Entropy-Related Rate Accelerations in the Micelle-Bound Carboxylate-Catalyzed Iodine Oxidation of Diethyl Sulfide

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Rate constants for the carboxylate-catalyzed iodine oxidation of diethyl sulfide in the presence of SDS micelles exhibit two linear first-order regions with respect to carboxylate ion concentration. This is in marked contrast to the oxidation in the absence of SDS where the reaction exhibits first- and second-order terms with respect to carboxylate. Second-order catalytic constants for acetate, propionate, butanoate, pentanoate, and hexanoate, when plotted aginst the micelle-induced pK_a shifts for these buffers, give a linear plot with β = 3.8 and 0.7 for data in the presence of SDS at low buffer and in the absence of SDS, respectively. Extrapolation of the nonmicelle data to hexanoate gives a 100-fold rate advantage for the micelle-catalyzed reaction. Activation parameters for the butanoate-catalyzed reaction are $\Delta H^{\ddagger}$ = 5.5 kcal/mol, $\Delta S^{\ddagger}$ = 9.1 eu for the micelle reaction at low buffer and $\Delta H^{\ddagger}$ = 5.5 kcal/mol, $\Delta S^{\ddagger}$ = 13.9 eu for the first-order nonmicelle process. The rate advantage for the micelle reaction is quantitatively accounted for by the $\Delta\Delta S^{\ddagger}$ = 4.8 eu. The 40-fold increase in micellar rate constants on going from acetate to hexanoate gives an average free-energy gain of −545 cal/mol per $-CH_2-$, representing utilization of over 80% of the available hydrophobic binding energy for rate acceleration.

It is well established that micellar aggregates can, in some instances, provide substantial rate enhancements for certain reactions relative to the rates that are observed in free solution.[1,2] The driving force for this catalysis can often be attributed to electrostatic or solvent-induced ground state destabilization which is relieved in the transition state and to entropy effects. All of these mechanisms undoubtedly play important roles in enzyme catalysis; however, it has been suggested that entropy loss may be especially important and rate accelerations of up to 10^8 have been attributed to this mechanism.[3,4] Surfactant micelles offer a system in which nonpolar interactions can be directly utilized to bind reactants and thereby reduce translational entropy losses associated with bi- or trimolecular reactions. This ability of micelles to serve as entropy sinks makes the study of catalyzed reactions on micellar surfaces especially important to the understanding of the mechanisms of enzymic rate accelerations.

The iodine oxidation of sulfides to produce sulfoxides has been observed to be strongly catalyzed by carboxylate buffers and to contain both first- and second-order buffer-dependent terms.[5] In order to investigate the possibility of micelle-induced, entropy-related effects in this reaction, we have investigated the iodine oxidation of diethyl sulfide catalyzed by carboxylate anions of increasing chain length, both in the presence and absence of the surfactant sodium dodecyl sulfate (SDS).

Experimental Section

Materials. Reagent grade organic acids and inorganic salts were used without further purification. Sodium dodecyl sulfate (SDS) was purified by recrystallization using the procedure of Duynstee and Grunwald.[6] Glass-distilled water was used throughout.

Stock solutions of organic acids, 50% ionized, were prepared by neutralizing solutions of the carboxylic acid with standard sodium hydroxide solution. Stock solutions of pentanoic and hexanoic acids were prepared in 2.4×10^{-2} M solutions of SDS to aid solubility. Iodine solutions were prepared from the solid to be 0.01 M in 1 M NaI. Diethyl sulfide solutions were prepared in methanol at 0.10 M.

Kinetic Measurements. The rates of disappearance of I_3^- were followed at 353 nm using a Hitachi 100-60 spectrophotometer equipped with an automatic cell changer and a digital printout. Constant temperature was maintained at 15, 25, or 42 °C by the use of a thermostated cell compartment; ionic strength was maintained at less than 0.05. First-order rate constants were determined from semilogarithmic plots of $A_\infty - A_t$ against time and were typically linear for over 3–4 half-times. The pH of each solution was determined at the completion of the experiment using a Corning 130 pH meter equipped with a combined glass electrode. Reactions were initiated by adding 10 μL of diethyl sulfide solution (0.10 M) to thermostated cuvettes containing 3.0 mL of the desired buffer solution and 10 μL of the stock iodine solution. SDS concentrations were maintained at 1.6×10^{-2} M, which is twice the literature value for the critical micelle concentration.[1] Apparent pK_a's for the carboxylic acids were determined by potentiometric titration of 0.20 M solutions using standard 0.20 M sodium hydroxide solution.

Results

The rate constants for the iodine oxidation of diethyl sulfide catalyzed by acetic, propionic, and butyric acids, 50% ionized, in the absence of micellar aggregates, show a nonlinear dependence on the concentration of carboxylate anion (Figure 1). Rate constants for first- and second-order processes were obtained from these data from plots of $k_{obsd}/[RCOO^-]$ vs. $[RCOO^-]$ and are listed in Table I. Rate constants for the carboxylate-catalyzed oxidation of diethyl sulfide in the presence of 1.6×10^{-2} M SDS also exhibit a nonlinear dependence on carboxylate concentration (Figure 2). At very low concentrations of carboxylate there is a rapid increase in the observed rate constant which breaks to a less steep, but nevertheless linear, second phase. Logarithmic plots of observed rate constants at the extremes of high and low buffer concentrations against log $[RCOO^-]$ are linear with unit slope. Rate constants for each first-order process (Table II) were determined from plots such as these or from the initial and final slopes of plots of observed rate constants vs. buffer concentration (Figure 2). Agreement between the methods was good, and the probable errors in derived rate and activation parameters are estimated to be <±5%. The hydroxide activity dependent rate constant for the oxidation process in the presence of SDS but in the absence of carboxylate buffer was determined to be 2.8×10^{-5} M^{-1} s^{-1} using dilute pyridine buffers. We have previously found that pyridine buffers do not catalyze the oxidation of sulfides under these conditions.[7] Activation parameters for the oxidation of diethyl sulfide in the presence and absence of SDS (Table III) were calculated from data obtained at 15, 25, and 42 °C. The apparent pK_a values of micelle-bound carboxylate buffers were determined by potentiometric titration, and these values, relative to acetate, are listed in Table II.

Discussion

The iodine oxidation of sulfides proceeds through the intermediate formation of an iodosulfonium ion which undergoes hydrolysis to give the sulfoxide.[5,8] Carboxylate ions have been found to catalyze the reaction, and the observed rate law contains both first- and second-order terms for carboxylate catalysis, resulting in nonlinear plots exhibiting significant upward curvature (Figure 1). The mechanism that is suggested

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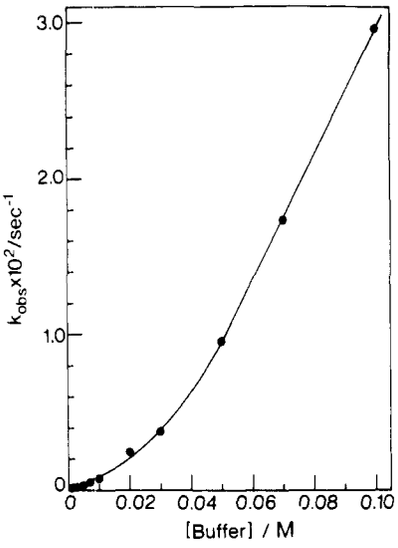

Figure 1. Observed rate constants for the oxidation of diethyl sulfide as a function of the concentration of butanoic acid buffer, 50% ionized, in the absence of SDS.

Table I. Iodine Oxidation of Diethyl Sulfide in the Absence of SDS[a]

buffer	k_B, M^{-1} s^{-1} [b]	k_2, M^{-2} s^{-1} [c]
acetate	4.0×10^{-2}	2.45
propanoate	5.0×10^{-2}	2.5
butanoate	5.2×10^{-2}	2.6

[a] In aqueous solution, 25 °C, $[I^-] = 3.3 \times 10^{-3}$ M, $[Et_2S] = 3.3 \times 10^{-4}$ M, $[I_2] + [I_3^-] = 3.3 \times 10^{-5}$ M. [b] Observed second-order rate constant for buffer catalysis. [c] Observed third-order rate constant for buffer catalysis.

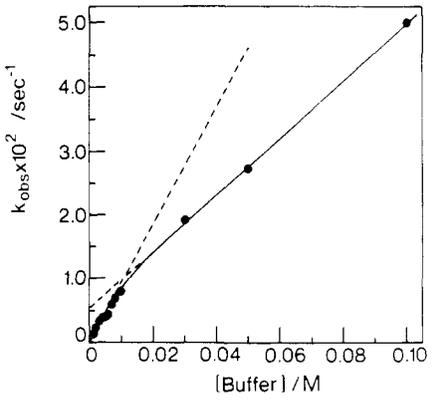

Figure 2. Observed rate constants for the oxidation of diethyl sulfide as a function of the concentration of pentanoic acid buffer, 50% ionized, in the presence of 1.6×10^{-2} M SDS.

Table II. Iodine Oxidation of Diethyl Sulfide in the Presence of SDS[a]

buffer	ΔpK_a [b]	k_B', M^{-1} s^{-1} [c]	k_b', M^{-1} s^{-1} [d]
acetate	0	0.2	0.095
propionate	0.14	0.5	0.23
butanoate	0.17	0.65	0.30
pentanoate	0.22	1.35	0.50
hexanoate	0.42	~8	2.75

[a] In aqueous solution, 25 °C, [SDS] = 1.6×10^{-2} M, $[I^-] = 3.3 \times 10^{-3}$ M, $[Et_2S] = 3.3 \times 10^{-4}$ M, $[I_2] + [I_3^-] = 3.3 \times 10^{-5}$ M. [b] pK_a increase relative to acetate, in the presence of SDS; $(pK^{SDS}_{RCOOH} - pK^{SDS}_{CH_3COOH})$. [c] Observed second-order rate constant for buffer catalysis at very low buffer concentration. [d] Observed second-order rate constant for buffer catalysis at high buffer concentration.

(Scheme I, pathway *A*) involves the formation of an *O*-acyl sulfoxide intermediate which gives sulfoxide by an uncatalyzed hydrolysis involving solvent (k_0) and by a catalyzed pathway involving either general catalyzed attack of solvent or through a nucleophilic mechanism which gives rise to anhydride. For dicarboxylic acids the anhydride product has been trapped as its anilide;[5] however, there is no firm evidence that this pathway is predominant for monocarboxylate buffers. The kinetic data obtained in this study for the oxidation of diethyl sulfide in the absence of SDS are consistent with the mechanism of Scheme I and with the results of Gensch and Higuchi[5] for the oxidation of other sulfides. Numerical data for the first- and second-order buffer-dependent terms are

Scheme I

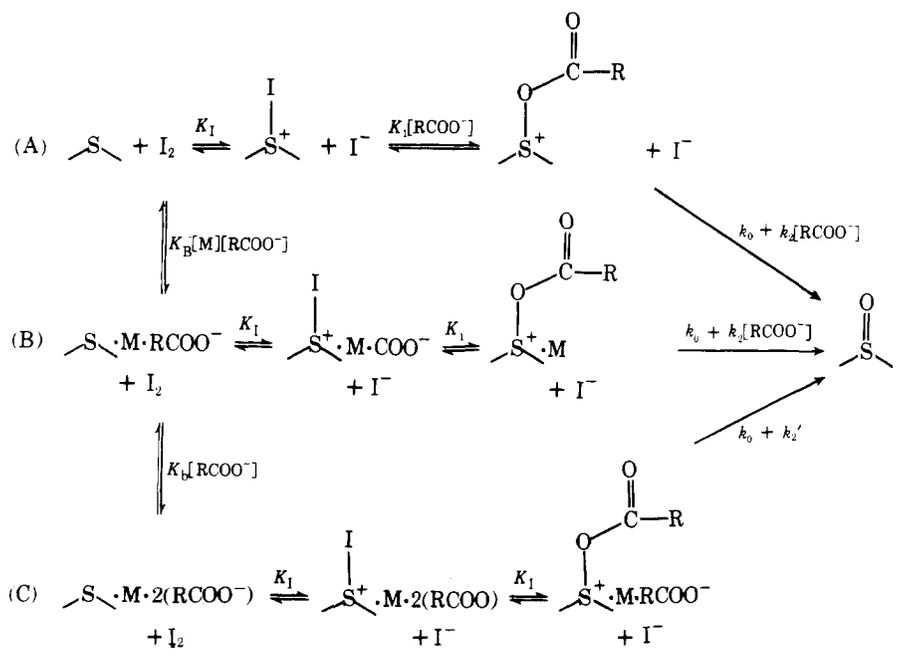

Table III. Activation Parameters for the Butanoate-Catalyzed Oxidation of Diethyl Sulfide [a]

	15 °C	25 °C	42 °C	$\Delta H^{\ddagger}$, kcal/mol[b]	$\Delta S^{\ddagger}$, eu[c]
		nonmicelle			
k_B, M^{-1} s^{-1} [d]	1.4×10^{-2}	5.2×10^{-2}	4.2×10^{-1}	5.5	13.9
k_2, M^{-2} s^{-1} [e]	0.76	2.68	15.3	5.0	7.6
		micelle[f]			
k_B', M^{-1} s^{-1} [g]	0.17	0.65	4.7	5.5	9.1
k_b', M^{-1} s^{-1} [h]	7.1×10^{-2}	0.30	1.86	5.5	9.3

[a] In aqueous solution, $[I^-] = 3.3 \times 10^{-3}$ M, $[Et_2S] = 3.3 \times 10^{-4}$ M. [b] Calculated from the slope of a plot of ln (k/T) vs. $1/T$. [c] Calculated from the intercept of a plot of ln (k/T) vs. $1/T$. [d] Observed second-order rate constant for buffer catalysis. [e] Observed third-order rate constant for buffer catalysis. [f] $[SDS] = 1.6 \times 10^{-2}$ M. [g] Observed second-order rate constant at low buffer concentration. [h] Observed second-order rate constant at high buffer concentration.

collected in Table I. The rate constants for these mechanisms increase very slightly through the series acetate, propionate, and butanoate.

The presence of small quantities of SDS results in a marked change in the dependence of the observed rate constants on buffer concentration (Figure 2). At very low concentrations of buffer the observed rate constants increase rapidly. Double logarithmic plots show that the reaction is clearly first order in carboxylate in this region. At higher buffer concentration the observed rate constants fall off to a less steep, but nevertheless linear, first-order region. This type of buffer dependence is most readily accounted for by either a change in rate-limiting step followed by a change in mechanism or by an equilibrium step which can be saturated with buffer followed by a second buffer-dependent mechanism. Since surfactant micelles are well known to exhibit saturation kinetics, this latter mechanism seems especially attractive. The mechanism presented in pathways B and C, Scheme I, is consistent with the observed data. For the effects at low buffer (pathway B) the binding constant for the carboxylate buffer and the micelle is denoted as K_B; k_0 represents the solvent-catalyzed hydrolysis of the *O*-acyl sulfoxide and k_2 represents the buffer-catalyzed hydrolysis to give the sulfoxide either directly or through the corresponding anhydride. The rate law corresponding to the mechanism B of Scheme I is given in eq 1. At very low buffer concentration this simplifies to eq 2, which is comparable to the second-order rate constant for the non-micelle oxidation ($k_{obsd} = K_I K_1 [RCOO^-] k_0$) with the simple inclusion of the micelle-binding equilibrium constant.

$$k_{obsd} = \frac{K_B[RCOO^-]}{K_B[RCOO^-] + 1} K_I K_1 (k_0 + k_2[RCOO^-]) \quad (1)$$

$$k_{obsd} = K_B[RCOO^-] K_I K_1 k_0 \quad (2)$$

Observed catalytic constants determined at low (k_B') and high (k_b') buffer concentrations in the presence of SDS are given in Table II. As the chain length increases from acetate to hexanoate, both catalytic constants increase by about 40-fold. This could be caused by either the utilization of hydrophobic binding energy to reduce translational entropy or by an increase in apparent pK_a of the carboxylate ion caused by binding to the anionic micelle. Since the mechanism of catalysis is nucleophilic, a fairly large dependence of the catalytic constant on the pK_a of the base might be expected.[9] The increases in apparent pK_a for the series of carboxylates in the presence of SDS, relative to acetate, are listed in Table II. Figure 3 is a plot of the catalytic constants from Table II against these pK_a increases. For k_B', the catalytic constants observed at low buffer concentration, the plot has a slope of $\beta = 3.8$. The fact that the slope is greater than unity means that the increased reactivity is not entirely due to the increased basicity of the carboxylate ion in the presence of the SDS micelles.

The second-order rate constants for the nonmicelle oxidation of diethyl sulfide are plotted as the triangles in Figure 3, giving $\beta = 0.7$. Extrapolating to hexanoate, the difference between the micelle and nonmicelle second-order rate constants is about 100-fold. In its simplest form, this ratio compares the micelle binding constant for hexanoate with the equilibrium constant for the formation of an encounter pair in free solution. Of course this comparison is valid only if the constants K_I, K_1, and k_0 are the same in both the micellar and nonmicellar phases. There is reason to believe that this may be at least approximately true. Activation parameters for the butanoate-catalyzed oxidation of diethyl sulfide are reported in Table III. For both the nonmicelle second-order term and the micelle term at low buffer, the enthalpy of activation is 5.5 kcal/mol. The entropies of activation are 9.1 and 13.1 eu, respectively, to give a $\Delta\Delta S^{\ddagger}$ of 4.8 eu at 25 °C. This difference in entropy of activation *quantitatively* accounts for the factor of about 12-fold in the rate constants between the two systems. The fact that the difference in rate appears *only* in the entropy terms suggests that the rate accelerations can be attributed to binding effects.

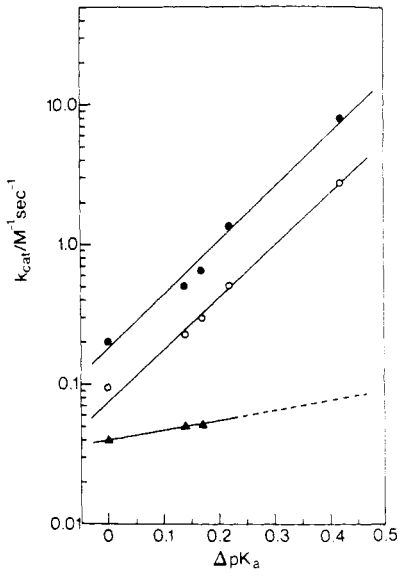

Figure 3. Observed catalytic rate constants for the carboxylate-catalyzed oxidation of diethyl sulfide as a function of the micelle-induced pK_a shift of the carboxylate catalyst: (▲) k_B for the nonmicelle oxidation; (●) k_B' for the micelle-catalyzed oxidation; (○) k_b' for the micelle-catalyzed oxidation at high buffer concentrations.

The difference in k_B' for hexanoate and acetate is about 40-fold. This represents a free-energy change of about −2.2 kcal/mol or −545 cal/mol per $-CH_2-$. It has been estimated that the free-energy change for the complete transfer of a single methylene unit from free solution to the micellar phase is −650 cal/mol per $-CH_2-$.[10,11] Thus, over 80% of the available hydrophobic binding energy is being *utilized* as the driving

force for catalysis and the mechanism of that catalysis appears to be through entropy loss.

The catalytic constants obtained for micellar oxidation at higher buffer concentrations, k_b', are plotted as the closed circles in Figure 3. These catalytic constants also show a large pK_a dependence with $\beta = 3.7$. This is much larger than the β of 0.1 that is observed for the second-order buffer term in the nonmicelle oxidation, and the magnitude of this value strongly suggests that the catalyzed reaction occurs on the micelle surface. The chemical nature of this step is not altogether clear. The pK_a dependence gives an observed free-energy change of −530 cal/mol per $-CH_2-$, strongly suggesting a binding step. The simplest model that is consistent with the data (Scheme I, pathway C) includes this second binding step as a parallel pathway to K_B. The binding constant, K_b, must be less favorable than K_B by at least 100-fold because no curvature can be detected in the plots of k_{obsd} vs. buffer concentration above 0.01 M. The fact that the rate constants for the second phase are only three fold smaller than the first means that the kinetic expressions differ in a more complex way than simply the magnitude of the binding constant. This is most easily explained by assuming a change in rate-limiting step between the accessible regions of the two pathways, i.e., rate-limiting hydrolysis at low buffer and rate-limiting attack with rapid anhydride formation at high buffer. The physical meaning of two parallel binding constants for the formation of the carboxylate–micelle can be envisioned as rapid binding of carboxylate to the available regions on the SDS micelle (K_B) followed by less favorable binding of carboxylate that results in some deformation of the micelle ultrastructure (K_b).

It is interesting to compare the factor of about 100-fold acceleration that has been observed here with what might be expected if all of the translational entropy were lost due to micelle binding. Following Jencks' arguments,[3] at the cmc of SDS the volume of the micelles comprises about one-thousandth of the volume of the aqueous phase. If all of the reaction was confined to this volume, this would represent a change in entropy of $\Delta S = R \ln (V_1/V_2) = -14$ eu, which is equivalent to a free energy of −4.1 kcal/mol or an observed rate acceleration of about 10^3 at 25 °C.[3] Based on linear extrapolation of Figure 3, this rate acceleration should be achieved at a ΔpK_a of about 0.76 or at approximately octanoate. Unfortunately, the long extrapolations involved and the extremely low buffer concentrations that would be required make it impractical to pursue this entropy-related limit. It is interesting to note that the prediction of a 1000-fold acceleration is general for any bimolecular reaction which occurs *entirely* in the micellar phase. This means that anything less than this factor of 10^3 actually represents an *inhibition* of the bimolecular reaction by the surfactant micelles. Since in the majority of the literature micellar rate accelerations are below this 1000-fold limit, special care should be exercised in interpreting such results in terms of ground state or transition state perturbations.

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Registry No.—Diethyl sulfide, 352-93-2; iodine, 7553-56-2; SDS, 151-21-3.

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Partial Molal Volumes of Organic Compounds in Carbon Tetrachloride. 3. Aromatic Hydrocarbons: Steric Effects[1]

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The partial molal volumes of 31 aromatic and alkylaromatic hydrocarbons in carbon tetrachloride solution at 25 °C may be calculated with reasonable accuracy by addition of group increments (=C<, 3.03; =CH–, 13.22 mL mol^{-1}; established values for methyl, methylene, and methine) to a covolume of 11.61 mL mol^{-1}, and subtraction of fixed amounts for structural features known to involve intramolecular overcrowding.

More than 30 years ago Newman[2] resolved 4,5,8-trimethyl-1-phenanthrylacetic acid and attributed its dissymmetry to the steric interference of the 4- and 5-methyl groups (situation e of Scheme I), which caused one methyl to be displaced above and one below the molecular plane. Even the interference of a 4-methyl group with a 5-hydrogen in phenanthrene (situation d) could give rise to dissymmetry.[3] Later many other cases of intramolecular overcrowding in aromatic compounds (e.g., octamethylnaphthalene,[4] 3,4-benzophenanthrene[5]) which caused them to be distorted from a planar shape were revealed by X-ray crystallography.[6] It should be expected that such overcrowding would show up in reduced molecular volumes,[7] but so far there have been (to our knowledge) no studies to confirm this. In the present paper we investigate the effect of overcrowding on the partial molal volumes $\bar{V}^0$ in carbon tetrachloride at 25 °C of a variety of aromatic compounds and their alkyl derivatives, shown in Table I.

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