Hydrolysis of Procaine and Its Quaternary Derivatives within Lyotropic Smectic Mesophases

K. S. MURTHY* and E. G. RIPPIE

Abstract □ The effect of solvent anisotropicity on ester hydrolysis was studied in lyotropic liquid crystalline phases. Procaine hydrochloride and two of its quaternary derivatives, procaine methyl chloride and procaine ethyl chloride, were employed as substrates, and an aqueous gel consisting of 55% polyoxyethylene tridecyl ether, identified as a neat smectic system, was chosen as the solvent medium. Pseudo-first-order rate constants for the hydrolysis were obtained in the apparent pH range 8.80–11.40, at a temperature of from 30 to 50°, over a surfactant span of 50–65% in the mesophase. Rate measurements were also carried out in aqueous media and in mixed aqueous systems containing polyethylene glycol 300 and 400. The esters were located within the aqueous polyoxyethylene layers as indicated by their UV spectral characteristics. The reaction rates were found to be considerably slower (300- to 1100-fold) in the liquid crystalline phases than in aqueous media. The reactions, as they occur within the smectic phase, are characterized by relatively low apparent activation energies and by large negative entropies of activation.

Keyphrases □ Procaine, quaternary derivatives, hydrolysis—lyotropic smectic mesophases □ Activation energies, entropies—procaine, derivatives, in lyotropic mesophases □ Hydrolysis rate constants—procaine, derivatives, in lyotropic mesophases □ UV spectrophotometry—solubilizate location, homogeneous gels

Mesophases, also called mesomorphs or liquid crystals, are states of matter intermediate between crystalline solids and isotropic liquids (1). Molecules in this anisotropic state are orientated with their long axes parallel to one another. The molecules are typically elongated and are generally characterized by the presence of strong dipoles near the centers and weak dipoles near the ends. The parallel orientation of the molecules results both from intermolecular attractions and from the shapes of the molecules. Due to differences in the strengths of the molecular linkages in different directions, for these systems, the transition from the solid to the liquid state takes place in stages, with rising temperature. At lower temperatures the weaker bonds break first, resulting in the formation of meosphases. This is followed at higher temperatures by the loosening of the residual molecular associations when a true liquid state is attained (2).

There are three different types of liquid crystalline phases (3). These are: smectic in which the molecules are arranged in the form of layers with their long axes parallel to each other in the layers and nearly normal to the plane of the layers; nematic where the molecules maintain parallel arrangement along their long axes but are not stratified; and cholesteric where the molecular axes are parallel to the plane of the layers, but the direction of the long axes of the molecules changes continuously in going from one layer to another, resulting in a helical structure. Cholesteric mesomorphism is exhibited by compounds derived from cholesterol, although cholesterol itself is not mesomorphic.

Liquid crystalline structures may be prepared either by heating the crystalline solid (thermotropic mesomorphism) or by the addition of controlled amounts of polar solvents, generally water, to certain organic compounds (lyotropic mesomorphism). Many amphiphilic compounds, such as soaps and surfactants, having a tendency to form lyotropic mesophases on the addition of water, show the following general sequence of phases (4):

crystalline solid → neat phase → viscous isotropic phase → middle phase → micellar solution → molecular dispersion in water

The term "neat phase" corresponds to the smectic mesophase where the molecules are arranged in the form of lamellar micelles consisting of parallel equidistant sheets of amphiphilic molecules separated by layers of water. In such systems, contact between the polar–polar and nonpolar–nonpolar portions of the molecules is maximized, resulting in a stable configuration. The "middle phase" is composed of long cylindrical micelles arranged in a two-dimensional hexagonal array with the polar groups forming the surface of the cylinders (5).

Several books and reviews dealing with liquid crystals have appeared in recent years indicating the importance of these structures to scientists in different disciplines (6–8). It is generally agreed that lipids exist in biological membranes as mesophases. The structural model for the plasma membrane proposed by Davson and Danielli (9) and Robertson (10) rests on the foundations of a bimolecular lipid leaflet with protein absorbed on both faces. Artificially constituted bimolecular lipid membranes composed of neat smectic structures are currently employed as models for the study of properties of natural membranes (11). In spite of the recognition of the role of mesophases in biological systems, reports of systematic studies of reaction kinetics utilizing these structures as solvent media have been scarce. This is probably related to the fact that nonmesomorphic solutes in relatively low concentrations often tend to destroy or disrupt the parallel orientation of the molecules composing the mesophases.

The only reported kinetic studies employing thermotropic mesophases as solvents were conducted by Svedberg (12, 13) nearly 50 years ago. He studied the unimolecular thermal decomposition of picric acid, pyrogallol, and trinitroresorcinol, at a temperature of 140°, using *p*-azoxyphenetole as the solvent system. Swarbrick and Carless (14) studied the rate of oxidation of benzaldehyde in lyotropic mesophases encountered in ternary systems consisting of betaine–benzaldehyde–water. The reaction rates were found to be significantly lower in the mesophases when compared with the corresponding rates in isotropic systems. Barry and Shotton (15) studied the acid-catalyzed hydrolysis of sodium dodecyl sulfate in the presence of 1-hexadecanol in a solvent medium containing perchloric acid at 60°. They

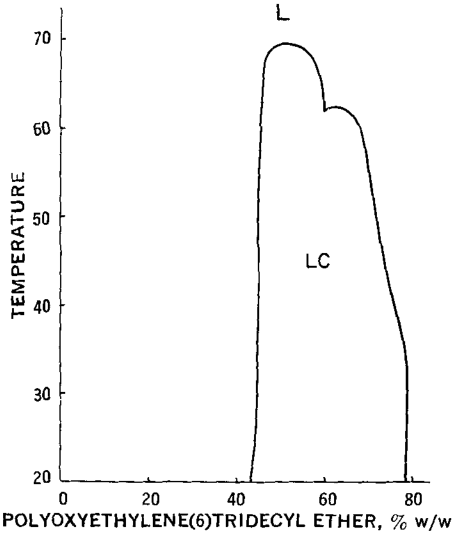


Figure 1—*Equilibrium phase diagram for the system polyoxyethylene (6) tridecyl ether + water showing regions of isotropic liquid (L) and liquid crystalline (LC) phases.*

found an increase in the rate of hydrolysis of the substrate in the liquid crystalline phase and attributed this to a decrease in the dielectric constant at the surface of the lamellar micelles constituting the phase.

Because of the ordered arrangement of molecules within mesophases, reaction rates in these systems would be expected to exhibit significant solvent effects in many instances. The aim of this study was to investigate the effect of the anisotropicity of the solvent on the kinetics of ester hydrolysis, utilizing lyotropic liquid crystalline phases as the solvent media. Procaine hydrochloride (PHC) was chosen as the ester substrate, and an aqueous gel consisting of 55% polyoxyethylene (6) tridecyl ether was selected as the solvent phase. In order to determine the importance of steric and inductive effects in mesophases, hydrolysis rates of two quaternary derivatives of procaine—procaine methyl chloride (PMC) and procaine ethyl chloride (PEC)—were also studied. For purposes of comparison, hydrolysis rates were also determined in aqueous and polyethylene glycol 300–water solutions.

EXPERIMENTAL

Materials—Polyoxyethylene (6) tridecyl ether.[1] As obtained commercially, this surfactant contained impurities exhibiting absorbance in the UV region. Attempts to eliminate these UV-absorbing materials by treatment with ion-exchange resins and washing with strong alkalies and acids proved to be unsuccessful. Polyethylene glycol 300[2] (PEG 300) and polyethylene glycol 400[2] (PEG 400) USP, procaine hydrochloride[3] USP. The two quaternary derivatives of procaine, PMC (m.p. 171–173°) and PEC (m.p. 202°), were synthesized according to the procedure of Einhorn and Uhlfelder (16). The compounds were recrystallized from a mixture of ethyl alcohol and ethyl acetate and dried under vacuum at 80° for 12 hr.

Anal.—Calcd. for $C_{14}H_{23}ClN_2O_2$: C, 58.63; H, 8.08; Cl, 12.36, N, 9.77. Found: C, 58.75; H, 8.35; Cl, 11.80; N, 9.38.

Anal.—Calcd. for $C_{15}H_{25}ClN_2O_2$: C, 59.89; H, 8.38; Cl, 11.79. Found: C, 60.01; H, 8.75; Cl, 11.50.

Table I—Ultraviolet Absorption Maxima of the Substrates in Various Solvent Media

Substrate	Solvent Medium	$\lambda_{max.}$
PHC	Distilled water[a]	286.0
	PEG 300–water (42%)[a]	295.0
	Mesophase (55% surfactant)[a]	295.0
	n-Hexane	270.5
PMC	Distilled water	290.5
	PEG 300–water (42%)	298.0
	Mesophase (55% surfactant)	298.0
PEC	Distilled water	290.5
	PEG 300–water (42%)	298.5
	Mesophase (55% surfactant)	298.0

[a] Conditions: solvents buffered to pH 11.40.

The buffers employed were as follows: for studies at pH 8.80 and 9.70, borate; for pH 10.60 and 11.40, carbonate. *n*-Hexane[4] spectroquality reagent. All other chemicals were reagent grade.

Equipment—Polarizing microscope[5] equipped with Koeffler hot stage, centrifuge,[6] spectrophotometer,[7] pH meter.[8] For kinetic measurements in aqueous buffer solutions at pH 11.40 where the reactions are relatively rapid (half-lives of less than 20 min.), the reactions were conducted directly in silica cells housed within the thermostated compartment of the recording spectrophotometer.[9]

Procedure—*Phase Diagram*—Mixtures containing different concentrations of surfactant were prepared by accurately weighing the surfactant and distilled water in small weighing bottles, melting in a water bath to obtain a homogeneous mass, stirring, and cooling to room temperature. The samples were allowed to equilibrate at room temperature for 48 hr. before being examined for liquid crystalline characteristics.

The identification of the sample as isotropic or liquid crystalline was made by visual and microscopic observations. In this system the mesophase was found to be a viscous, transluscent gel. The isotropic liquid was found to be fluid and transparent. Microscopic examination was conducted on a small quantity of the sample placed on a clean glass slide with a coverslip placed lightly on top. The existence of birefringence was verified by observation under crossed polars employing a magnification of 100×. The temperature of phase transition was determined by heating the sample on the hot stage. The rate of heating was at first rapid; but as temperatures came close to the transition temperatures, the rate was maintained at 1° for every 5 min. The temperature at which there was complete disappearance of birefringence, when viewed in the microscope under polarized light, was taken as the temperature of transition. At each surfactant concentration, three such determinations were made and the average value was used. The phase diagram was also determined with the same concentrations of buffer salts as were later used in the kinetic experiments. No significant differences in visual appearance or microscopic features of the mixtures were observed due to the presence of the buffer salts. In all cases there was a slight lowering of transition temperatures of the order of 2° or less.

Assay—The concentrations of the substrates, PHC, PMC, and PEC, in the various solvent systems were followed by measuring the absorbance at 306 mμ. Para-aminobenzoic acid, the degradation product of the substrates, does not absorb appreciably at this wavelength and the observed absorbance change was, therefore, taken as exclusively due to the presence of the substrates. Due to the insolubility of the surfactant in dilute aqueous solutions, the absorbance measurements were made for systems containing the surfactant in 20% ethanol–water solutions. All the kinetic studies were performed at an ionic strength of 0.1 adjusted with potassium chloride.

Systems containing polyoxyethylene chains are generally found to be susceptible to auto-oxidative degradation (17, 18). Such a breakdown of the polyoxyethylene in the systems under study would result

---

[1] Marketed as Renex 36, lot no. 8404 B, Atlas Chemical Industries Wilmington, Del.

[2] Ruger Chemical Co., Irvington, N. Y.

[3] Matheson, Coleman & Bell, East Rutherford, N. J.

[4] Mallinckrodt Chemical Works, St. Louis, Mo.

[5] Bausch & Lomb, C. Reichert Optische Werke A. G.

[6] Servall Superspeed Centrifuge, type ss, Ivan Servall, Inc., Norwalk, Conn.

[7] Beckman model DU, Beckman Instruments, Inc., Fullerton, Calif.

[8] Beckman model GS, Beckman Instuments, Inc., Fullerton, Calif.

[9] Cary model 14, Applied Physics Corp., Monrovia, Calif.

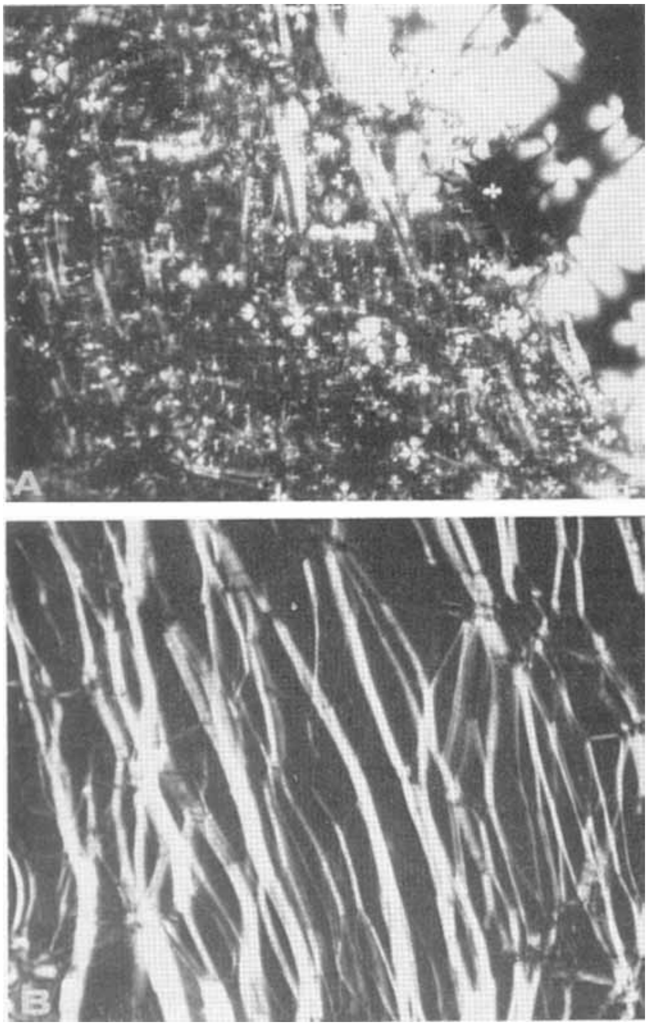


Figure 2—*Typical photomicrographs of the mesophase containing 55% surfactant, polyoxyethylene (6) tridecyl ether, at room temperature under crossed polars and magnification 100×;* (A) *typical anisotropic spherulites;* (B) *network of anisotropic threads and oily streaks.*

in a significant drop in pH. After some preliminary experimentation, a combination of sodium sulfite and hypophosphorous acid in concentrations of 0.1% each was found to be effective in stabilizing against oxidation. In the course of preliminary experiments, it was also found that reaction rates were extremely low below an apparent pH of 8.00. Studies were, therefore, conducted at higher pH's.

In a typical experiment the following procedure was employed. The theoretically calculated quantities of the buffer salts and the substrates were dissolved in distilled water. A measured volume of this buffer solution was pipeted into a conical flask containing a previously weighed quantity of the surfactant such that the resultant gel contained the required concentration of the surfactant and was of the desired apparent pH. The ionic strength of the gel was maintained at 0.1 by the addition of potassium chloride to the aqueous solution whenever necessary. In order to obtain a homogeneous gel, the mixture of the surfactant and the aqueous salt solution was melted in a water bath and cooled. The necessary adjustments in the apparent pH of the mesophase were made by the addition of concentrated solutions of sodium hydroxide or hydrochloric acid to the aqueous buffer solution. The gel was then subdivided accurately into 5-g. portions in flasks of 10-ml. capacity. A similar set of flasks containing reference gel was also prepared at the same time in a manner identical to that of the sample gel but without substrate. To suppress any possible oxidation of the surfactants, the gels were degassed with a stream of nitrogen and the flasks were tightly stoppered, sealed, and protected from light. At appropriate intervals, duplicate samples were withdrawn, diluted with 40% ethanol-water solution, and analyzed spectrophotometrically with an appropriately treated blank in the reference compartment of the spectrophotometer.

Table II—Effect of the Solvent Medium on the Apparent First-Order Rate Constants for the Hydrolysis of the Substrates

Substrate	Mesophase Apparent First-Order Rate Constant,[a] $k \times 10^3$ hr.$^{-1}$	Buffered Aqueous Solution Apparent First-Order Rate Constant,[b] k, hr.$^{-1}$
PHC	5.53[c]	1.69[f]
PMC	3.70[d]	4.09[g]
PEC	7.39[e]	4.34[h]

[a] Conditions: pH 11.40, temperature 50°, surfactant concentration 55%. [b] Conditions: pH 11.40, temperature 50°. [c] SD = ± 3.0%. [d] SD = ± 1.9%. [e] SD = ± 3.9%. [f] SD = ±1.8%. [g] SD = ±2.3%. [h] SD = ±2.1%.

Table III—pH Dependency of the Apparent First-Order Rate Constants for the Hydrolysis of PHC in the Mesophase[a]

Apparent pH of the Mesophase	Apparent First-Order Rate Constant, $k \times 10^3$ hr.$^{-1}$
8.80	1.19[b]
9.70	1.29[c]
10.60	3.35[d]
11.40	5.52[e]

[a] Conditions: temperature 50°, surfactant concentration in the mesophase 55%. [b] SD = ± 4.1%. [c] SD = ±4.5%. [d] SD = ±2.5%. [e] SD = ±3.0%.

The apparent pH of the mesophase was determined at a room temperature of about 25° at the start of each kinetic experiment. At subsequent intervals, the pH of the solutions used for the assay were measured to monitor the pH of the gel.

UV Absorption Spectra—The UV absorption spectra of solubilizates have been utilized for determining their location within the different regions of the micelle (19, 20). To prepare the mesophase for UV examination, the homogeneous gel was introduced into the cells with the aid of a syringe. The cells were held in a water bath at 75° until the air bubbles entrapped in the gel were driven off. Because of this procedure, the theoretically added amounts of the substrates could not be retained in the samples. Comparisons

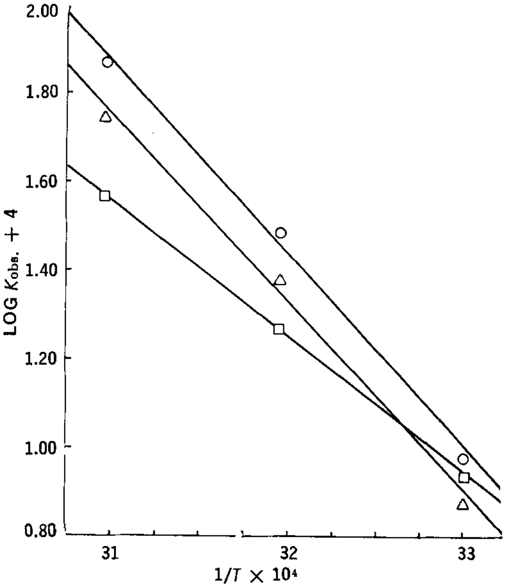


Figure 3—*Arrhenius plots of the hydrolysis reaction in the mesophase containing 55% surfactant at pH 11.40. Key:* △, *PHC;* □, *PMC; and* ○, *PEC.*

Table IV—Activation Parameters for the Hydrolysis Reactions in the Mesophase and in the Aqueous Solution

Substrate	Energy of Activation, kcal./mole	Entropy, e.u.	Frequency Factor, sec.$^{-1}$
PHC[a]	7.60	−26.9	3.3×10^6
PMC[a]	2.21	−43.8	1.9×10^3
PEC[a]	8.08	−24.8	2.5×10^6
PHC[b]	13.80	−23.8	4.0×10^7

[a] Conditions: solvent, mesophase, pH 11.40, surfactant concentration 55%. [b] Conditions: solvent, aqueous solution, parameters obtained from *Reference 25.*

Table V—Apparent First-Order Rate Constants for the Hydrolysis Reaction of the Substrates in PEG 300–Water (42%) Medium[a]

Substrate	Apparent First-Order Rate Constant, $k \times 10^2$ hr.$^{-1}$
PHC	3.06[b]
PMC	2.09[c]
PEC	1.99[d]

[a] Conditions: pH 11.40, temperature 50°. [b] *SD* = ±3.8%. [c] *SD* = ±3.1%. [d] *SD* = ±1.8%.

were, therefore, made on the basis of wavelength of maximum absorption.

RESULTS AND DISCUSSION

The regions of temperature and composition for the occurrence of mesophase and isotropic liquid in the surfactant-water mixtures are presented in Fig. 1. The general features of the diagram are similar to that reported in the literature for systems of this type (21). At room temperature, liquid crystalline phases were found to occur in the surfactant concentration range 44–76% w/w. It has not been possible to determine the region where both the phases, isotropic liquid and mesophase, coexist. Typical photomicrographs of the mesophase observed under crossed polars are presented in Fig. 2. The anisotropic spherulites, both positive (extinction arms narrowest at the center of the cross) and negative (extinction arms broadest at the center of the cross), encountered in this system represent one form of focal conic texture characteristic of smectic structures. Current theories do not consider the middle phase to be smectic (22) since it does not assume any focal conic arrangement. Mixtures containing 50, 55, and 65% surfactant did not show any phase separation when equilibrated at 50° or when centrifuged at room temperature for 7 hr. at 7000 r.p.m. The temperature of transition from the mesophase to the isotropic liquid at 50, 55, and 65% surfactant concentrations are 69, 69, and 64°, respectively. For nonionic surfactant systems, the two-phase region consisting of isotropic liquid and liquid crystalline phases is narrow, and it is reasonable to assume that at 50°, the highest temperature at which the rate studies were carried out, the system is composed of neat smetic phase only.

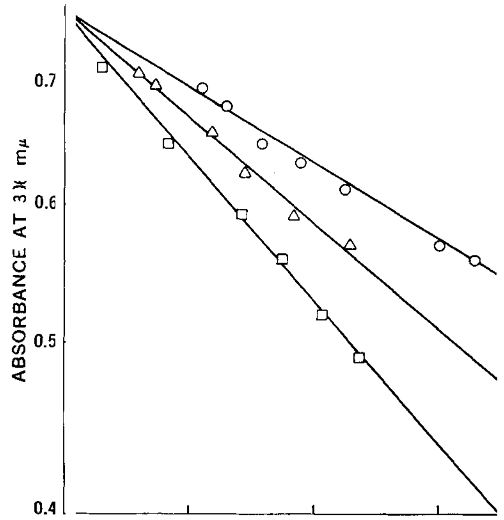


Figure 4—*Plot showing the effect of surfactant concentration in the mesophase on the rate of hydrolysis of PHC at 50° and at pH 9.70. Key:* ○, *65%;* △, *55%; and* □, *50%.*

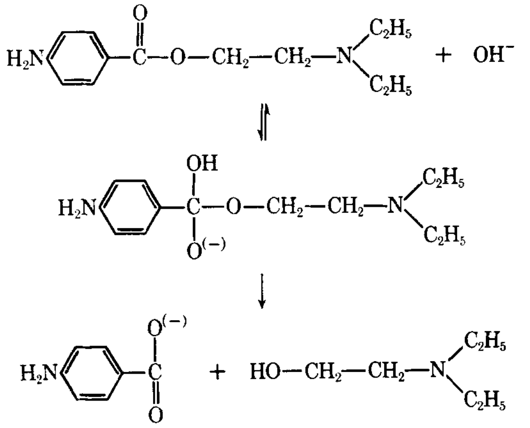
Table VI—Effect of PEG 400 on the Apparent First-Order Rate Constants for the Hydrolysis of PHC[a]

Surfactant Concn., % w/w	Apparent First-Order Rate Constant, $k \times 10^3$ hr.$^{-1}$
50	2.04[b]
55	1.29[c]
65	0.97[d]

[a] Conditions: apparent pH of the mesophase 9.70, temperature 50°. [b] *SD* = ±4.9%. [c] *SD* = ±4.5%. [d] *SD* = ±5.1%.

From the data presented in Table I, it is apparent that the wavelength of maximum absorption for all three substrates in the mesophase are very close to those in the PEG 300–water mixtures but significantly different from those in *n*-hexane and in distilled water. This indicates that the esters are located within the polyoxyethylene layers of the lamellar micelle.

Kinetic Studies—Pseudo-first-order rate constants for the hydrolysis of the substrates were obtained from least-squares calculations of the slopes of the plots of log absorbance *versus* time. The apparent first-order rate constants for the hydrolysis of the substrates in the mesophase containing 55% surfactant and the corresponding rate constants in simple aqueous buffered solutions at pH 11.40 are presented in Table II. The pH dependence of the pseudo-first-order rate constants in the mesophase is shown in Table III. A typical Arrhenius plot for the hydrolysis reaction in the mesophase is shown in Fig. 3. The value of the heat of ionization of water taken from the literature (23) (12.27 kcal./mole) was subtracted from the observed values to obtain the apparent energies of activation as given in Table IV. The entropy of activation and the frequency factors were calculated from the well-known Eyring equation on absolute reaction rates (24). All data are consistent with the mechanism of hydrolysis (see Scheme I) proposed by Higuchi *et al.* (25) for procaine in strongly alkaline solutions (Fig. 4).



Scheme I

Since the UV absorption data of the esters in the various solvent phases indicated that these substrates were located within the aqueous polyoxyethylene layers of the micelle, the reaction rates were also determined in a medium simulating the environment of the substrates in the mesophase. If the substrates are protected from hydrolytic reaction by the polyoxyethylene chains, then a medium which corresponds in molecular composition to the polyoxyethylene

Table VII—Effect of PEG 400 on the Apparent First-Order Rate Constants for the Hydrolysis of PHC[a]

PEG 400 Concn., % w/v	Apparent First-Order Rate Constant, $k \times 10^2$ hr.$^{-1}$
35	4.46[b]
40	2.87[c]
45	2.32[d]

[a] Conditions: pH 11.40, temperature 50°. [b] $SD = \pm 2.2\%$. [c] $SD = \pm 1.8\%$. [d] $SD = 1.7\%$.

portion of the surfactant in the mesophase should result in a significant lowering of the observed rates. The results of the rate constants determined in such a medium are given in Table V.

Also, under these conditions, increase in the concentration of ethylene oxide in the solvent system should lower the observed rates. Such an increase in the ethylene oxide concentration can be brought about either by an increase in the PEG concentration or by an increase in the surfactant concentration. Rate constants obtained in both cases are presented in Tables VI and VII. An examination of this data shows that, although polyoxyethylene exerts a shielding action, reducing the rates of decomposition, the observed rates in PEG 300–water systems are higher than in the mesophase. While no definite arguments can be offered to explain the observed differences in the two media, it is probable that these results may reflect differences in the precise orientation of the esters in the two media and their accessibility to hydrolytic attack. This is especially important in view of the results indicating that the reactions are strongly inhibited with an increase in surfactant concentration in the medium.

The degree of protection conferred by polyoxyethylene chains appears to be dependent more on the concentration than on the chain length. The small differences observed in the rates of hydrolysis between the two quaternary compounds, PMC and PEC, both in aqueous and in PEG 300–water mixtures, are within the range of experimental error, and no significance can be attached to them.

SUMMARY

Equilibrium conditions of temperature and composition at which lyotropic mesophases occur were established for the system polyoxyethylene (6) tridecyl ether–water. Employing substrate concentrations of the order of 1×10^{-4} *M*, hydrolytic decomposition rates of procaine and two of its quaternary derivatives, PMC and PEC, were determined spectrophotometrically in a medium consisting of 55% surfactant and identified to be of neat smectic type. Apparent energies and entropies of activation were calculated for the reactions in the mesophase from rate measurements in the temperature range 30–50°. The reactions, as they occur in the mesophase, appear to be characterized by low Arrhenius energies of activation and large negative entropies. On the basis of UV spectral characteristics, it was inferred that the substrates are located in the polyoxyethylene region of the lamellar micelles. Kinetic measurements in a 42% PEG 300–water system, which corresponds in composition to the polyoxyethylene portion of the micelle, indicate that the reaction rates are significantly retarded by the polyoxyethylene chains. The degree of retardation appears to be dependent upon the concentration of PEG in the system. The available data do not appear to indicate any change in the reaction mechanism for the hydrolysis of procaine in the mesophase from that in simple aqueous solutions.

REFERENCES

(1) O. Lehmann, *Z. Phys. Chem.* (Leipzig), **4**, 462(1889).

(2) G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049(1957).

(3) G. Friedel, *Ann. Phys.* (*Paris*), **18**, 273(1922).

(4) R. R. Balambra, J. S. Clunie, and J. F. Goodman, *Proc. Roy. Soc. London*, **A285**, 535(1965).

(5) P. A. Winsor, *Chem. Rev.*, **68**, 1(1968).

(6) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic, New York, N. Y., 1962.

(7) "Ordered Fluids and Liquid Crystals," Advan. Chem. Ser. 63, Amer. Chem. Soc., Washington, D. C., 1967.

(8) A. Saupe, *Angew. Chem. Int. Ed. Engl.*, **7**, 97(1968).

(9) J. F. Danielli and H. Davson, *J. Cell. Comp. Physiol.*, **5**, 495(1935).

(10) J. D. Robertson, in "Cellular Membranes in Development," M. Locke, Ed., Academic, New York, N. Y., 1964, p. 1.

(11) H. T. Tien and A. L. Diana, *Chem. Phys. Lipids*, **2**, 55 (1968).

(12) T. Svedberg, *Kolloid Z.*, **18**, 54, 101(1916).

(13) *Ibid.*, **21**, 19(1917).

(14) J. Swarbrick and J. E. Carless, *J. Pharm. Pharmacol.*, **16**, 596(1964).

(15) B. W. Barry and E. Shotton, *ibid.*, **19**, 785(1968).

(16) A. Einhorn and E. Uhlfelder, *Ann. Chem.*, **372**, 138(1910).

(17) F. E. Bailey, Jr., and J. V. Koleske, in "Nonionic Surfactants," vol. 1, M. J. Schick, Ed., Marcel Dekker, New York, N. Y., 1967, p. 807.

(18) C. W. McGary, *J. Polym. Sci.*, **46**, 51(1960).

(19) S. Riegelman, N. A. Allawala, M. K. Hrenoff, and L. A. Strait, *J. Colloid. Sci.*, **13**, 208(1958).

(20) M. Donbrow and C. T. Rhodes, *J. Pharm. Pharmacol.*, **18**, 424(1966).

(21) B. A. Mulley and A. D. Metcalf, *J. Colloid. Sci.*, **19**, 501 (1964).

(22) F. B. Rosevear, *J. Soc. Cosmet. Chem.*, **19**, 581(1968).

(23) H. S. Harned and B. B. Owens, "The Physical Chemistry of Electrolytic Solutions," 3rd ed., Reinhold, New York, N. Y., 1967, p. 754.

(24) S. Glasstone, "Text Book of Physical Chemistry," 2nd ed., D. Van Nostrand, Princeton, N. J., 1946, p. 1103.

(25) T. Higuchi, A. Havinga, and L. W. Busse, *J. Amer. Pharm. Ass., Sci. Ed.*, **39**, 405(1950).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 29, 1969, from the *Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455*

Accepted for publication November 21, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 1969.

Abstracted in part from a thesis submitted by K. S. Murthy to the University of Minnesota in partial fulfillment of Doctor of Philosophy degree requirements.

* Present address: Product Development Department, Parke Davis & Co., Detroit, MI 48232