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Hydrolysis Reactions in Lamellar Liquid Crystalline Media and Octanol/Water Partition Coefficients

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Cationic lamellar liquid crystalline morphologies decrease rates of hydrolysis of a series of 4-substituted benzylidene *t*-butylamine *N*-oxides as the electron releasing effect increases and they are linear when plotted against σ^+ -substituent constants. Rho-values indicate a more sensitive reactivity series in lamellar than in aqueous solvent. Reaction rates in the former solvent parallel the partition coefficients in octanol/water except for the methoxy-derivative.

INTRODUCTION

Biological membranes contain lipoproteins, acyl esters of cholesterol and water arranged in alternate layers of lipoprotein molecules and water. This bilayer arrangement results from the greater affinity of hydrophilic head groups of the lipoproteins for water compared with the cholesterol derivatives. The lipoprotein, dimyristoyl lecithin for example, forms both the open and closed bilayers in aqueous disper-

sion¹ and Fendler² reported the latter type, called vesicles as membrane mimetic agents.

Several investigators have suggested bilayer arrangements of lamellar liquid crystalline media as potential biomembrane models¹⁻⁷ but experimental data correlating rates of hydrolysis with the partition coefficients between the aqueous and lipophilic regions of the lamellar system has not been reported.

Aqueous dispersions of dodecylammonium chloride (DdAC) as well as mixed DdAC and didodecyldimethylammonium chloride (DdDMAC) also form lamellar bilayers of both types.⁸ The theory of self-assembly of lipid bilayers and vesicles that explains the formation of bilayers and vesicles and accounts quantitatively for many of their physical properties cannot be used because the concentration of surfactants approaches 1 M in this work. At high lipoprotein concentrations, above 10^{-3} M vesicles interact significantly.⁹ Investigation of the hydrolysis of a series of substituted benzylidene *t*-butylamine *N*-oxides in these media presents a convenient method of evaluating the influence of lamellar liquid crystalline structures upon chemical reactions.¹⁰ These bilayer structures require a concentration of cationic surfactants about one hundred times the cmc accounting for new structural growth and numerous anomalies. The presence of large alkylammonium ions tend to strengthen the hydrogen bonds between water molecules and the cationic micelles. In addition they cause a significant increase in the solubility of nonelectrolytes.¹¹

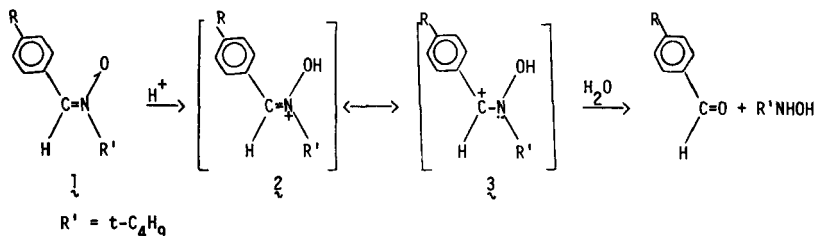
The hydrolysis reactions in the lamellar bilayer prepared from surfactants with primary polar head groups, i.e. DdAC, were less inhibited than in the mixed lamellar system, i.e. DdAC/DdDMAC, even though the concentration of the mixed surfactants was about one half. We suggested this rate difference was due to the greater partitioning of the substrate into the hydrocarbon region of the lamellar mixed surfactant solvent.⁸ The rate of hydrolysis is a combination of the rate in the aqueous and in the hydrocarbon regions.

This is the initial report of an investigation of a series of reactions in lamellar solvents to determine the electronic effects of substituent groups compared with the aqueous solvent containing the cmc of the mixed surfactants. Rate constants for all hydrolysis reactions in the two different solvents will be correlated with partition coefficients for each member of the series.

RESULTS AND DISCUSSION

Rate constants for the hydrolysis of a series of substituted amine oxides in lamellar solvent decreases as the electron release effect

increases as shown in Table I, with an overall rate change of about ten times. These results suggest a mechanism outlined in the following equation:^{10,12,13}



The addition of water to the protonated intermediate **2** or **3** appears to be the rate determining step.

The introduction of substituent groups in **1** causes a change in electron density at the reaction site and this perturbation can be expressed as a linear property. Figure 1 illustrates such a linear free energy relationship for reactions in the lamellar solvent. Least square analysis gives $\rho = 1.27$ compared with 0.85 for aqueous media¹⁰ indicating a more sensitive reactivity series in the lamellar solvent. The linear relationship suggests a possible mechanism for the operation of the electrical effects is through the π -electrons in the unsaturated system of the benzene rings.

The rate of hydrolysis for this series is inhibited by cationic surfactants; however, the sequence of inhibition is the same whether the solvent is the aqueous lamellar bilayer or the cationic surfactant at the cmc even though the concentration differs by a factor of one hundred. The mechanism of inhibition is twofold: (a) electrostatic influences of the cationic bilayers upon intermediates **2** or **3** and (b) substrate partitioning.¹⁴

The determination of partition coefficients of reactive solute molecules in lamellar liquid crystalline solvents has not been accomplished. However, the use of partition coefficients of solute molecules between two-phase water/organic solvents has had considerable success.¹⁵ In many two-phase systems such as the octanol/water system, the biological response or activity of different solutes may be related to their

TABLE I
Rate of hydrolysis of **1** in lamellar liquid crystalline solvent

4-Substituent	H	F	CH ₃	C ₂ H ₅	CH ₃ O
Rate ^a ·10 ⁵ sec ⁻¹	19.91	13.80	7.94	5.00	1.77

^aPseudo first-order at pH 1.00 and 25°.

partition coefficients, P by the relationship:¹⁶

$$\log x = \alpha \log P_{oct} + \beta \quad (1)$$

where α and β are constants. As a consequence the partition coefficient of solutes in different two-phase media (1) and (2) are often related to one another by the relationship

$$\log P_1 = a \log P_2 + b. \quad (2)$$

The empirical coefficients a and b have been used to extract information on the relative hydrophobicity or lipophilicity of various two-phase

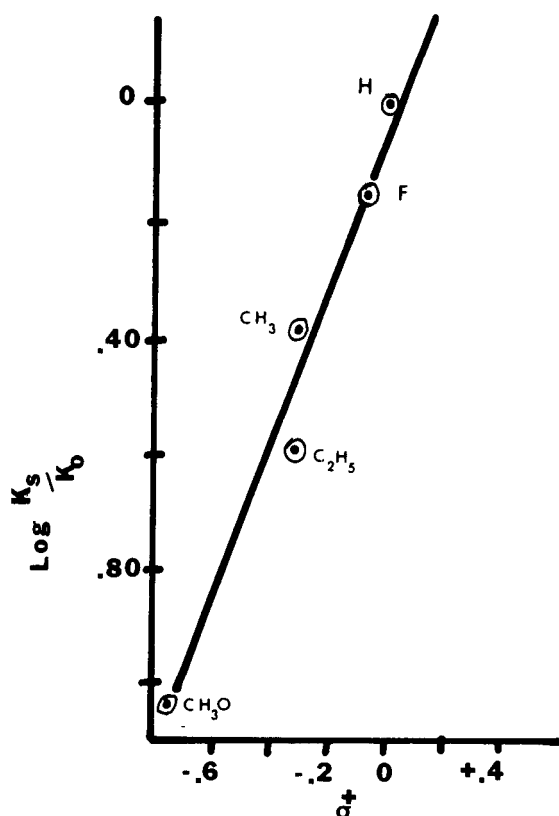


FIGURE 1 Relative rates of hydrolysis of substituted 1 in lamellar solvent at 25° and pH 1.00 vs substituent parameters.

media such as bulk solvents or even proteins as solubilization sites for solutes.¹⁶ According to Eq. (2) the partition coefficients of solutes with equivalent hydrogen bond properties in two different two-phase media are often correlated to a second system. This is interpreted as evidence for a similar partitioning process in water/organic solvent system indicating the hydrophobic phenomena as the driving force for the transfer of the solute from water to a non-aqueous phase.

We have investigated micellar effects of the lamellar solvent on the hydrolysis of a series of 4-substituted amine oxides in order to learn the effects of substituent hydrophobicity on the rate of reaction.¹⁰ The hydrophobicity or lipophilicity effects of the substituents can be empirically evaluated by the substituent parameter, π . These values¹⁶ are determined from the logs of the partition coefficients of the series of compounds partitioned in the octanol/water system. Recently we determined the partition coefficients for the 4-substituted amine oxide series in octanol/water for the calculation of functional group values.¹⁷ Table II shows the partition coefficients for this series.

The correlation between the rate constants and the partition coefficients for the series in lamellar bilayer solvent is good for the first four members as shown in Figure 2. The equation of the line is:

$$\log k = -0.618 \log P_{oct} - 2.975 \quad (r^2 = .981).$$

Although the partitioning of substrate molecules between aqueous and micellar environment parallel the partition coefficients in octanol/water system for the first four members of the series it is unequivocally out of correlation for the methoxy-derivative. Aqueous cationic surfactant at cmc as the solvent also shows the same deviation.

We can only speculate about the reasons for the deviation of the methoxy compound until we develop a method to determine the partition coefficients for this series in lamellar systems. Currently our interest is the determination of the substrate-micelle association con-

TABLE II
Octanol/water partition coefficients of 1

R Equals	H	F	CH ₃	C ₂ H ₅	CH ₃ O
log P^a	1.22	1.42	1.74	2.19	1.21

^aAccuracy within $\pm .04$ at 25°.

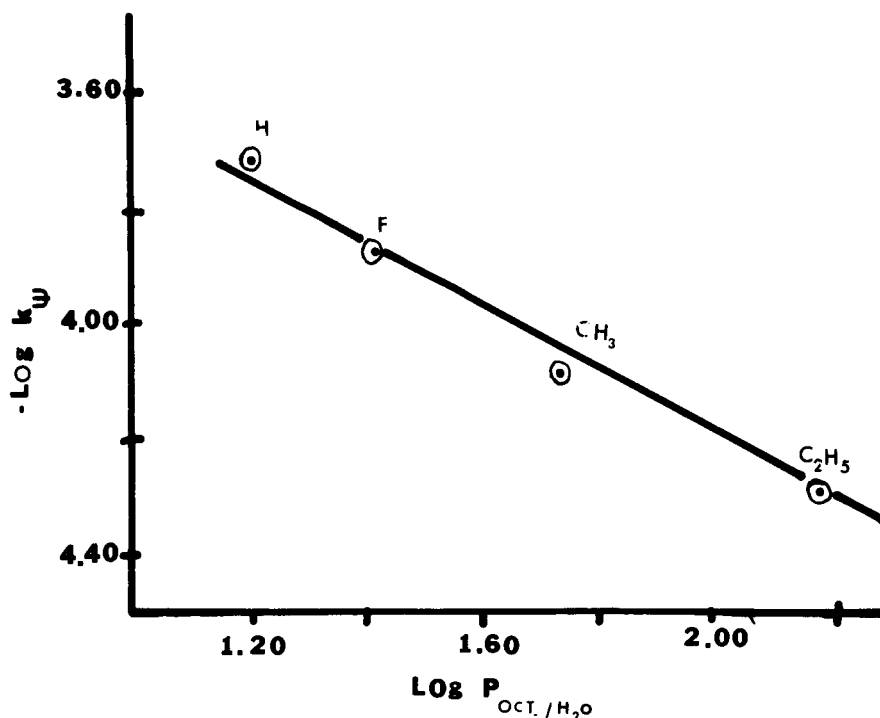


FIGURE 2 Hydrolysis rate constants of substituted **1** in lamellar solvent at 25° and pH 1.00 vs octanol/water partition coefficients.

stants for the series in cationic surfactants to correlate with partition coefficients.

A comparison of the partition coefficients of the series of amine oxides in the lamellar bilayer solvent with those in the octanol/water system would be instructive; however, such reactive solute molecules are not conveniently measured. Similar comparison of seventeen unreactive polar solute molecules in cationic micelles at the cmc with the octanol/water system show a good linear correlation with the exception of three; namely, chloroform, diethyl ether and tetrahydrofuran.¹⁸

The rate of hydrolysis of **1** ($\text{R}=\text{H}$) decreases as the concentration of DdAC in water increases until the lamellar liquid crystalline system is formed. Based on the aggregate-substrate association constant plot the substrate partitioned into the hydrocarbon region has a rate of hydrolysis within experimental error of zero.¹⁴ Therefore as the partition coefficient of the substituted amine oxide in the lamellar solvent increases then the rate of hydrolysis decreases as shown in Figure 2.

EXPERIMENTAL

Didodecyltrimethylammonium chloride (DdDMAC) was prepared from the corresponding bromide⁸ and the purification of dodecylammonium chloride (DdAC) was described previously.¹⁹ The lamellar phase of the mixed surfactants was prepared in small batches and used immediately. DdDMAC, 5.00 g, 0.012 M and deionized water 20.00 g, 1.111 M were mixed, heated 78–85° with stirring to give a smooth paste and cooled to 55–60°. DdAC, 2.5 g, 0.011 M, was added and the mixture reheated to 85–90° with stirring until it was optically clear; 5–10 min. The solution was adjusted to pH 1.00 with conc. HCl using a Fisher Acumet pH Meter with an expanded scale, equipped with a Corning combination electrode. The addition of HCl caused a precipitate to form which was dissolved by heating. These solutions remained optically clear over periods of months. The microscopic classification of these solutions as lamellar was reported.⁸

4-Substituted benzylidene t-butylamine *N*-oxides were prepared as reported.¹⁰ Each member of the series and the 1-octanol/water solvent was automatically shaken for twenty-four hours at 25°, over a six-fold range of concentration. The layers were analyzed spectrophotometrically at the following wavelengths: R=H, 290, F 285; CH₃, 294; C₂H₅, 300; CH₃O 310 nm for the Beer's Law plot. The values taken at the extrapolated zero concentration were taken to calculate partition coefficients.

Rates of hydrolysis were determined spectrophotometrically at 25° ± .05°, with substrate concentrations 1.3×10^{-4} M. The lamellar phase is pseudoisotropic and the solutions are clear before and after reaction. The pseudo first-order plots were linear to greater than 90% reaction, and reproducibility with 5%.

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