-toluenesulfonate (Table I) show that very little rate effect can be attributed to simple salt effects.

A standard kinetic scheme[1] for micellar catalysis is shown in Scheme I, where M and S are micelle and substrate, respectively, and k_0 and k_m are the rate constants for product formation outside and within the micelle, respectively. This model leads to the relationship[1]

Scheme I



$$\frac{1}{k_0 - k_1} = \frac{1}{k_0 - k_m} + \left(\frac{1}{k_0 - k_m}\right)\left(\frac{N}{K(C_D - \mathrm{cmc})}\right)$$

in which k_1 is the observed pseudo-rate constant, K is an equilibrium constant, N is the micellar aggregation number, and C_D is the total surfactant concentration. A graph of the left side of this equation vs. $1/(C_D - \mathrm{cmc})$ in which the cmc is taken as 10^{-3} M and C_D is in the range 0.01–0.06 M is a good linear plot within experimental error. (The standard deviation of the slope is 1.8% of the slope, correlation coefficient 0.9998.) Evaluation of the slope and intercept yields $k_m = 44.8 \times 10^{-5}$ s^{-1} and $K/N = 119$. The catalytic ratio k_m/k_0 is 9.74.

Table II. Kinetic Data for Hydrolysis of $PhCH_2CONHOH$ in 0.314 N HCl at 55.0 °C with SDS[a]

SDS, M[b]	$10^5 k$[c]	SDS, M[b]	$10^5 k$[c]
0	4.89	0.04	11.1
10^{-4}	5.28	0.16	19.4
10^{-3}	6.19	0.32	17.6
0.02	6.06		

[a] Sodium dodecyl sulfate. [b] Ambient temperature, three significant figures. [c] Average pseudo-first-order constant, s^{-1}; initial concentration of phenylacetohydroxamic was 5×10^{-4} M.

Table II shows the effect of sodium dodecyl sulfate on the rate of acidic hydrolysis of phenylacetohydroxamic acid. The catalytic effect is similar, although considerably reduced in magnitude, under comparable conditions to that observed with octanohydroxamic acid (Table I). This indicates, as would be anticipated,[1] that micellar effects vary as a function of substrate structure.

The hydrolysis mechanism in the micellar environment might be expected to be analogous to that[6] in the absence of micelles with the micelles performing either or both of two functions.[1] The first function is an orientation effect in which the micelle attracts the neutral substrate and a reagent, such as H_3O^+, of charge opposite to the charge of the micelle. The other mode of action is micellar stabilization of a transition state of charge opposite to that of the micelle relative to its stabilization of the reagent, in turn relative to stabilization by water, leading to rate enhancement.

Experimental Section

Octanohydroxamic acid, mp 77.8–78.3 °C (lit.[9] 78–79 °C), was prepared from methyl octanoate according to the general procedure described before.[6] Phenylacetohydroxamic acid has been described previously.[10] Sodium dodecyl sulfate was purified according to literature[1] procedures. Solutions of sodium dodecyl sulfate and hydrochloric acid were prepared within several hours of use and stored in the cold to prevent hydrolysis of the sodium dodecyl sulfate (the half-life[11] of sodium dodecyl sulfate in 0.1 N HCl, 50 °C, at concentrations above its cmc is 7 days). Mallinckrodt analytical reagent sodium chloride and Eastman sodium p-toluenesulfonate (97% minimum of the sulfonate, 1% maximum of H_2O) were used as received.

The kinetic measurements were made by the spectrophotometric method reported previously[6] except that sufficient acidity had to be maintained in the ferric chloride solutions to prevent precipitation in the presence of sodium dodecyl sulfate. Beer's law was shown to hold for the ferric ion–hydroxamate complex under these conditions.

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Registry No.—Sodium dodecyl sulfate, 151-21-3; sodium p-toluenesulfonate, 657-84-1; octanohydroxamic acid, 7377-03-9; phenylacetohydroxamic acid, 5330-97-2.

Table I. Kinetic Data for Hydrolysis of $CH_3(CH_2)_6CONHOH$ in 0.203 N HCl at 50.7 °C with Various Salts

Salt	None	SDS[a]	SDS	SDS	SDS	SDS	SDS
Concn[b]		10^{-4}	10^{-3}	0.01	0.02	0.04	0.06
$10^5 k$[c]	4.60	4.68	6.96	25.2	32.3	37.7	40.1
Salt		NaCl		NaCl	NaTs[d]		NaTs
Concn[b]		0.01		0.06	0.01		0.06
$10^5 k$[c]		4.85		4.86	4.87		5.00

[a] Sodium dodecyl sulfate. [b] Molarity, ambient temperature, three significant figures. [c] Average pseudo-first-order constant, s^{-1}; initial concentration of octanohydroxamic acid was 5×10^{-4} M. [d] Sodium p-toluenesulfonate.

References and Notes

(1) For general discussion and leading references, see J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975.

(2) W. Tagaki, S. Kobayashi, K. Kurihara, A. Kurashima, Y. Yoshida, and Y. Yano, *J. Chem. Soc., Chem. Commun.*, 843 (1976).

(3) C. N. Sukenik and R. G. Bergman, *J. Am. Chem. Soc.*, **98**, 6613 (1976).

(4) D. Piszkiewicz, *J. Am. Chem. Soc.*, **98**, 3053 (1976).

(5) V. Gani, C. Lapinte, and P. Viout, *Tetrahedron Lett.*, 4435 (1973).

(6) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **39**, 841 (1974), and references cited therein.

(7) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973).

(8) E. Matijevic and B. A. Pethica, *Trans. Faraday Soc.*, **54**, 587 (1958).

(9) W. P. Jencks, M. Caplow, M. Gilchrist, and R. G. Kallen, *Biochemistry*, **2**, 1313 (1963).

(10) D. C. Berndt and J. K. Sharp, *J. Org. Chem.*, **38**, 396 (1973).

(11) V. A. Motsavage and H. B. Kostenbauder, *J. Colloid Sci.*, **18**, 603 (1963).

Deamination of 2-Phenyl-2-(2-methoxyphenyl)ethylamine

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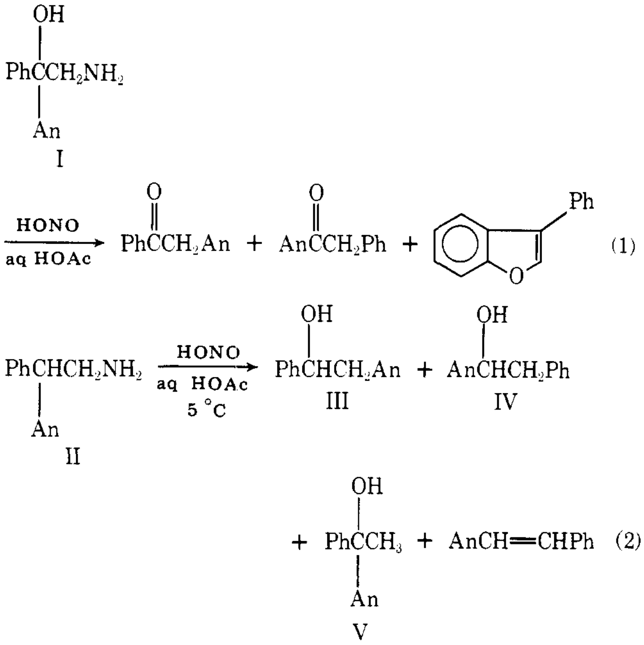
Previously we reported[1] the results of deamination of amino alcohol I, which demonstrated the first example of *o*-MeO-5 participation[2] in such rearrangements (eq 1). We now report the deamination of the related amine II (eq 2).



Ph = C_6H_5 ; An = *o*-$C_6H_4OCH_3$

Treatment of the hydrochloride of II with sodium nitrite in aqueous acetic acid at 5 °C produced (after treatment of the reaction mixture with lithium aluminum hydride to cleave any acetates) alcohols III,[3,4] IV,[3,5,6] a minor amount (<5%) of V,[7] and an alkene fraction consisting of *o*-methoxystilbenes.[5,8,9] There is no indication of *o*-MeO-5 participation in the present case, in direct contrast to the deamination of I.

Typical migratory aptitudes of aryl groups in such reactions of diarylethylamines (Ph = 1.00) are *p*-tolyl, 1.18,[10] and *p*-anisyl, 1.44.[11] Such results have been interpreted in terms of ground-state conformational control in both amino alcohol and amine cases.[12,13] The migratory ability of the *o*-anisyl group in various rearrangements has been shown to be <1.[1,14,15,16] In the present case, the migratory ratio for the *o*-anisyl group (III/IV by ^{1}H NMR analysis) is 2.67. This appears to be substantially the highest migratory aptitude observed for any aryl group in reactions of this kind, for reasons about which we can only speculate at this time. Furthermore, we find no evidence of *o*-MeO-5 participation in the present case. We are attempting experiments designed to provide information about ground-state conformations in diarylethylamines and diarylethyl amino alcohols and thus yield some insight into the reasons for the observed migration tendencies.

Experimental Section

2-Methoxybenzophenone. Addition of phenylmagnesium bromide to *o*-methoxybenzaldehyde (Aldrich Chemical Co., Inc.), followed by oxidation of the crude product with Jones reagent in benzene (48 h reflux), provided 2-methoxybenzophenone: mp 36–37 °C (lit.[17] mp 39 °C).

2-Phenyl-2-(2-methoxyphenyl)ethanal (VI). 1-Phenyl-1-(2-methoxyphenyl)ethene[18] was prepared by treatment of 2-methoxybenzophenone with methylmagnesium iodide in tetrahydrofuran, followed by dehydration of the alcohol product (V[7]) with H_2SO_4 (pH 1) during workup: yield 89%; bp 120–125 °C (2 Torr). H_2O_2 (30%, 21 mL) was added dropwise to formic acid (97%, 100 mL) and the solution was allowed to stand for 1 h. Then a solution of the alkene[18] (31.0 g) in benzene (100 mL) was added dropwise and the mixture was stirred overnight. The layers were separated and the benzene layer was extracted with water, saturated $NaHCO_3$, and water, and dried. The benzene was removed at reduced pressure and the aldehyde was distilled: yield 23.7 g (71%); bp 135 °C (~1 Torr) [lit.[19] bp 198–200 °C (16 Torr)]; IR (neat) 2715, 1723 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (3 H, s, OCH_3), 5.05 (1 H, d, J = 3 Hz, CH), 7.19 (9 H, m, ArH), 9.83 (1 H, d, J = 3 Hz, CHO).

2-Phenyl-2-(2-methoxyphenyl)ethanal Oxime (VII). A mixture of aldehyde VI (8 g), hydroxylamine hydrochloride (8 g), sodium hydroxide (8 g), water (160 mL), and ethanol (150 mL) was heated at reflux for 1 h. Standard workup yielded 3.4 g of the oxime: mp 112–114 °C; IR ($CHCl_3$) 3200, 1245, 1039 cm^{-1}; NMR ($CDCl_3$) δ 3.69 (3 H, s, OCH_3), 5.25 (1 H, d, J = 8 Hz, CH), 7.2 (9 H, m, ArH), 7.83 (1 H, d, J = 8 Hz, CHN), 8.70 (1 H, s, OH).

2-Phenyl-2-(2-methoxyphenyl)ethylamine Hydrochloride (II HCl). Oxime VII was reduced with lithium aluminum hydride in refluxing diethyl ether for 24 h. Saturated Na_2SO_4 was added dropwise to quench the reaction. The ether layer was dried ($MgSO_4$) and then saturated with anhydrous HCl. The crystals of II HCl which formed were recrystallized from ethanol–acetone: mp 215–217 °C; IR (KBr) 3400, 1245, 1030, 908 cm^{-1}; NMR (free base, $CDCl_3$) δ 3.25 (2 H, d, J = 8 Hz, CH_2), 3.74 (3 H, s, OCH_3), ~3.74 (2 H, br s, NH_2), 4.50 (1 H, t, J = 8 Hz, CH), 7.25 (9 H, m, ArH).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.78; N, 5.31; Cl, 13.44. Found: C, 68.60; H, 7.04; N, 4.93; Cl, 13.44.

Deamination Reactions. In a typical run 40 mg of amine hydrochloride II HCl and 40 mg of $NaNO_2$ were dissolved in 10 mL of 50% acetic acid and allowed to stand for 4 h at 5 °C. Then 1 mL of saturated NH_2SO_3H was added, followed by 15 mL of 6 N NaOH. The reaction mixture was extracted with CH_2Cl_2 (three 10-mL portions) and the combined extracts were dried ($MgSO_4$). Solvent was removed at reduced pressure and 30 mL of anhydrous ether was added. Then ~50 mg of lithium aluminum hydride was added to cleave any acetates. The reaction was quenched with saturated Na_2SO_4, and the aqueous layer was extracted with CH_2Cl_2 (three 10-mL portions). The combined organic layers were dried and solvent was removed at reduced pressure to leave an oil, which was diluted with 1 mL of diethyl ether and chromatographed on thick-layer silica gel plates with acetone–benzene (1:99). The alcohol fraction was removed and analyzed by ^{1}H NMR using the methoxyl singlets (solvent $CDCl_3$, δ 3.70 for III, 3.65 for IV, 3.42 for V) at expanded sweep width for quantification. Duplicate runs gave the same results.

A similar run with 328 mg of II HCl (1.24 mmol) and 390 mg of $NaNO_2$ but without the $LiAlH_4$ treatment allowed isolation of 113 mg (0.497 mmol) of mixed alcohols, 46.2 mg (0.143 mmol) of mixed acetates, and 61.4 mg (0.290 mmol) of an alkene fraction which appeared by ^{1}H NMR to be a mixture of *o*-methoxystilbenes;[5,8,9] net recovery, 75%.

The alkene fraction isolated above was subjected to the deamination conditions and shown to be unchanged; the alcohols were also shown to be stable to the reaction conditions, as judged by TLC and ^{1}H NMR.