Journal of Pharmaceutical Sciences

DECEMBER 1976
VOLUME 65 NUMBER 12

RESEARCH ARTICLES

Effect of Micellization on Rate of Cupric-Ion-Promoted Hydrolysis of Dicarboxylic Acid Hemiesters

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Abstract □ The effect of micellar sodium lauryl sulfate on the rate of cupric-ion-promoted hydrolysis of some dicarboxylic acid hemiesters was investigated at pH 5, ionic strength 0.1 *M*, and 40, 45, and 50°. The rate of cupric-ion-promoted hydrolysis of sodium *n*-decyl oxalate in the micellar phase is about 50 times as fast as that in the bulk solution. The formation constant of the intermediate chelate complex, cupric decyl oxalate, was decreased in the micellar phase, while the rate of attack of hydroxide ion upon the chelate complex was increased. The overall rate increase is attributed to the increase in the entropy of activation for the reaction in the micellar phase. The rates of hydrolysis of sodium hydrocortisone 21-hemisuccinate and sodium hydrocortisone 21-hemi-(3,3-dimethylglutarate) were unaffected by copper ion.

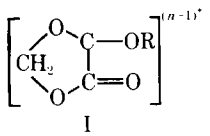
Keyphrases □ Micellization—sodium lauryl sulfate, effect on rate of cupric-ion-promoted hydrolysis of dicarboxylic acid hemiesters □ Sodium lauryl sulfate—micellization, effect on rate of cupric-ion-promoted hydrolysis of dicarboxylic acid hemiesters □ Cupric-ion-promoted hydrolysis—dicarboxylic acid hemiesters, effect of micellar sodium lauryl sulfate on rate □ Hydrolysis, cupric ion promoted—dicarboxylic acid hemiesters, effect of micellar sodium lauryl sulfate on rate □ Dicarboxylic acid hemiesters—cupric-ion-promoted hydrolysis, effect of micellar sodium lauryl sulfate on rate

Monoesters of some dicarboxylic acids are subject to metal-ion catalysis, as indicated by the unusually large kinetic salt effects exerted by Tl^{+}, Ba^{+2}, Ca^{+2}, and $Co(NH_3)_6^{+3}$ ions on the rate of hydrolysis of ethyl esters of oxalic, malonic, and adipic acids (1). The catalytic effect of a series of divalent metal ions on the hydrolysis of potassium ethyl oxalate has been interpreted in terms of a mechanism in which the ester, which is coordinated to the metal ion to form an intermediate chelate complex (I) in a prior rapid equilibrium, is attacked by OH^{-} in the rate-determining step (2).

The present study was undertaken to assess the possible influence of micellization on the metal-ion-promoted hydrolysis of a dicarboxylic acid hemiester. Succinate or glutarate hemiesters of 21-hydroxy steroids have been commonly employed as water-soluble derivatives of several important corticosteroid drugs. There is evidence that corticosteroid 21-phosphate esters are capable of association colloid formation (3), and it is conceivable that corticosteroid 21-hemiesters of dicarboxylic acids might also exhibit either self-aggregation or association with micellar surface-active agents. It was of interest to evaluate the potential of such association colloids for increasing product lability to metal-ion-promoted hydrolysis.

Furthermore, although metal ions are sometimes required as a cofactor for reactions occurring in the organized structure characteristic of an enzyme system, the mechanisms of such reactions are commonly studied in nonenzymatic model systems (4, 5). The present work involves a detailed study of a model system that incorporates the effects of both metal ion and micellization on the rate of ester hydrolysis.

For this study, it was necessary to use an ester that would: (*a*) be sufficiently soluble so that the reactions could be carried out in aqueous solution, (*b*) exhibit metal-ion-catalyzed hydrolysis, and (*c*) have sufficient hydrophobic properties to either undergo self-aggre-



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gation or be strongly bound to added surfactant micelles. Sodium *n*-decyl oxalate was selected as the model compound for extensive study. Since Cu^{+2} would form a sparingly soluble salt with the long chain oxalate, it was necessary to run the nonmicellar reactions in relatively dilute solutions.

EXPERIMENTAL

Materials—Sodium *n*-decyl oxalate, $C_{10}H_{21}OCOCOONa$, was prepared by means of half-saponification of bis(*n*-decyl) oxalate according to a modified procedure of Backer and Hóman (6) for the preparation of potassium *tert*-butyl oxalate, using dioxane as solvent and for recrystallization of the product, mp 202–205° dec. (uncor.). The IR and NMR spectra were consistent with the structure, and elemental analysis[1] gave the expected content of carbon (calc. 57.13; found 57.20) and hydrogen (calc. 8.39; found 8.42).

Bis(*n*-decyl) oxalate was prepared by esterification of oxalic acid with *n*-decyl alcohol, following the method of Bondar *et al.* (7).

Sodium lauryl sulfate was prepared from dodecyl alcohol and chlorosulfonic acid by the method of Dreger *et al.* (8). To remove trace quantities of dodecyl alcohol, the product was extracted with petroleum ether (bp 30–80°) in a soxhlet apparatus for 36 hr, recrystallized twice from absolute ethanol, and dried under vacuum. A plot of apparent surface tension–concentration did not show any minimum (9).

Sodium hydrocortisone 21-hemisuccinate[2] and sodium hydrocortisone 21-hemi-(3,3-dimethylglutarate)[3] were used as received.

Standard cupric nitrate solution[4] and analytical grade sodium nitrate were used in all experiments. The water was distilled water redistilled from glass.

Kinetics—Rates of hydrolysis were determined by a pH-stat technique[5]. The reaction flask was immersed in a constant-temperature water bath (±0.1°). Inserted into the reaction vessel was a glass electrode, a saturated calomel reference electrode, a stirrer, and a delivery tube for the sodium hydroxide titrant. The proportional band was set at 0.1.

The amount of sodium hydroxide solution delivered, which corresponded to the amount of ester hydrolyzed, was recorded as a percentage of the total capacity of the syringe buret. Pseudo-first-order rate constants, k_{obs}, were calculated from the slopes of the logarithm of the rate of sodium hydroxide consumed, $\Delta\%/\Delta t$, against time at the midpoint of the time interval. The plots were linear to about two half-lives. Reactions were run at constant pH 5.00, ionic strength 0.1 *M* with sodium nitrate, and 40, 45, and 50°.

For reactions in micellar systems, the concentrations of the components were 0.0200 *M* NaOH, 5×10^{-4} *M* sodium *n*-decyl oxalate, $4–30 \times 10^{-3}$ *M* sodium lauryl sulfate, and $2–5 \times 10^{-3}$ *M* $Cu(NO_3)_2$.

For reactions in nonmicellar systems, concentrations were 0.000475 *M* NaOH, $3–6 \times 10^{-5}$ *M* sodium *n*-decyl oxalate, and $0.4–1.25 \times 10^{-3}$ *M* $Cu(NO_3)_2$.

For hydrolysis of sodium hydrocortisone 21-hemisuccinate and sodium hydrocortisone 21-hemi-(3,3-dimethylglutarate), the procedure was the same as for sodium *n*-decyl oxalate hydrolysis.

Cu^{+2}-Ion Activity—The activity of Cu^{+2} ion in the bulk of the solution was measured using a specific cupric-ion electrode[6] in conjunction with a single-junction reference electrode[7]. The potentials were read on a digital, expanded scale, pH meter[8]. Calibration plots of the logarithm of activity *versus* potential were made at 40, 45, and 50° using cupric nitrate standard solution within the range of the activity of Cu^{+2} used in the reactions.

Critical Micelle Concentration (CMC)—The CMC of sodium *n*-decyl oxalate was determined at 40° and ionic strength 0.1 *M* using the surface tension method[9] and was 2.4×10^{-3} *M*.

[1] Performed by Micro-Analysis, Inc., Wilmington, Del.
[2] U-4905, batch MR 676, The Upjohn Co., Kalamazoo, Mich.
[3] U-5242, batch 3059-ESG-84, The Upjohn Co., Kalamazoo, Mich.
[4] Orion 0.1 *M* standard, Orion Research Inc., Cambridge, Mass.
[5] Radiometer A/S (Copenhagen, Denmark) comprised of TTT2 automatic titrator, TTA3 titration assembly, SBR2c titrigraph, and ABU 11 autoburet (2.5 ml).
[6] Orion 94-29, Orion Research Inc., Cambridge, Mass.
[7] Orion 90-01, Orion Research Inc., Cambridge, Mass.
[8] Model 110, Corning Scientific Instruments, Medfield, Mass.
[9] Fisher surface tensiometer, model 20, Fisher Scientific Co., Pittsburgh, Pa.

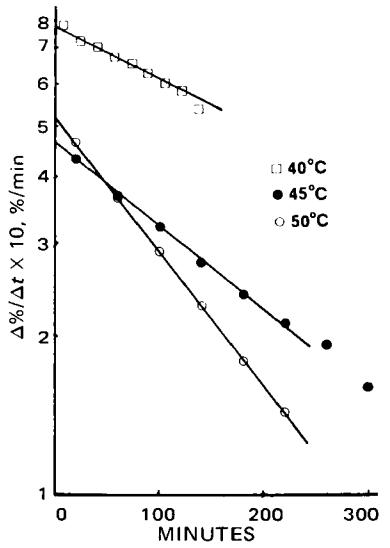

Figure 1—*Finite increments of sodium hydroxide solution and time as a function of time for representative studies of sodium* n*-decyl oxalate hydrolysis in the absence of sodium lauryl sulfate micelles at pH 5.00 and ionic strength 0.1* M.

RESULTS AND DISCUSSION

Kinetics in Absence of Sodium Lauryl Sulfate Micelles—The mechanism of sodium *n*-decyl oxalate hydrolysis should follow that proposed (2) for potassium ethyl oxalate shown in Scheme I.

$$DOx^- + Cu^{+2} \underset{}{\overset{K_f}{\rightleftharpoons}} CuDOx^+$$

$$CuDOx^+ + OH^- \xrightarrow[\text{slow}]{k_o} CuOx + DOH$$

Scheme I

The rate law can be written as:

$$\text{rate} = k_o[OH^-][CuDOx^+] \qquad \text{(Eq. 1)}$$

$$\text{rate} = \frac{k_o K_f a_{Cu^{+2}}[OH^-]}{1 + K_f a_{Cu^{+2}}}[DOx^-]_{total} \qquad \text{(Eq. 2)}$$

where $a_{Cu^{+2}}$ is the activity of Cu^{+2} ion in the bulk of the solution; K_f is the formation constant of the $CuDOx^+$ chelate complex; and subscript *o* denotes a nonmicellar system.

The pseudo-first-order rate constant, k_{obs}, is:

$$(k_{obs})_o = \frac{k_o K_f a_{Cu^{+2}}[OH^-]}{1 + K_f a_{Cu^{+2}}} \qquad \text{(Eq. 3)}$$

Figure 1 illustrates a typical plot of the logarithm of the rate of hydroxide consumption *versus* time, from which $(k_{obs})_o$ is calculated. Rearranging Eq. 3 gives:

$$\frac{[OH^-]}{(k_{obs})_o} = \frac{1}{k_o K_f a_{Cu^{+2}}} + \frac{1}{k_o} \qquad \text{(Eq. 4)}$$

Therefore, a plot of $[OH^-]/(k_{obs})_o$ *versus* $1/a_{Cu^{+2}}$ should give a straight line with the slope of $1/k_o K_f$ and the intercept of $1/k_o$. From the extrapolated intercept and slope, the values of k_o and K_f can be determined.

The value of $[OH^-]$ was calculated at pH 5.00 from the data given by Harned and Hamer (10). In solution of ionic strength 0.1 *M*, $[OH^-]$ is 3.06×10^{-9}, 4.23×10^{-9}, and 5.69×10^{-9} *M* at 40, 45, and 50°, respectively.

Figure 2 shows plots according to Eq. 4 at 40, 45, and 50°. Linear regression lines were drawn to obtain the best fit. The values of k_o and K_f are recorded in Table I.

Kinetics in Presence of Sodium Lauryl Sulfate Micelles—Both substrate and micelle have a similar long hydrocarbon hydrophobic group. The interaction would be very strong, and thus the solubilization would be such that the hydrocarbon hydrophobic group would be in the core of the micelle while the polar oxalate group would be exposed on the micelle surface to coordinate with Cu^{+2} and subsequently react with OH^-. The reactions involved in the micellar sodium

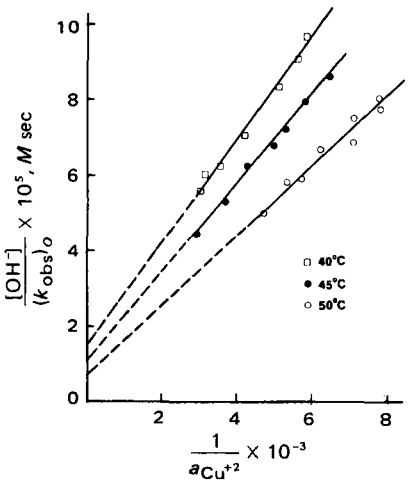

Figure 2—*Plots according to Eq. 4 for studies of sodium* n*-decyl oxalate hydrolysis in the absence of sodium lauryl sulfate micelles at pH 5.00 and ionic strength 0.1* M. *The lines were determined by linear regression analysis of the individual studies.*

lauryl sulfate system can then be written as shown in Scheme II, where M is the sodium lauryl sulfate micelles; K_b and K are the substrate–micelle and Cu^{+2}–micelle binding constants, respectively; K_f and K_f' are the formation constants of the chelate complex $CuDOx^+$ in nonmicellar and micellar phases, respectively; subscript o denotes the nonmicellar phase; and m denotes the micellar phase.

$$(DOx^-)_o + M \overset{K_b}{\rightleftharpoons} (DOx^-)_m$$

$$Cu^{+2} + M \overset{K}{\rightleftharpoons} (Cu^{+2})_m$$

$$(DOx^-)_o + Cu^{+2} \overset{K_f}{\rightleftharpoons} (CuDOx^+)_o$$

$$(CuDOx^+)_o + OH^- \overset{k_o}{\underset{\text{slow}}{\rightleftharpoons}} \text{products}$$

$$(DOx^-)_m + Cu^{+2} \overset{K_f'}{\rightleftharpoons} (CuDOx^+)_m$$

$$(CuDOx^+)_m + OH^- \overset{k_m}{\underset{\text{slow}}{\longrightarrow}} \text{products}$$

Scheme II

The rate law is given by:

$$\text{rate} = k_o[OH^-][CuDOx^+]_o + k_m[OH^-][CuDOx^+]_m \quad \text{(Eq. 5)}$$

$$\text{rate} = \frac{k_o K_f a_{Cu^{+2}}[OH^-]}{1 + K_f a_{Cu^{+2}}}[DOx^-]_o^{\text{total}} + \frac{k_m K_f' a_{Cu^{+2}}[OH^-]}{1 + K_f' a_{Cu^{+2}}}[DOx^-]_m^{\text{total}} \quad \text{(Eq. 6)}$$

$$\text{rate} = \left[\frac{k_o K_f a_{Cu^{+2}}[OH^-]}{(1 + K_f a_{Cu^{+2}})(1 + K_b[M])} + \frac{k_o K_f' a_{Cu^{+2}}[OH^-]K_b[M]}{(1 + K_f' a_{Cu^{+2}})(1 + K_b[M])}\right][DOx^-]_{\text{total}} \quad \text{(Eq. 7)}$$

The pseudo-first-order rate constant is given by:

$$k_{obs} = \frac{k_o K_f a_{Cu^{+2}}[OH^-]}{(1 + K_f a_{Cu^{+2}})(1 + K_b[M])} + \frac{k_m K_f' a_{Cu^{+2}}[OH^-]K_b[M]}{(1 + K_f' a_{Cu^{+2}})(1 + K_b[M])} \quad \text{(Eq. 8)}$$

Figure 3 illustrates a typical plot of the logarithm of the rate of hydroxide consumption *versus* time, from the slope of which the pseudo-first-order rate constant, k_{obs}, can be determined.

According to Eq. 8, at constant $a_{Cu^{+2}}$ in the bulk of the solution, k_{obs} will increase with increasing micelle concentration [M] until an asymptotic value is reached with [M] → ∞. This asymptotic value is given by:

$$k_{obs}^{max} = \frac{k_m K_f' a_{Cu^{+2}}[OH^-]}{1 + K_f' a_{Cu^{+2}}} = (k_{obs})_m \quad \text{(Eq. 9)}$$

which is the observed rate constant in the micellar phase. The asymptotic value is approached when $K_b[M] \gg 1$. Thus, at sufficiently

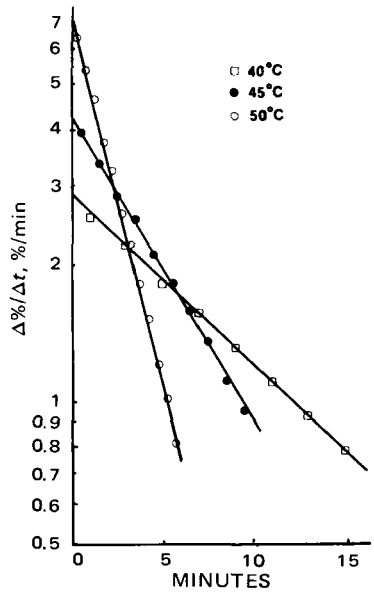

Figure 3—*Finite increments of sodium hydroxide solution and time as a function of time for representative studies of sodium* n*-decyl oxalate hydrolysis in the presence of sodium lauryl sulfate micelles at pH 5.00 and ionic strength 0.1* M.

high [M], there is no contribution of $(k_{obs})_o$, all of the n-decyl oxalate substrate being solubilized in the micelles.

Equation 9 predicts that, if $a_{Cu^{+2}}$ is held constant, further increases in [M] should give no observable change in the asymptotic value. In the experiments, a constant concentration of Cu^{+2} was added to the solution, so that $a_{Cu^{+2}}$ decreased with increasing [M] because more Cu^{+2} bound as counterions of the anionic micelles (11). However, a plot of $k_{obs}/a_{Cu^{+2}}$ reaches an asymptotic value and remains constant with a further increase of micelle concentration [M] or surfactant concentration. Such plots are shown in Fig. 4 at three different temperatures. At the asymptotic level:

$$\frac{(k_{obs})_m}{a_{Cu^{+2}}} = \frac{k_m K_f'[OH^-]}{1 + K_f' a_{Cu^{+2}}} \quad \text{(Eq. 10)}$$

This value is essentially constant since $a_{Cu^{+2}}$ is small and the denominator on the right-hand side is ≈1. An inhibitory salt effect with a higher concentration of surfactant was not observed in the present study because of the relatively high ionic strength maintained and the range of the surfactant concentration used.

It was observed from Fig. 4 that all of the substrate is in the micellar phase at surfactant concentrations above 20×10^{-3} *M*. Therefore, to simplify the system, all kinetic runs in the micellar system were carried out at a surfactant concentration of 24×10^{-3} *M*. Under this condition, rearrangement of Eq. 9 gives:

$$\frac{[OH^-]}{(k_{obs})_m} = \frac{1}{k_m K_f' a_{Cu^{+2}}} + \frac{1}{k_m} \quad \text{(Eq. 11)}$$

Equation 11 is analogous to Eq. 4 for nonmicellar systems.

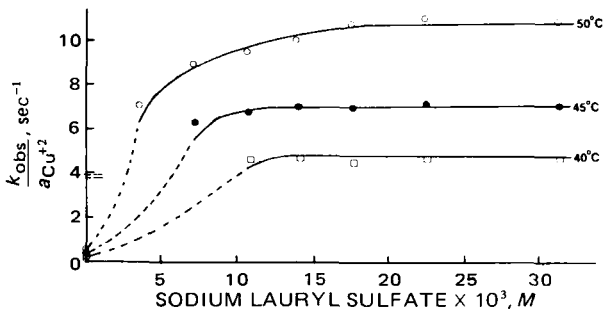

Figure 4—*Observed pseudo-first-order rate constant per unit activity of cupric ion as a function of sodium lauryl sulfate concentration for studies of sodium* n*-decyl oxalate hydrolysis in a micellar system at a constant cupric-ion concentration added of 22.1* × 10^{-4} M, *pH 5.00, and ionic strength 0.1* M.

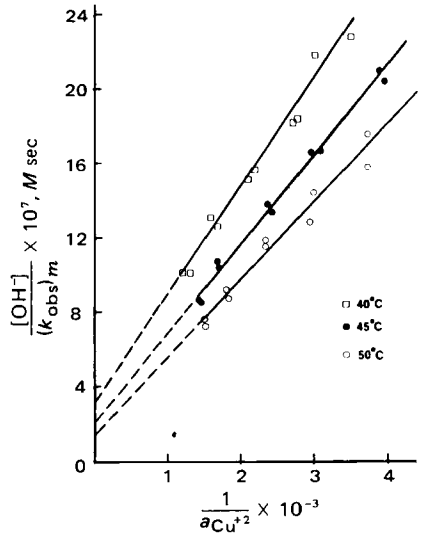

Figure 5—*Plots according to Eq. 11 for studies of sodium* n-*decyl oxalate hydrolysis in the presence of sodium lauryl sulfate micelles at pH 5.00 and ionic strength 0.1* M. *The lines were determined by linear regression analysis of the individual studies.*

Figure 5 shows plots according to Eq. 11 at 40, 45, and 50°. By using linear regression analysis, the extrapolated intercepts and slopes were determined, from which k_m and K_f' were calculated (Table I).

The extent of the rate enhancement can be taken as the ratio of k_m/k_o; at 40, 45, and 50°, this ratio was 47.8, 50.5, and 46.9, respectively.

Under the conditions of the present study, no observable reaction occurred in the absence of Cu^{+2}. Also, micellar sodium lauryl sulfate, which is known to undergo an enhanced rate of H^+-catalyzed hydrolysis compared to the monomer (12, 13), did not hydrolyze appreciably in this weakly acidic solution.

Estimate of Substrate–Sodium Lauryl Sulfate Binding Constant—The constant K_b for binding of the substrate sodium *n*-decyl oxalate to micelles of sodium lauryl sulfate can be estimated from Eq. 8, using data obtained at 50° and a surfactant concentration of 3.47×10^{-3} *M*, at which the substrate was not completely solubilized in the micelles (Fig. 4). The measured $a_{Cu^{+2}}$ was 7.75×10^{-4} *M*, and the k_{obs} was 56.6×10^{-4} sec^{-1}. If it is assumed that the CMC of sodium lauryl sulfate does not change appreciably with temperature in the range of 5–90° (14), the CMC might be taken as 1.46×10^{-3} *M* at 25° and ionic strength 0.1 *M* (15). Although this CMC value is for sodium lauryl sulfate in the absence of Cu^{+2}, it is quite reasonable because the CMC of pure cupric lauryl sulfate micelles is 1.2×10^{-3} *M* in a salt solution (16). If the aggregation number *N* is taken as 62 (17) in the presence of 25×10^{-4} *M* added Cu^{+2} and ionic strength 0.1 *M*, compared to 52 in the presence of 4.83×10^{-4} *M* Cu^{+2} (11), then the concentration of micelles [M] is:

$$[M] = \frac{[\text{sodium lauryl sulfate}] - CMC}{N} = 3.24 \times 10^{-5} M \qquad \text{(Eq. 12)}$$

Substituting all known parameters into Eq. 8 gives $K_b = 7.83 \times 10^4$ M^{-1} at 50°. This high value indicates a strong interaction between the substrate and micelle. It is comparable to that obtained for the binding constant of mono-*p*-nitrophenyl dodecanedioate to sodium laurate, which was 4.5×10^3 M^{-1} (18).

Table I—Second-Order Rate Constants for Hydroxyl Attack on the Chelate Complex (k_o and k_m) and Formation Constants (K_f and K_f') of the Complex in the Absence and Presence of Sodium Lauryl Sulfate Micelles at pH 5.00 and Ionic Strength 0.1 *M*

	Nonmicellar		Micellar	
Temperature	$10^{-5}\ k_o$, M^{-1} sec^{-1}	$10^{-3}\ K_f$, M^{-1}	$10^{-7}\ k_m$, M^{-1} sec^{-1}	$10^{-3} K_f'$, M^{-1}
40°	0.67 ± 0.09	1.09 ± 0.25	0.32 ± 0.06	0.54 ± 0.13
45°	0.93 ± 0.09	0.94 ± 0.13	0.47 ± 0.07	0.43 ± 0.07
50°	1.45 ± 0.39	0.74 ± 0.29	0.68 ± 0.22	0.32 ± 0.05

Table II—Activation Parameters Associated with the Second-Order Rate Constants, k_o and k_m, at pH 5.00 and Temperature 318°K

	E_a, kcal/mole	ΔH^*, kcal/mole	ΔS^*, eu
Micellar solution	15.1 ± 0.1[a]	13.5 ± 0.1[a]	14.3 ± 0.4[a]
Nonmicellar solution	15.5 ± 0.1	13.9 ± 0.1	7.8 ± 0.4

[a] Standard deviation.

Formation Constant for Chelate Complex—Surprisingly, the formation constant K_f of the chelate complex $CuDOx^+$ was not increased in the anionic micellar phase. This finding could be explained by considering the nature of counterion binding to the micelle. Generally, the binding is nonspecific and the counterions or oppositely charged reactants form a "mobile monolayer" in the Stern layer (19–22). The micelles concentrate the reactants on the surface and, in the case of an equilibrium, the apparent formation constant is increased (23).

In the particular case of interaction between the transition metal Cu^{+2} and the negatively charged micelles of sodium lauryl sulfate, it is possible that a coordinate covalent bond is formed, as is the case with polycarboxylic acid anion (20). It was suggested that micelles of divalent metal lauryl sulfate be treated as weak electrolytes (16). The Cu^{+2} bound covalently to sodium lauryl sulfate micelles would not be available to chelate with the substrate, or at least there would be a competitive binding between the micelle and solubilized substrate for the Cu^{+2}. Thus, sodium lauryl sulfate micelles do not appreciably serve to increase the concentration of reactants as generally is the case.

Steric factors could also have some influence. In the micellar phase, the formation of the copper chelate complex could be somewhat more difficult. After one coordination with the anion oxygen, the Cu^{+2} should coordinate with the carbonyl oxygen, which might be located farther inside the micelle. This second coordination might be hindered by the crowded neighboring lauryl sulfate ions. These could be the reasons that the formation constant K_f was not increased but rather decreased by twofold in the micellar phase. The rate enhancement must then be attributed to some other factors, which will be discussed further.

Effect of Temperature—Arrhenius-type plots (Fig. 6) for the hydrolysis of sodium *n*-decyl oxalate in nonmicellar and micellar systems are parallel, indicating similar temperature dependencies for the hydrolysis reactions in both systems. Experimental energy of activation was calculated from the slope of each plot. The enthalpy of activation was calculated from $\Delta H^* = E_a - RT$ for reactions in solution (24) and corrected for the enthalpy associated with the coordination of a carboxylate donor ligand to Cu^{+2}. The entropy of activation, ΔS^*, was calculated from the Eyring method (25):

$$k = \frac{RT}{Nh} e^{-\Delta H^*/RT} e^{\Delta S^*/R} \qquad \text{(Eq. 13)}$$

The values of E_a, ΔH^*, and ΔS^* are given in Table II.

It appears that the enhanced rate for the reaction in the micellar system is associated with an increase in ΔS^* rather than a decrease in ΔH^*. The larger entropy change can be attributed to the larger hydration and electrostatic entropy changes in the micellar phase. In terms of hydration of ions, the explanation of the entropy factor is that the two ions coming together to form a neutral molecule become partially dehydrated in the transition state so that some "frozen" water molecules are released, resulting in an increase of the entropy. The large charge density of the sodium lauryl sulfate micelle causes the formation of a more ordered structure, consisting of water molecules and counterions about its outer, polar surface. There is evidence from hydrodynamic data that, in dilute solution, sodium lauryl sulfate micelles are spherical and highly hydrated, with 10–12 water molecules bound by each surfactant molecule in the micelle (26). On the other hand, sodium lauryl sulfate is hydrated by only two or three water molecules when present in solution below the CMC (27). The sodium *n*-decyl oxylate in the present study contains about the same hydrocarbon chain length and would be expected to follow the same pattern of hydration. Thus, there would be a greater overall change

Table III—Studies of Cupric-Ion-Promoted Hydrolysis[a] of Sodium Hydrocortisone 21-Hemisuccinate and Sodium Hydrocortisone 21-Hemi-(3,3-dimethylglutarate) in the Absence and Presence of Sodium Lauryl Sulfate Micelles

Hydrocortisone 21-Hemi-(3,3-dimethylglutarate), m*M*	Hydrocortisone 21-Hemisuccinate, m*M*	$Cu(NO_3)_2$, m*M*	Sodium Lauryl Sulfate, m*M*	pH	Temperature
—	0.5	—	—	6.0	40°
—	0.5	0.5	—	6.0	40°
—	0.5	1.0	—	5.0	40°
—	0.05	0.5	—	5.0	50°
0.05	—	0.5	—	5.0	50°
0.5	—	2.0	24.3	5.0	50°

[a] No reactions occurred after 3–4 hr.

in randomness in the micellar phase, since the quantity of electrostatically bound water molecules released in the formation of the neutral transition state would be considerably greater than the amount released in the single ion state.

In terms of electrostatic interaction between the two reacting ions, the free energy change resulting solely from bringing two ions from infinite separation to the equilibrium distance in the activated complex is given by (28):

$$\Delta F^*_{el} = \frac{Z_A Z_B e^2}{Dr_*} \qquad \text{(Eq. 14)}$$

where Z_A and Z_B are the charges on the ions forming the activated complex; D is the dielectric constant of the medium; and r_* is the equilibrium separation of the charges in the transition state. The change in entropy can be written as:

$$\Delta S^*_{el} = \frac{Z_A Z_B e^2}{Dr_*}\left(\frac{\partial \ln D}{\partial T}\right)_p \qquad \text{(Eq. 15)}$$

The quantity $(\partial \ln D/\partial T)$ is always negative, because thermal motion overcomes the orientation of dipoles in an electric field (29). Therefore, for a reaction of two opposite charges, ΔS^*_{el} has a positive value and is inversely proportional to the dielectric constant of the medium. The surface of micelles appears to be less polar than water itself (30). For instance, Mukerjee and Ray (31) assigned an approximate value of 36 for the dielectric constant of the surface of micelles derived from *N*-dodecylpyridinium iodide. In the present system, the oxalate charged group might be regarded as being attached to a region of lower dielectric constant than water in the bulk of the solution; therefore, ΔS^*_{el} is larger and more positive than in nonmicellar solution.

It is apparent that the micellar rate enhancement was completely controlled by the entropy factor. The increase in entropy of activation was sufficient to overwhelm the unfavorable electrostatic repulsion of OH^- by the sodium lauryl sulfate micelles. The observed micellar rate enhancement for attack of hydroxide ion upon the positively charged intermediate chelate complex is in contrast to the inhibition by micellar sodium lauryl sulfate of attack of hydroxide ion upon a neutral solubilizate such as benzocaine (32) and upon lauryl sulfate anion (13).

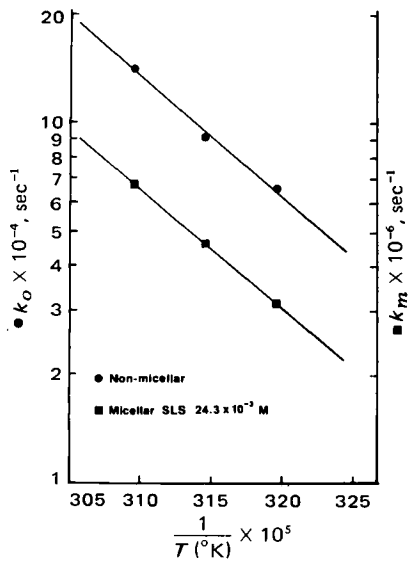

Figure 6—*Temperature dependence of the second-order rate constant for the cupric-ion-promoted hydrolysis of sodium* n*-decyl oxalate in the absence and presence of sodium lauryl sulfate (SLS) micelles at pH 5.00 and ionic strength 0.1* M.

The results in Table III clearly indicate that no copper-ion catalysis was observed in the hydrolysis of hydrocortisone hemisuccinate and hemi-(3,3-dimethylglutarate). The formation of a chelate complex is necessary for a metal ion to exert a catalytic effect on ester hydrolysis (4), and generally the extent of catalysis parallels the stability of the corresponding chelate complex. For example, Hoppe and Prue (1) reported that divalent cations such as barium and calcium show a lesser catalytic effect with malonate than with oxalate. The formation constants of barium and calcium oxalate are 213 and 1000 M^{-1} (33), compared to 51 and 313 M^{-1} for the respective malonate complexes (34). Going from oxalate to glutarate, the metal ion forms five- through eight-membered ring complexes with a decreasing order of stability. For the succinate complexes, the chelate effect may be almost entirely lost (35).

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 28, 1975, from the *Division of Pharmaceutics and Pharmaceutical Analysis, College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication February 13, 1976.

Abstracted in part from a thesis submitted by J. T. H. Ong to the Graduate School, University of Kentucky, in partial fulfillment of the Doctor of Philosophy degree requirements.

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Optimally Predictive *In Vitro* Drug Dissolution Testing for *In Vivo* Bioavailability

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Abstract □ A systematic method for optimally adjusting the conditions for *in vitro* drug dissolution testing is presented. Although the basic approach also can be applied to other types of dissolution apparatus, a scheme is described using a flow-through dissolution apparatus for the design and implementation of *in vitro* drug release tests. The tests have an optimized capability to simulate and, under predetermined conditions, predict *in vivo* drug bioavailability, blood levels, or pharmacological response *versus* time profiles of appropriate drug products. The apparatus is operated in two (simulative and predictive) stages. First, different dosage forms are used to calibrate the apparatus by operating it in a feedback-controlled mode to find a program for varying the composition, recycle flow, and flow rate of the dissolution medium that provides *in vitro* results that best simulate the different *in vivo* drug release properties of the dosage forms. The variables governing the operation of the apparatus are systematically modified until the differences between the *in vitro* and *in vivo* behavior of the dosage forms become: (*a*) minimized, (*b*) the same for every dosage form, and (*c*) independent of time. Second, predictive tests of the *in vivo* behavior of other drug formulations are performed. The apparatus is now operated without feedback control, using the program determined to be optimal in Stage 1. If necessary, an analog computer is used to vary continuously the composition and recycle flow of the dissolution medium. Mathematical expressions for the performance criteria on which the optimization of the apparatus is based are derived. The optimization procedures are described, and limitations of the method are discussed.

Keyphrases □ Dissolution, drug—flow-through-type apparatus described, used to predict *in vivo* bioavailability □ Drug release tests—flow-through-type dissolution apparatus described, used to predict *in vivo* bioavailability □ Bioavailability—predicted using flow-through-type dissolution apparatus

The advent of potent drugs emphasizes the need to develop pharmaceutical dosage forms that possess optimal effectiveness, safety, and reliability. Although approaches to rationally designing the dynamic bioavailability properties of dosage forms have been described (1–3), it is seldom practical to perform the exhaustive *in vivo* testing required to develop new oral drug products possessing the desired behavior. An inexpensive and rapid *in vitro* method of evaluation is needed.

It has become apparent in recent years that the formulation and manufacturing specifications of different manufacturers, while conforming to USP and NF requirements, can vary and alter the bioavailability characteristics of a drug. Such variations in bioavailability of drug products have often only been detectable by extensive human testing. Consequently, in some cases, products with inadequate *in vivo* drug bioavailability have been marketed and sold for long periods prior to the discovery of their inadequacy. Commonly prescribed drugs continue to be released from patent. Not only does this situation serve as a stimulus for increased generic usage, it also makes it necessary for medical researchers to have a ready means for evaluating the bioavailability of chemical equivalents of these drugs as they enter the market. The compendia should have precise laboratory tests for gauging their bioavailability, but only *in vivo* testing in humans is fully reliable at present.

In the extensive literature on *in vitro* drug release testing (3–17), it is often stated that the problem is quite complicated because a correlation of *in vivo* to *in vitro* release found with a particular test for a particular drug in a particular dosage form may not exist if another drug is substituted or the dosage form is altered. Few attempts have been reported to determine the full extent to which this is the case. The *in vitro* to *in vivo* drug availability correlations found have always been after the fact, as were the single-point correlations of 50% *in vitro–in vivo* release times (7) and the multiple-point correlations (8–11) that linearly related the cumulative amounts of drug released from the dosage form *in vitro* to similar amounts absorbed *in vivo*.

Previous reports from this laboratory (3, 4, 12) sug-