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Kinetic Studies on the Acid and Alkaline Hydrolysis of *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide in Dioctadecyldimethylammonium Chloride Vesicles

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The acid and alkaline hydrolyses of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in the presence of cationic vesicles of the surfactant dioctadecyldimethylammonium chloride (DODAC) were studied. The ion-exchange pseudophase model adapted to vesicle systems was used to fit the experimental results. An association constant for MNTS with the vesicles of $380 \pm 30 \text{ M}^{-1}$ was determined by kinetic and spectrophotometric methods. The rate constant for the alkaline hydrolysis of MNTS in the vesicular pseudophase was also determined, and its value ($0.0084 \text{ M}^{-1} \text{ s}^{-1}$) was found to be about one-tenth that in water and slightly smaller than that in CTABr or TTABr micelles. This intrinsically decreased reactivity is related to the different polarities in these three media.

Introduction

In addition to micelles and microemulsions, vesicles and closed bilayers are the most simple systems for modeling biological membranes.¹ Research on them has grown dramatically since the late 1970s, when the methods formerly used to obtain phospholipid dispersions were adapted for preparing vesicles of synthetic surfactants² with a double hydrophobic chain and a hydrophilic polar headgroup.

The physical properties of vesicles depend on headgroup packing, which changes as a function of aggregate diameter (D_h).³ For a given surfactant and medium composition, the stability, osmotic behavior, and flocculation rate of vesicles depend on their size, which is determined by the preparation method used.⁴ The most widely used choices in this respect are sonication and ethanol injection methods, which yield small vesicles ($D_h = 30\text{--}50 \text{ nm}$),^{2b,2c,5a} and the chloroform injection method, which produces large vesicles ($D_h \approx 300 \text{ nm}$).^{2d,2e,5a} Also, extrusion methods^{5b} are widely used for the production of large unilamellar vesicles. Salt concentration and pH significantly control the degree of vesicle packing and, hence, vesicle size.⁶

Kinetically, vesicles make a highly appealing reaction medium. Because of their structure, they can inhibit chemical reactions by encapsulating a reactant within;⁷

conversely, they can catalyze reactions by having the reactants concentrated at the water–bilayer interface, thus acting as microreactors.^{2,7,8} The catalytic capacity of vesicles surpasses that of micelles^{9,10} and depends on aggregate size (i.e., vesicles obtained by sonication have greater catalytic efficiency than those prepared by chloroform injection).¹¹ The influence of the size of vesicles on their catalytic power arises essentially from the fact that the degree of dissociation of the vesicle counterion (α)^{5a} and the capacity of vesicles to dissolve reagents^{11,12} are both influenced by the size of the aggregates. It is possible to study reactivity in the inner and/or outer side of the vesicle bilayer by selecting carefully the surfactant and the reagents.^{7,13,14} This usually results in two-phase kinetics, where the rate-determining step is permeation of one reagent across the bilayer.

In this work, we present a study on the acid and alkaline hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in the presence of cationic vesicles of dioctadecyldimethylammonium chloride (DODAC) prepared by sonication. The mechanisms for both acid¹⁵ and alkaline hydrolysis¹⁶ of MNTS in water are well known. In acidic media, the slow step is the proton transfer from the medium to the substrate, while in alkaline media it is the nucleophilic attack of OH^- on the sulfur atom (see Scheme 1).

In previous work,¹⁷ we investigated the potential catalytic or inhibitory effect of micelles on both kinds of hydrolysis reactions. The kinetic data were quantitatively

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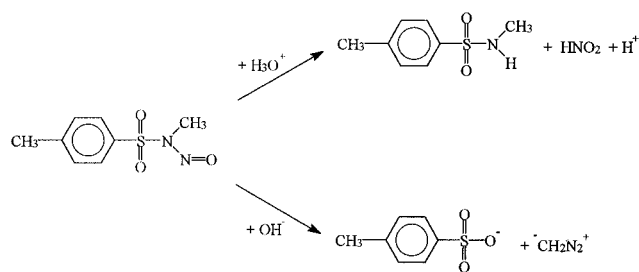
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Scheme 1



explained by using the ion-exchange pseudophase model.^{9,18} Also, a quantitative interpretation for reactivity in microemulsions based on a modified pseudophase model was successfully applied to alkaline hydrolysis reactions and transnitrosations.¹⁹ In this article, we extended our work on hydrolysis reactions to a different microheterogeneous medium, viz., aqueous dispersions of vesicular surfactant.

Experimental Section

All reagents used, of the highest available grade, were obtained from Merck or Sigma and used without further purification. Hydrochloric acid concentrations were determined by titration with NaOH solutions that were previously standardized with potassium hydrogen phthalate. All aqueous solutions were prepared in bidistilled water. The low solubility of MNTS in water made it necessary to prepare its solutions in acetonitrile. The percentage of acetonitrile in the reaction mixture was always 1% by volume. DODAC vesicles were prepared from the commercially available dioctadecyldimethylammonium bromide (DODAB) product, using Fendler's procedure.²⁰ Typically, vesicle preparation consisted of the sonic dispersion of 70–90 mg of solid DODAC in 12–15 mL of water using a Branson 250 sonicator at an average temperature of 53–60 °C for 25 min, followed by centrifugation and passage through a 0.45 μm pore size filter to remove tip residues. Although the vesicles were assumed to be stable, we always used dispersions within 8 h after preparation.

Kinetic profiles were studied by monitoring the decrease in absorbance ($\lambda = 250$ nm) due to MNTS disappearance with a Spectronic 3000 spectrophotometer at 25 °C. The initial concentration of MNTS (approximately 4×10^{-5} M) was always much smaller than those of the other reagents used. The reagents addition sequence was always the same, viz., presonicated DODAC, followed by the alkaline or acid solution, depending on the type of hydrolysis to be studied, and, finally, MNTS. Since the acid hydrolyses were slow, their reaction rates were determined by the initial rate method using the absorbance–time data for less than 10% of the reaction (no deviation from linearity was appreciable in these absorbance–time traces). For faster reactions, the integration method was used, and absorbance–time data were fitted with the first-order integrated equation,

$$\ln(A_t - A_\infty) = \ln(A_0 - A_\infty) - k_0 t \quad (1)$$

by means of a one-dimensional optimization routine.²¹ All values of the pseudo-first-order rate constant (k_0) were reproducible to within $\pm 5\%$.

Results and Discussion

Characterization of Vesicles. The size and shape of vesicles depend on the sonication time and the temperature at which it is carried out. Turbidity measurements have shown^{2c} that, below the transition temperature (36–

38 °C),^{2c,4} it is not vesicles but one-dimensional bilayers that are formed. Sonication above that temperature leads to larger, multicompartiment vesicles that gradually become single-compartment vesicles as the sonication time is extended. Our vesicles were obtained by sonicating DODAC dispersions at 53–60 °C for 25 min. Their size was determined from dynamic light-scattering measurements at a constant temperature of 25 °C. Samples were irradiated with an Ar⁺ laser at $\lambda = 514.5$ nm, data were recorded at three different angles (45°, 90°, and 120°), and measurements were analyzed by an ALV-5000 digital correlator. Correlation functions were fitted by using the contin cumulant methods.²² A hydrodynamic diameter $D_h = 40$ nm and a polydispersity of 0.10 were obtained. These values confirm that the vesicles were single-compartment and that their size was consistent with previously reported values.^{2c,5a,8}

It is well known that the presence of salts can affect the sonicated vesicles.²³ They may undergo adhesion and/or fusion. In the present work, we study the acidic and basic hydrolyses of MNTS, so in our reaction mixtures NaOH or HCl was added. To check whether the presence of these electrolytes affects the stability of vesicles under our experimental conditions, the variation of D_h with time in the presence of HCl and NaOH has been studied in the absence of MNTS (Table 1). We can see in Table 1 that D_h remains constant during the reaction time. Besides, all kinetic profiles were monitored at $\lambda = 400$ nm in order to follow the possibility of adhesion and/or fusion of the vesicles.⁴ In all cases, the absorbance at 400 nm remained constant during the reaction time.

Determination of the Association Constant for MNTS. The association constant for MNTS with DODAC cationic vesicles was determined spectrophotometrically by using reported procedures.²⁴ Mixtures containing variable concentrations (0 – 8.0×10^{-3} M) of DODAC and a constant amount of MNTS were thermostated at 25 °C and their spectra were recorded against a suitable reference. The association constant was obtained from the following equation,

$$A = \frac{A_w + A_{\text{ves}} K_{\text{MNTS}} [\text{DODAC}]}{1 + K_{\text{MNTS}} [\text{DODAC}]} \quad (2)$$

which can be linearized to

$$\frac{A - A_w}{A_{\text{ves}} - A} = K_{\text{MNTS}} [\text{DODAC}] \quad (3)$$

where K_{MNTS} is the association constant for MNTS with the vesicles. Absorbance values were measured at 250 nm, A_w ($A_w = 1.262$, $[\text{MNTS}] = 1.3 \times 10^{-4}$ M) being the absorbance for MNTS in pure water, A that in the presence of DODAC vesicles, and A_{ves} the limiting absorbance (viz., that measured when all MNTS had been incorporated into the vesicular pseudophase; in our case, $A_{\text{ves}} = 0.952 \pm 0.011$ was obtained by fitting eq 2 to the experimental data). As can be seen in Figure 1, eqs 2 and 3 fit the results quite well, and a K_{MNTS} value of $390 \pm 15 \text{ M}^{-1}$ was obtained.

Throughout this work, we assumed that all the DODAC in the medium was incorporated in vesicles. Although there is a surfactant concentration threshold (somewhere

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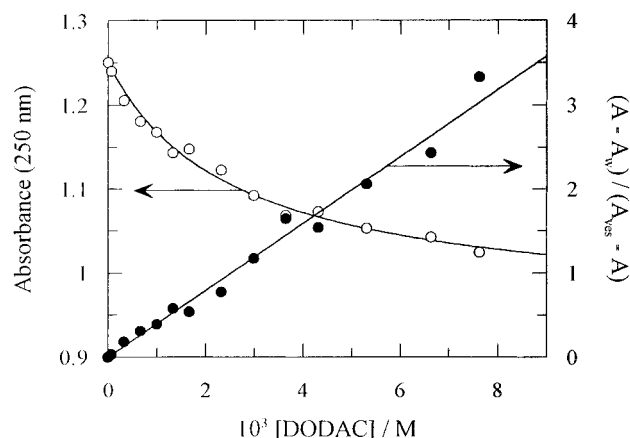
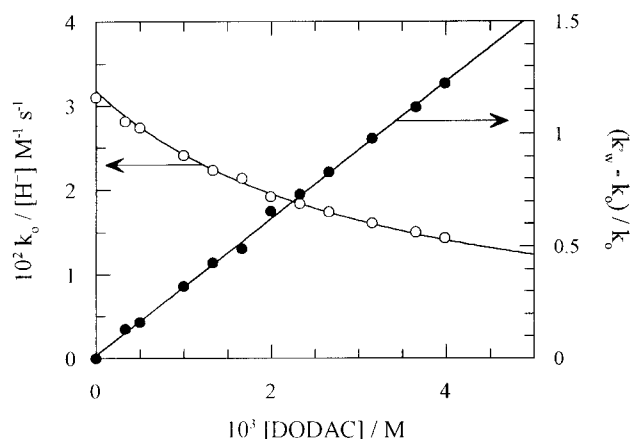
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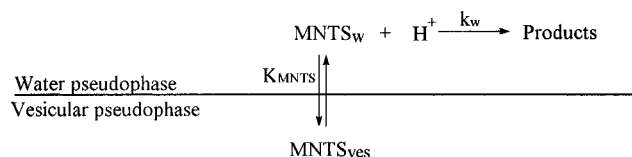
Table 1. Variation of D_h with Time in Different Reaction Mixtures

[DODAC] = 1.82×10^{-3} M [OH ⁻] = 3.90×10^{-3} M $t_{1/2}$ = 3 min		[DODAC] = 1.10×10^{-3} M [OH ⁻] = 1.10×10^{-3} M $t_{1/2}$ = 10 min		[DODAC] = 1.10×10^{-3} M [H ⁺] = 1.50×10^{-3} M $t_{1/2}$ = 310 min	
t/min	D_h/nm	t/min	D_h/nm	t/min	D_h/nm
0	40.0	0	40.0	0	40.2
7.03	39.8	8.25	38.3	45.8	42.0
8.74	39.4	14.72	39.9	78.2	38.9
10.38	42.0	18.11	41.2	132.21	41.5
13.75	41.1	26.48	39.4	214.81	39.5
17.08	40.4	32.15	41.1	291.28	41.0
18.82	40.8	48.65	40.8	327.14	42.1

**Figure 1.** Fitting of the absorbance values to eqs 2 and 3.**Figure 2.** Influence of the DODAC concentration on the acid hydrolysis of MNTS at [H⁺] = 2.5×10^{-3} M. Solid lines are the result of fitting eqs 6 and 7 to the experimental data.

in the range of 4×10^{-6} – 8×10^{-6} M)^{10,25} below which vesicles do not form, this threshold is not the result of a dynamic equilibrium between free and vesicular surfactant, like the critical micelle concentration of micellar media. Once formed, vesicles are not destroyed by dilution. In fact, they have been detected at surfactant concentrations²⁶ as low as 10^{-8} M, which is far below the concentrations used in this work.

Acid Hydrolysis of MNTS. The effect of vesicles on the acid denitrosation of MNTS was examined at three constant concentrations of protons (3.66×10^{-3} , 2.46×10^{-3} , and 1.52×10^{-3} M) and DODAC concentrations ranging from 0 to 4.0×10^{-3} M. As can be seen from Figure 2, the observed rate constant decreased upon increasing the DODAC concentration. This behavior can

Scheme 2

be explained on the basis of the pseudophase model,^{9,18} assuming a two-pseudophase model in which the reaction is treated as occurring in both a vesicular pseudophase (representing the DODAC bilayer) and an aqueous pseudophase (representing both the bulk medium and the intravesicular compartment) and assuming an equilibrium distribution of MNTS between both pseudophases. The overall reaction rate will be the sum of the rates in both pseudophases. This model leads to the following equation,

$$k_0 = \frac{k_w + K_{\text{ves}} K_{\text{MNTS}} [\text{DODAC}]}{1 + K_{\text{MNTS}} [\text{DODAC}]} \quad (4)$$

where K_{ves} and k_w are the first-order rate constants for the vesicular and aqueous pseudophases, respectively, and K_{MNTS} is the association constant or constant of substrate distribution between the two pseudophases:

$$K_{\text{MNTS}} = \frac{[\text{MNTS}]_{\text{ves}}}{[\text{MNTS}]_w [\text{DODAC}]} \quad (5)$$

Based on electrostatic considerations,²⁷ the proton concentration at the DODAC bilayer must be very low, due to the cationic character of the vesicles. This virtually complete exclusion of H⁺ means that the reaction is taking place only in the aqueous pseudophase, as shown in Scheme 2. This model predicts the simpler expression,

$$k_0 = \frac{k_w}{1 + K_{\text{MNTS}} [\text{DODAC}]} \quad (6)$$

which can be rearranged into

$$\frac{(k_w - k_0)}{k_0} = K_{\text{MNTS}} [\text{DODAC}] \quad (7)$$

The solid line in Figure 2 represents the best fit of eqs 6 and 7 to the experimental data. On the assumption that DODAC vesicles are H⁺ permeable,^{2c,8} the K_{MNTS} values given in Table 2 were obtained. The mean value for the association constant of MNTS to the vesicles was $ca. 370 \pm 30 \text{ M}^{-1}$, which is in good agreement with the spectrophotometric value. A comparison with the values obtained in micellar media¹⁷ confirms that the MNTS association constant increases upon increasing the number of carbon atoms in the surfactant chain and suggests that

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Table 2. K_{MNTS} Values Obtained at Different H^+ Concentrations, Using Various Methods

method	$10^3 [\text{H}^+]/\text{M}$	$k_w^a/\text{M}^{-1} \text{s}^{-1}$	$K_{\text{MNTS}}/\text{M}^{-1}$
spectrophotometric			390
kinetic	1.50	0.031	350
kinetic	2.50	0.031	370
kinetic	3.70	0.031	395

^a Experimental value for the pseudo-first-order rate constant for MNTS hydrolysis in water.

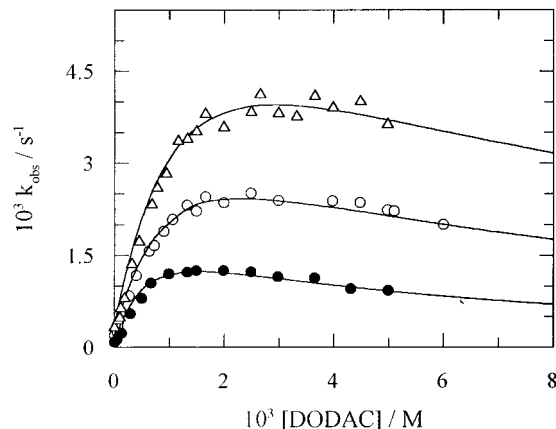
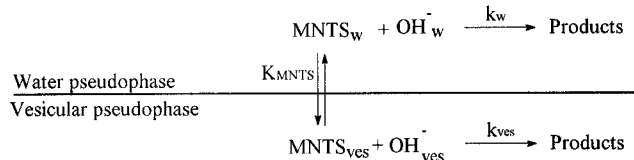


Figure 3. Influence of the DODAC concentration on the alkaline hydrolysis of MNTS at $[\text{MNTS}] = 2.0 \times 10^{-5} \text{ M}$ and $[\text{NaOH}] = (\bullet) 1.0 \times 10^{-3}$, $(\circ) 2.5 \times 10^{-3}$, and $(\Delta) 3.9 \times 10^{-3} \text{ M}$. The solid lines are the result of fitting eq 10 to the experimental data.

Scheme 3



the substrate association with the vesicles is primarily controlled by hydrophobic forces^{17,28} (see Table 4).

Alkaline Hydrolysis of MNTS. The effect of DODAC vesicles on the alkaline hydrolysis of MNTS was studied at three constant NaOH concentrations (1.0×10^{-3} , 2.5×10^{-3} , and $3.9 \times 10^{-3} \text{ M}$) and DODAC concentrations ranging from 0 to $6.0 \times 10^{-3} \text{ M}$. Figure 3 shows that reaction rate increases with increasing DODAC concentration up to a maximum, after which a slight decrease in k_0 is observed. A similar behavior was previously reported for other bimolecular reactions in the presence of vesicles obtained by the sonication method.^{10,11}

Kinetic data were quantitatively explained by using the ion-exchange pseudophase model. Unlike the acid hydrolysis, where H^+ ions are virtually completely excluded from the interface, the cationic nature of the surfactant favored the presence of OH^- at the vesicular pseudophase. The overall reaction rate was, therefore, equal to the sum of the rates at the vesicular and aqueous pseudophases (see Scheme 3, where subscripts w and ves again denote the aqueous and vesicular pseudophases, and k_w and k_{ves} are the bimolecular rate constants in the respective pseudophases).

From eq 4, taking into account that

$$K'_w = k_w[\text{OH}^-]_w \quad (8)$$

and

$$K_{\text{ves}} = \frac{k_{\text{ves}}[\text{OH}^-]_{\text{ves}}}{[\text{DODAC}]} = k_{\text{ves}}m_{\text{OH}} \quad (9)$$

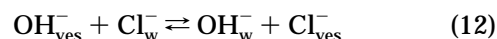
the following equation is obtained:

$$k_0 = \frac{k_w[\text{OH}^-]_{\text{total}} + (k_{\text{ves}}K_{\text{MNTS}} - k_w)m_{\text{OH}}[\text{DODAC}]}{1 + K_{\text{MNTS}}[\text{DODAC}]} \quad (10)$$

where K_{MNTS} is the association constant of MNTS to vesicles, and m_{OH} , which denotes the $[\text{OH}]_{\text{ves}}/[\text{DODAC}]$ ratio, satisfies the equation

$$m_{\text{OH}}^2 + m_{\text{OH}} \left[\frac{[\text{OH}^-]_{\text{total}} + K_{\text{Cl}}^{\text{OH}}[\text{Cl}^-]_{\text{total}}}{(K_{\text{Cl}}^{\text{OH}} - 1)[\text{DODAC}]} - \beta \right] - \left[\frac{\beta[\text{OH}^-]_{\text{total}}}{(K_{\text{Cl}}^{\text{OH}} - 1)[\text{DODAC}]} \right] = 0 \quad (11)$$

where $K_{\text{Cl}}^{\text{OH}}$ is the ion-exchange constant for the equilibrium



and β is the fraction of surfactant ions neutralized by counterions, which the ion-exchange pseudophase model assumes to be constant and independent of the concentration of surfactant and nature of the counterion.¹⁸

We used optimization software based on the Marquardt algorithm²⁹ to fit our experimental data to eqs 10 and 11. The K_{MNTS} value used in the calculations was that obtained previously spectrophotometrically and in the study of the acid hydrolysis of MNTS, viz., 380 M^{-1} . We used $K_{\text{Cl}}^{\text{OH}} = 1.6$, calculated by using a simulation procedure to obtain the m_{OH} values that resulted in the best fit of the experimental results to eq 10. Parameter β (the fraction of charge neutralized by the counterion) was taken to be 0.8, which was the value obtained by Chaimovich et al.^{5a} for DODAC vesicles of a similar size. We also assumed β to be identical at the inner and outer surfaces of vesicles.²⁰ As can be seen from Figure 3, the experimental results conformed satisfactorily to this model; i.e., increasing the amount of DODAC in the medium increased the catalytic effect up to a maximum value when all MNTS was associated with vesicles. A further increase in the DODAC concentration decreased the reaction rate through the displacement of reactive ions (OH^-) from the bilayer surface by the effect of the increased concentration of nonreactive ions (Cl^-). Table 3 summarizes the kinetic data obtained. The reactivity constant for the vesicular pseudophase, k_{ves} , was calculated to be $0.015 \pm 0.002 \text{ s}^{-1}$.

In applying the pseudophase model, we assumed a single k_{ves} value corresponding to the reactivity at the inner and outer sides of the vesicle bilayer and a fast equilibrium of MNTS between both reaction sites. The assumption of a single rate constant for the vesicles is quite reasonable. Chaimovich et al.^{13b} showed that the reactivities of OH^- on both sides of the bilayer are comparable. On the other hand, we did not observe two-phase kinetics in our study. Moss et al.^{7,14} and Chaimovich et al.^{13b} encountered two-phase kinetics in some bimolecular reactions in a vesicle medium. The inner and outer sides of the vesicle can be discriminated only when permeation of OH^- (or another reagent) across the bilayer is the rate-determining step. Our system is much less reactive than those studied by these authors; hence, reaction of OH^- with MNTS is slower

Table 3. Kinetic Parameters Obtained for the Alkaline Hydrolysis of MNTS in the Presence of DODAC Vesicles^a

$10^3 [\text{NaOH}]/\text{M}$	$K_{\text{OH}}^{\text{Cl}}$	$10^2 k_{\text{ves}}/\text{s}^{-1}$	$10^3 k_{\text{ves}}^{\text{m}}/\text{M}^{-1} \text{s}^{-1}$
1.0	1.6	1.45	8.12
2.5	1.6	1.40	7.84
3.9	1.6	1.64	9.18

^a Results were obtained with $K_{\text{MNTS}} = 380 \text{ M}^{-1}$, $k_{\text{w}} = 0.083 \text{ M}^{-1} \text{s}^{-1}$, and $\beta = 0.8$.

Table 4. Comparison of the Kinetic Parameters Obtained by Applying the Pseudophase Model to DODAC Vesicles and Various Types of Cationic Micelles

surfactant	$K_{\text{MNTS}}/\text{M}^{-1}$	$k_{\text{ves}}/\text{s}^{-1}$	$k_{\text{ves}}^{\text{m}}/\text{M}^{-1} \text{s}^{-1}$
LTABr micelles ^a	164		
TTABr micelles ^b	208	0.080	0.0112
CTABr micelles ^b	238	0.104	0.0146
DODAC vesicles ^c	380	0.015	0.0081

^a Reference 17a. ^b Reference 17b. ^c This work.

than permeation of OH^- across the bilayer. This led to a pure monophasic chemical process. The rate of transmembrane equilibration of fairly low molecular weight hydrophobic substrates (such as MNTS) is fast relative to the time scale of our reaction.³⁰ Indirect evidence for this rapid equilibrium between the inner and outer sides of the vesicle was obtained by comparing the values of k_0 obtained at 25 °C with those determined by repeating some kinetic experiments at the same temperature but after keeping the MNTS-vesicle mixtures at 45 °C for 10 min—this temperature is higher than that for transition from the ordered gel phase to the fluid liquid-crystalline state ($T_{\text{C}} = 36\text{--}38$ °C)—and subsequently cooling the mixture to 25 °C and adding OH^- . Both sets of experiments lead to similar k_0 values.

The k_{ves} value obtained (0.015 s^{-1}) cannot be directly compared to k_{w} (the bimolecular rate constant in water), because the two constants are defined in different terms (k_{ves} in terms of mole per mole concentration in DODAC; k_{w} in terms of mole per volume concentration). However, assuming the molar volume of DODAC determined by several authors (0.56 M^{-1}),^{10,11} we have calculated the bimolecular reactivity constant in the bilayer, $k_{\text{ves}}^{\text{m}}$, to be $0.0084 \text{ M}^{-1} \text{s}^{-1}$. It is about one-tenth that in pure water ($k_{\text{w}} = 0.083 \text{ M}^{-1} \text{s}^{-1}$).^{17a} This suggests that the hydrolysis rate in the bilayer is intrinsically one-tenth that in the aqueous pseudophase, which confirms that the origin of the catalytic effect observed in the presence of vesicles does not correspond to an increase in reactivity but, rather, to a local increase in the reagent concentration in the DODAC bilayer. This intrinsically decreased reactivity may be attributed to the polarity at vesicular pseudophase, which is lower than that in water. Also, as can be seen in Table 4, the $k_{\text{ves}}^{\text{m}}$ value in DODAC was lower than those obtained for the same reaction in micelles of TTABr and CTABr,^{17a} which is consistent with decreased polarity or increased hydrophobicity in DODAC vesicles relative to micelles, as suggested by Fendler and Hinze.¹⁰ The catalytic efficiency of DODAC vesicles (viz., the ratio of the maximum reaction rate at a given OH^- concentration to the corresponding surfactant concentration) in the hydrolysis of MNTS is about 25 times higher than that for the same reaction in the presence of CTABr micelles.^{17a} The higher catalytic efficiency of vesicles is a result of the larger association constant, K_{MNTS} , which in turn is a consequence of the high substrate dissolving capacity of DODAC vesicles—particularly of small vesicles obtained by sonication—relative to that of micelles.

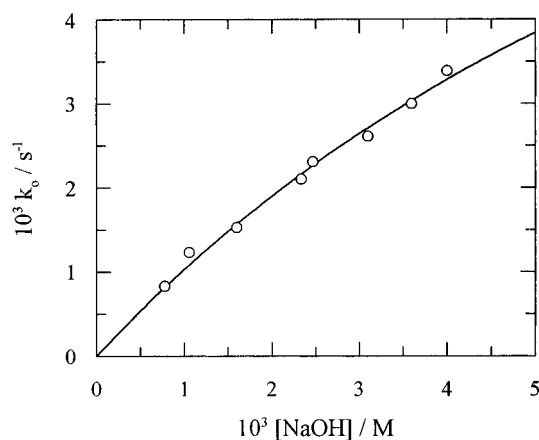


Figure 4. Influence of the NaOH concentration on the pseudo-first-order rate constant k_0 . $[\text{DODAC}] = 1.33 \times 10^{-3} \text{ M}$. The solid line is merely a visual aid.

The hydrolysis of MNTS in water is first-order in the OH^- concentration. We checked whether this held in the presence of vesicles. We performed a series of kinetic experiments where the OH^- concentration was varied from 7×10^{-4} to $4 \times 10^{-3} \text{ M}$ at a constant DODAC concentration of $1.33 \times 10^{-3} \text{ M}$. As can be seen from Figure 4, k_0 varied in a slightly nonlinear fashion with the OH^- concentration, with a zero intercept. This nonlinear dependence may be a result of the amount of OH^- that is incorporated onto the vesicle surface not being a linear function of the total amount of OH^- added, as previously suggested by some authors.^{10,31} Also, it may arise from the fact that, as vesicles saturate with OH^- ions, neutralization of the charge of polar heads by an ion with a high charge density such as OH^- induces structural changes in the system, similarly to other microheterogeneous media,³² thus causing vesicles to aggregate.³³

Conclusions

In the range of experimental conditions studied, the ion-exchange pseudophase model was found to explain satisfactorily the results. The inhibitory effect observed on the acid hydrolysis of MNTS in the presence of vesicles is not a result of decreased reactivity in this medium but rather of the virtually complete exclusion of H^+ ions from the vesicular pseudophase. By contrast, the catalytic effect observed in the alkaline hydrolysis of MNTS is due to the increase of local reagents concentrations at the vesicle interface rather than to the decrease in the energy of activation required for the OH^- attack to take place.

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