Effects of Zwitterionic Vesicles on the Reactivity of Benzoyl Chlorides

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A systematic study on the solvolysis reaction of substituted benzoyl chlorides in the presence of zwitterionic vesicles of dipalmitoyl phosphatidylcholine (DPPC) has been performed. Size, shape, surface charge, and polarity of the interface of the vesicular aggregates were determined using various techniques. The application of the pseudophase formalism allowed us to obtain the thermodynamic and kinetic coefficients characteristic of the reaction. The effects of vesicular aggregates on the solvolysis of benzoyl chlorides, which are known to be sensitive to the physical properties of the medium, depend on the nature of the substrate. For benzoyl chlorides with electron-donating groups, which react predominantly through a dissociative mechanism which is strongly affected by medium properties, the rate constant decreases as the vesicle concentration increases. On the other hand, for benzoyl chlorides with electron-withdrawing groups, which react mainly via an associative pathway, DPPC vesicles catalyze the solvolysis reaction.

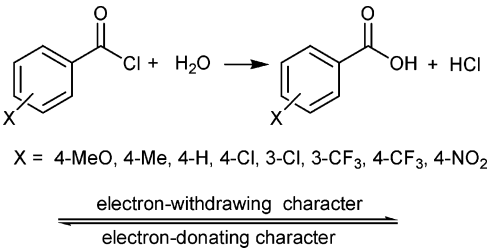
Introduction

Vesicles[1,2] are closed bilayer aggregates, which have received a rapidly evolving interest in both basic and applied sciences and engineering. They have been utilized as models for cell membranes and drug delivery systems.

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 common choices in this respect are sonication, injection, and extrusion methods,[5,6] but vesicles[7,8] spontaneously formed from various surfactant mixtures in aqueous solutions are used as well. Salinity,[9,10] pH,[10,11] temperature,[12,13] and aging[14] significantly affect the degree of vesicle packing and hence vesicle size and aggregation.

Owing to the physical and chemical characteristics of the vesicles and to their available interaction sites, the vesicular aggregates offer a large possibility of solubilization and compartmentalization for substrates of different nature and consequently provide suitable media for reactivity control. Vesicles can inhibit chemical reactions when only one of the two reactants binds to the aggregate;[15−17] conversely, they can catalyze reactions by having the reactants concentrated at the water−bilayer interface, thus acting as microreactors.[15−21] Charged vesicles provide a good environment for hydrophobic and oppositely charged molecules to bind, and an efficient catalysis is found when the other reactant can bind as a counterion to the aggregate.[20] Another effect to be considered stems from the decreased local polarity at vesicular binding sites compared to that of water. This latter effect leads to catalysis only when the organic reaction is accelerated in less polar environments. The catalytic ability of vesicles surpasses that of micelles[17,19,22] and depends on aggregate size.[22] 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)[5] and the capacity of vesicles to dissolve reagents[23,24] are both influenced by the size of the aggregates.

SCHEME 1



Solvolysis reactivity of benzoyl chlorides entails a high sensitivity on media properties. In this article, a systematic kinetic study has been performed for a series of these substrates, varying the electron-withdrawing character of the substituent (see Scheme 1), in the presence of zwitterionic vesicles of dipalmitoyl phosphatidylcholine (DPPC). For the vesicles used, size, shape, surface charge, and polarity of the interface region were obtained using different techniques. In a previous work,[25] we investigated the potential catalytic/inhibitory effect of nonionic microemulsions on this reaction. The purpose of the present work was to gain insight into the interfacial effects on the reactivity of organic chemical processes in vesicle systems and to compare both reaction rate and solubilization of the benzoyl chlorides in the vesicular aggregates with those previously determined in the presence of microemulsions[25] and micelles.[26,27]

Experimental Section

All the reagents (from Sigma) were of the highest available grade and were used without further purification. The stock

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solutions of benzoyl chlorides were prepared in acetonitrile. For aqueous solutions double-distilled and deionized water was used. All experiments were carried out at 25.0 ± 0.1 °C.

Vesicle Preparation. Dipalmitoyl phosphatidylcholine (DPPC) stock solutions were prepared by weighing the required amount of solute, adding water, and keeping the solution for 30 min in a water bath at 65 °C. Then the solution was sonicated with a tip sonicator (Bandelin UW 2200) for 30 min at 65 °C. After those samples were equilibrated to room temperature and filtered through a 0.45 μm pore size filter twice, the stock solution was diluted to the desired concentration to prepare samples for kinetic measurements. Although the vesicles were assumed to be stable, we always used dispersions within 3 h after preparation.

Fluorescence Measurements. The desired amount of Nile Red was deposited by evaporation into a vial from a stock solution of the probe in ethanol. A volume of DPPC vesicle solution was added to the vial, and the solution was gently mixed until the probe was dissolved. Fluorescence measurements were performed in a Spex FluoroMax-3 spectrofluorometer, with an excitation wavelength of 490 nm.

Dynamic Light Scattering Measurements. Samples were irradiated with an Ar^+ laser at $\lambda = 514.5$ nm, and data were recorded at three different angles (60°, 90°, and 120°). Scattering data were analyzed by means of a Malvern Autosizer 4700 digital correlator. Correlation functions were fitted by using the CONTIN and cumulants methods.

ζ-Potential Measurements. Vesicle electrophoretic mobilities were measured using a Malvern Zetasizer 2000. The ζ-potentials were calculated using the Smoluchowski equation. All samples were diluted and filtered prior to the measurement. All experiments were performed at 25 °C.

Transmission Electron Microscopy (TEM). Vesicles were imaged with a JEOL JEM-1010 transmission electron microscope using the negative staining method.[8] A drop of vesicle solution was spread on a 200-mesh copper grid coated with a Formvar film, and the extra droplet was instantly wiped off by filter paper. After being naturally desiccated, a drop of 2% uranyl acetate in ethanol solution was dripped on the copper grid for about 60 s and the extra droplet was also removed. Then the grid was dried naturally for about 3 h before TEM observation.

Cryo-TEM. The vesicles were prepared by the usual procedure. A 5 μL drop of the solution was pored on a 200-mesh carbon-coated copper grid and covered with a Formvar film. After gently blotting the drop with filter paper in order to create a thin film over the grid, the sample was immediately plunged into liquid ethane to obtain a vitrified film using a Gatan cryoplunge. The vitrified sample was transferred using a Gatan CT3500 cryo-transfer under liquid nitrogen environment into the electron microscope (JEOL JEM 2010 FEG).

Kinetic Measurements. Solvolysis reactions were carried out in an Applied Photophysics SX-18MV stopped-flow reaction analyzer thermostated with a Polyscience water bath. All kinetic experiments were performed using a 1:25 asymmetric mixing kit so that the percentage of acetonitrile in the reaction mixture was always less than 4 vol %. Kinetic profiles were followed by monitoring the absorbance of the aromatic reactants. The wavelengths used for the kinetic studies fell between 285 and 300 nm for 4-MeO, 4-Me, 4-H, 4-Cl, 3-Cl, 3-CF_3, 4-CF_3, and λ was 245 nm for 4-NO_2. The concentration range was 3×10^{-4} for 4-H, 4-Cl, 3-Cl, 3-CF_3, and 4-CF_3 and 4×10^{-5} for 4-MeO, 4-Me, and 4-NO_2. Kinetic data were always satisfactorily fitted by the first-order integrated rate equations, and therefore, in what follows, k_{obs} denotes the pseudo-first-order rate constant. Experiments were reproducible to within 3%.

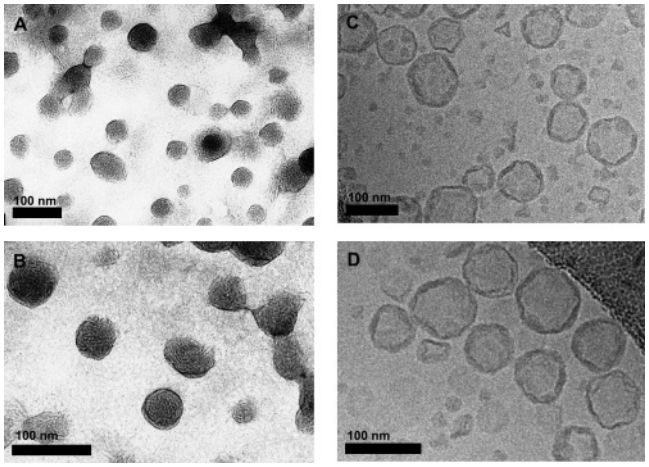


Figure 1. (A and B) Transmission electron micrographs (negative staining method) and (C and D) cryo-TEM images of DPPC vesicles; [DPPC] = 5 mM.

Results

Characterization of Vesicles. The size and shape of vesicles depends on the sonication time and temperature at which they are prepared. Sonication above the transition phase temperature (42 °C)[6] leads to larger, multicompartment vesicles that gradually become single-compartment vesicles as the sonication time is extended. We prepared vesicles by sonicating the DPPC dispersions at 65 °C for 30 min. Their size was determined from dynamic light scattering measurements at a constant temperature of 25 °C. A hydrodynamic diameter $D_h = 69 \pm 5$ nm was consistently obtained, pointing toward the presence of small unilamellar vesicles. To check the stability of the vesicles under our experimental reaction conditions, the variation of D_h with time was monitored. The size of the vesicles was found to remain constant for periods of time of at least 3 h, significantly longer than the reaction time of the slowest reaction (less than 3 min). Additionally, all kinetic profiles were monitored at $\lambda = 400$ nm so as to follow the possibility of adhesion or fusion of the vesicles.[4]

TEM observation clearly confirmed the formation of vesicles in solution. In Figure 1 (left) TEM micrographs are shown for DPPC vesicles. They clearly show nearly spherical shapes, low polydispersity, and an average diameter similar to that obtained with DLS measurements (69 nm). We have not observed one-dimensional bilayer fragments. On the other hand cryo-TEM micrographs show the presence of collapsed vesicles and bilayer fragments (most likely arising from the sample preparation procedure) but mean vesicle size is in good agreement with that determined by both DLS and TEM.

Nile Red solvatochromic probe has been used to estimate the polarity of the vesicular pseudophase. The Nile Red emission band red-shifts as the medium becomes more polar. Emission spectra for Nile Red in DPPC vesicles were measured, with emission bands centered at 614 nm, while the emission maximum for water is 640 nm, i.e., the interface is less polar than water. This value can be related to the empirical polarity scale $E_T(30)$, obtaining values of 44, which corresponds to a polarity similar to that of *tert*-butyl alcohol and consequently lower than water.

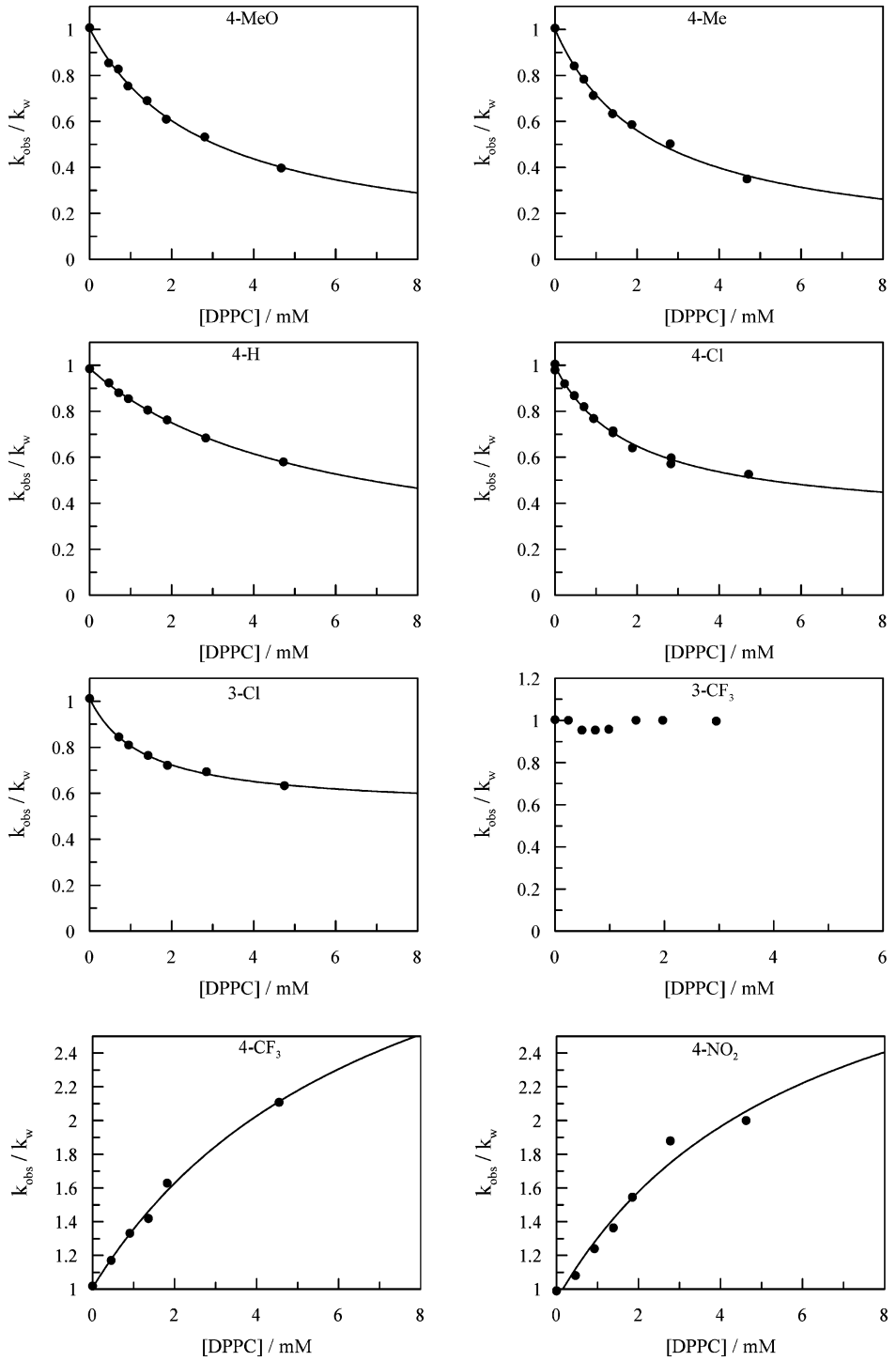
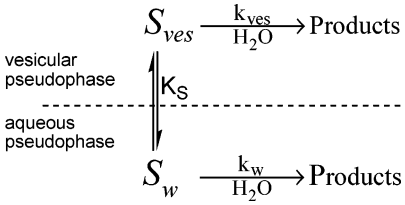


Figure 2. Normalized observed rate constant (k_{obs}/k_w) vs [DPPC] for the different benzoyl chlorides. The solid lines represent the best fit of eq 1 to the experimental data.

Vesicular Effects on Reactivity. A study was carried out on the influence of DPPC vesicles on the pseudo-first-order rate constant for the solvolysis of benzoyl chlorides with different functional groups varying the concentration of vesicles from 0 to 5 mM. As can be seen from Figure 2, the effects of vesicular aggregates depend on the substituent of the aromatic ring. Different behaviors can be observed when moving along the scale of electron-donating character for the substituents (see Scheme 1). The rate constants decrease as the vesicle concentration increases, for electron-donating groups or with weak electron-withdrawing character (from 4-MeO to 3-Cl). This means that the electron-donating character of the substituent decreases (4-MeO > 4-Me > 4-H > 4-Cl > 3-Cl), the inhibition effect of vesicles is smaller. While 3-CF_3 shows no dependence with vesicle concentration, for substituents with higher electron-withdrawing character (4-CF_3 and 4-NO_2) DPPC vesicles catalyze the reaction.

The reactivity of benzoyl chlorides can thus be modified upon the presence of vesicles. Kinetic effects on the pseudo first-order rate constant can be analyzed on the basis of the pseudophase model[28,29] which considers the systems divided in two different regions (see Scheme 2), the vesicular pseudophase, representing the DPPC bilayer, and an aqueous pseudophase, representing both the bulk medium and the intravesicular

SCHEME 2



compartment. The substrate would be distributed between the two regions, and therefore the reaction can take place in either of them.

In applying the pseudophase model we assumed a single k_{ves} value corresponding to the solvolysis at the inner and outer sides of the vesicle bilayer and a fast equilibrium of substrate for binding at both reaction sites. The assumption of a single rate constant seems reasonable, considering that we did not observe two-phase kinetics.[16,30−32]

The proposed model leads to the following equation

$$k_{obs} = \frac{k_w + k_{ves}K_S[DPPC]}{1 + K_S[DPPC]} \quad (1)$$

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

$$K_S = \frac{[S]_{ves}}{[S]_w[DPPC]} \quad (2)$$

Throughout this work we assumed that all the DPPC in the medium was incorporated in vesicles. Although there is a surfactant concentration threshold below which vesicles do not form,[22,33] this threshold is not the result of a dynamic equilibrium between free and vesicular surfactant, like the critical micelle concentration (cmc) of micellar media. Once formed, vesicles are not destroyed by dilution. In fact, they have been detected at surfactant concentration[34] as low as 10^{-8} M which is far below the concentrations used in this work.

To provide a quantitative analysis of the data, eq 1 was used to fit the experimental data. Table 1 shows the values of rate constants in the vesicular interface and in water, as well as the distribution constant.

When the reaction takes place only in the aqueous pseudophase, the model predicts the simpler expression 3

$$k_{obs} = \frac{k_w}{1 + K_S[DPPC]} \quad (3)$$

which can be rearranged into

$$\frac{k_w}{k_{obs}} = 1 + K_S[DPPC] \quad (4)$$

Equations 3 and 4 can provide information about the extent of the reaction in vesicular medium. A linear relationship between the inverse of k_{obs} and vesicle concentration indicates that the reaction in vesicles is nonexistent or negligible with respect to the reaction in water.

Figure 3 displays the inverse of the observed rate constant with DPPC concentration. The linear relationship that is observed for 4-MeO (eq 4) indicates that the reaction in the vesicle is nonexistent or negligible as was noted above. The

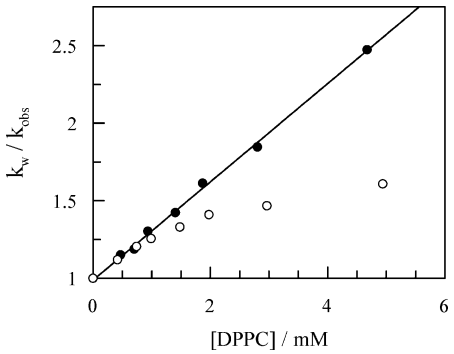


Figure 3. Inverse of the normalized observed rate constant (k_w/k_{obs}) vs DPPC concentration for (●) 4-MeO and (○) 3-Cl. The solid line shows the linear fit of eq 4 to experimental data for 4-MeO.

TABLE 1: Kinetic Parameters for Solvolysis of Benzoyl Chlorides in the Vesicular System at 25 °C

substrate	k_w/s^{-1}	k_{ves}/s^{-1}	K_S/M^{-1}	k_{ves}/k_w
4-MeO	55.9 ± 0.8	≈3	317 ± 32	0.00
4-Me	6.68 ± 0.14	≈0.4	417 ± 38	0.00
4-H	1.06 ± 0.03	0.202 ± 0.050	227 ± 21	0.19
4-Cl	0.195 ± 0.003	0.064 ± 0.005	544 ± 44	0.33
3-Cl	0.046 ± 0.001	0.024 ± 0.001	698 ± 60	0.53
3-CF_3	0.031 ± 0.001			1.00
4-CF_3	0.037 ± 0.001	0.140 ± 0.015	147 ± 31	3.78
4-NO_2	0.055 ± 0.002	0.223 ± 0.079	114 ± 75	4.05

TABLE 2: Comparison of the Association Constants Obtained by Applying the Pseudophase Model to DPPC Vesicles and Various Types of Micelles

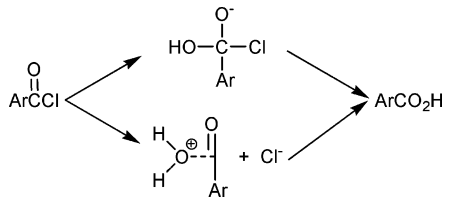
benzoyl chloride	K_S/M^{-1}		
	DPPC[a]	CTACl[b]	SDS[b]
4-MeO	317	100	
4-Me	417	250	150
4-H	227	130	130
4-Cl	391	500	270
4-NO_2	114	100	80

[a] This work. [b] Ref 26.

value provided in Table 2 for 4-MeO from the fit of eq 1 to experimental data (3 s^{-1}) is just an approximation taking into account the large error arising from the limitation that only experimental data for the first stage of the inhibition curve can be obtained. The same behavior is observed for 4-Me. As the electron-withdrawing character of the substituent increases so also does the deviation from linearity. In Figure 3, the inverse of the observed rate constant for 3-Cl deviates clearly from a linear trend, pointing out that the substrate reacts in water as well as in the vesicular interface. Deviations from linearity were also observed for 4-H and 4-Cl as expected.

The catalytic or inhibitory effects of vesicles upon the solvolysis reaction of benzoyl chlorides can be quantified by using the ratio between the rate constants in vesicles and in water (k_{ves}/k_w). As we can see in Table 1, this ratio increases with the electron-withdrawing character of the substituents studied. The values of k_{ves} become more similar to the rate constant in water as we approach 3-CF_3, and from that point the rate constant at the vesicular pseudophase starts to deviate again. The inhibition observed in Figure 2 for 4-MeO, 4-Me, 4-H, 4-Cl, and 3-Cl can be attributed to the association of the substrates to the vesicles. The association prevents the access of the substrate to the bulk water reducing the observed reaction rate. Although reaction in the vesicular peudophase is taking place, the rate constant is smaller than that in water. On the other hand, for 4-CF_3 and 4-NO_2 benzoyl chlorides solvolysis

SCHEME 3



is catalyzed in the vesicles (see Figure 2). In that case, the substrates react both in water and at the vesicle pseudophase. The observed catalysis indicates that the rate constant at the vesicle is higher than in water. The solvolysis of 3-CF_3 is insensitive to the variation of vesicle concentration. It can be concluded, according to the observed trend for the other substrates, that the rate constant in water and in vesicles has the same value. Consequently, the overall rate constant is insensitive to the association of the substrate to the interface.

Mean values for the association constants of different benzoyl chlorides to the vesicles (K_S) are also shown in Table 1. The association constants are similar and independent for all substituents, with substrates with substituents with high electron-withdrawing character (4-CF_3 and 4-NO_2) showing slightly lower values.

Discussion

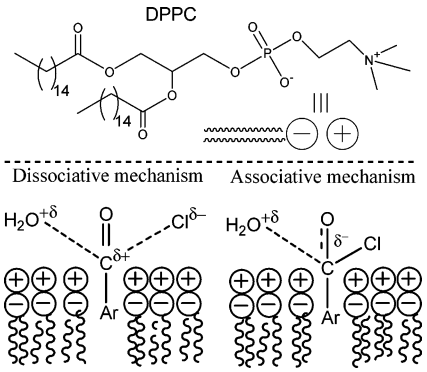
As we have already mentioned, the effects of vesicular aggregates on the solvolysis of benzoyl chlorides depend on the nature of the substrate. The solvolysis of benzoyl chlorides is a well-known process.[35] The reaction can occur via two mechanisms: (a) dissociative mechanism, through a carbocationic intermediate and (b) associative mechanism, or addition−elimination, through a tetrahedral intermediate. A third concerted pathway with associative or dissociative character can be considered. In a reaction series a small change in the structure of reactants or in the reaction conditions leads to a change from a dissociative to an associative mechanism. In Scheme 3 the two extreme possibilities are sketched.

Vesicular and substituent effects can be explained in terms of a duality of reaction paths (associative and dissociative). Benzoyl chlorides with electron-donating groups react through a dissociative mechanism giving rise to an acylium intermediate and Cl^- as the leaving group, whereas electron-withdrawing groups favor an associative mechanism with a tetrahedral intermediate.

The influence of the DPPC vesicles on the reaction depends on the operating reaction mechanism. The dissociative mechanism is strongly affected by the properties of the medium, in particular polarity and ability to solvate the leaving group.[35,36] The vesicular interface is less polar; water located in that region has a lower electrophilic character than bulk water and consequently has a lower ability to solvate the leaving group. This means that for electron-donating substrates (4-MeO, 4-Me, 4-H, 4-Cl, 3-Cl), that react via a dissociative pathway, the reaction rate is strongly affected by the variation of polarity, decreasing as the water content does and polarity gets lower.

As we commented in the Results, Nile Red solvatochromic probe has been used to estimate the polarity of the vesicular pseudophase. The Nile Red emission band is shifted to higher wavelengths as the medium becomes more polar.[37] The values obtained for vesicles on the empirical polarity scale (see Characterization of Vesicles in the Results) correspond to an environment which is less polar than water. Therefore, vesicles provide a more apolar medium for solvolysis of benzoyl chlorides leading to a decrease in the reaction rate. The lower polarity of the vesicular interface with respect to that of water also explains that as the electron-withdrawing character of the substituent increases (from 4-MeO to 3-Cl), the inhibition effect of vesicles gets progressively smaller. The dissociative pathway, hardly dependent on water polarity, becomes less and less dominant, and the percentage of the associative channel, which is less sensitive to polarity, becomes higher. A comparison between the plots of k_{obs}/k_w versus vesicle concentration for the different substrates pointed out this behavior (see Figure 2).

SCHEME 4



As the electron-donating character of the substituent decreases, the inhibition effect of vesicles (k_{obs}/k_w) becomes smaller. For electron-withdrawing substituents (4-CF_3, 4-NO_2) the solvolysis reaction is catalyzed by DPPC vesicles (see Figure 2). This catalysis is not easy to explain since benzoyl chlorides always show a decrease in rate constant when polarity and ionizing power decrease. This decrease in the rate constant could be minimized when the second possible mechanism, the associative pathway (independent of polarity and dependent on solvent nucleophilicity), is present and contributes to the rate constants.

A similar behavior, i.e., rate constants increasing as polarity decreases, has been noted earlier for the solvolysis of benzoyl chlorides in different systems. In the presence of alcohol/water mixtures the rate constant increases as the amount of water in the mixture decreases;[38] in this case the catalysis is due to alcohol acting as a nucleophile. Nonionic and anionic microemulsions[25,39] show catalysis for benzoyl chlorides with a higher tendency to react via an associative mechanism (more electron-withdrawing substituents). Since the associative pathway strongly depends on solvent nucleophilicity, an unusual enhancement of the nucleophilic character of water, due to interactions between the polar headgroups and water molecules, was postulated to explain the observed behavior. The hydrolysis of the 4-NO_2 derivative is also accelerated by cationic and zwitterionic micelles[26,27] because of favorable interactions with the developing negative charge at the reaction center.

Vesicles provide a favorable environment for binding of hydrophobic and oppositely charged molecules. Interactions of the transitions state for the solvolysis of a benzoyl chloride with the vesicular headgroup are illustrated in Scheme 4. The transition state involves significant C−Cl bond breaking for the dissociative mechanism or is similar to a tetrahedral intermediate for the associative channel.

The positive charge in the nucleophilic water molecule is dispersed within the solvent by hydrogen bonding, and the partial charges, δ^+ and δ^-, on the water molecule, the leaving Cl^-, and the reaction center are without numerical significance and depend on electronic substituent effects. We assume that the development of negative charge at the reaction center

increases as the substituents become more electron-withdrawing. Such negative charge development is favored by the cationic headgroups of the zwitterionic DPPC vesicles. Experimental[40,41] and simulation[42] studies about headgroup conformation for DPPC bilayers show that the dipolar head of DPPC lies almost parallel to the plane of the bilayer with the vector between the phosphorus and nitrogen atoms oriented near-parallel to the surface with an angle between 15° and 30°. This means that the ammonium groups are placed further out than the phosphate groups, and consequently the substrates feel a cationic environment. Thus, the observed catalysis for electron-withdrawing substituent is because of the enhanced stabilization of the associative intermediate due to the surface charge of the vesicle. The surface charge of the vesicles can be estimated using ζ-potential measurements. For our DPPC vesicles the ζ-potential is slightly negative, $\zeta = -4 \pm 2$ mV. This value can be probably attributed to fatty acid impurities in the sample.[43] Nevertheless, that low value can be considered compatible with zero.

A similar description has been made by Bunton and coworkers to explain the acceleration of the hydrolysis of 4-NO_2 derivative by cationic and zwitterionic micelles.[26,27] The observed catalytic effect is similar for both types of micelles. This similarity is explained considering a zwitterionic micelle as a cationic one with high counterion binding to the micelle surface and, therefore, with high degree of neutralization of headgroup charges. Unfortunately, we could not perform the reaction in the presence of cationic vesicles (DODAC or DODAB) because of undesirable impurities which react with the substrate. Anyway, reactivity studies on electron-transfer reactions[30] have shown that DPPC phospholipids have the same effect on the reaction as cationic vesicles.

Vesicular effects on solvolysis of benzoyl chlorides with electron-withdrawing groups (4-CF_3, 4-NO_2) can be understood on the assumption that the charge asymmetry in the interface of DPPC vesicles makes solvolysis become faster than in water, and conversely, the interface properties (low polarity and decrease of water content) plus the charge asymmetry make the solvolysis of benzoyl chlorides with electron-donating groups be slower than in water.

Another explanation for favoring the associative channel as the electron-withdrawing character of the substituent increases is the role of general base catalysis. A base, or in our case water, can assist the attack of water to the substrate. To explore that possibility an isotopic effect experiment was carried out. The solvolysis of 4-CF_3 in the presence of vesicles has been performed both in H_2O and D_2O. The isotopic effect in the absence of vesicles is $k^H_{obs}/k^D_{obs} = 1.4$, slightly lower than the values obtained for similar substrates.[38] When vesicles are present the ratio between the observed rate constant k^H_{obs}/k^D_{obs} for the same concentration of vesicles falls between 1.1 and 1.3. These results are not conclusive but suggest no general base assistance to solvolysis reaction.

As we mentioned in the Introduction, the catalytic ability of vesicles surpasses that of micelles[17,19,22] We can compare our results with those obtained in micelles[26,27] for the same reaction. We find slightly larger values of the association constants in vesicles than in micelles (see Table 2), as a consequence of the high substrate dissolving capacity—primarily controlled by hydrophobic forces—of DPPC vesicles relative to that of micelles.

We also find a larger catalytic or inhibiting efficiency in these vesicular systems than in the micellar aggregates. For example, for 4-MeO which reacts predominantly through a dissociative mechanism, the observed rate constant is reduced to half of its value at [DPPC] = 3×10^{-3} M (see Figure 2). To obtain the same effect in the presence of CTACl micelles it is necessary to have a much higher concentration. The dissociative channel is strongly affected by the properties of the medium, in particular polarity and ability to solvate the leaving group. Vesicles supply a more hydrophobic environment than micelles, leading to a larger inhibition. On the other hand, 4-NO_2 reacts mainly through an associative pathway catalyzed by our vesicles; a concentration of DPPC of 5 mM (Figure 2) makes the reaction 2 times faster than in water. In the presence of CTACl micelles it is again necessary to have a higher surfactant concentration to observe the same catalysis. The associative mechanism is independent of polarity. The larger catalytic efficiency of vesicles is due to the much lower critical vesicle concentration of DPPC, as compared to the cmc of CTACl. As a result, hydrophobic microdomains are present at lower concentrations and benzoyl chlorides can bind more efficiently.

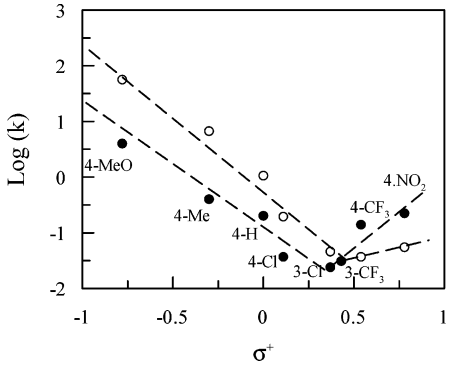


Figure 4. Hammet plots for the solvolysis of substituted benzoyl chlorides in (○) water (k_w) and (●) DPPC vesicles (k_{ves}). Lines are a guide for the eye.

If we compare the kinetic effects of vesicles and microemulsions, both anionic and nonionic, it is worth noting that the observed rate constants in microemulsions are in all cases, except for 4-NO_2 in nonionic microemulsions, and for all compositions lower than those in vesicles even though the response to modifications in microemulsion composition varies with the electron-withdrawing character of the substituent. This effect could arise from the dissolution of the substrate into the oil phase of the microemulsion where the reaction does not take place. For 4-NO_2, the observed rate constant increases as the water content of the microemulsion decreases due to an enhancement on the nucleophilic character of the interface water. Such catalytic behavior leads to rate constants higher than those in water, which has the same order of magnitude as the rate constant in vesicular media.

The analysis of Hammet correlations shows the effects of the substituent on the solvolysis reaction of benzoyl chlorides in the presence of DPPC vesicles. In the presence of water,[35] organic solvent,[44] and microemulsions[25,39] the plots show a sharp change of the Hammet slopes indicating a change in the solvolysis mechanism. In our study we observed a similar behavior (see Figure 4).

Hammet plots for reactions in water show a change in slope from negative values ($\rho^+ = -2.8$) to a positive value which is indicative of a change of mechanism at about $\sigma^+ = 0.50$, in accordance with literature values.[35] Figure 4 shows that in DPPC vesicles, like in water, there is indeed a switch from the dissociative to the associative mechanism that occurs around $\sigma^+ = 0.40$, (somewhere between 3-Cl and 3-CF_3). The effect of the switch in the reaction mechanism is highlighted by comparing the rate constants for 4-NO_2 with the expected values

for a dissociative mechanism at this σ^+ value: the actual rate constant exceeds the expected value by a factor of about 12 for water and by a factor of 100 for vesicles. For low σ^+ values (from 4-MeO to 3-Cl), the Hammet slope for vesicles has a negative value around $\rho^+ = -2.3$, close to the value in water. This small variation in the slopes indicates that the electronic effects of the substituents on the solvolysis reaction are similar in both cases. The values of the rate constant at the vesicular pseudophase are lower due the decrease of polarity and the amount of water, but these differences between k_w and k_{ves} become lower as the electron-withdrawing character of the substituents is increased. This behavior is due to the increase in the percentage of the associative channel as σ^+ increase. For these substrates, the interactions between the surfactant headgroups and the transition state have no relevant role since the dissociative pathway is mainly affected by the polarity of the reaction medium. Conversely, Hammet slopes for substrates reacting through an associative mechanism have different values (ρ^+ for high σ^+ values cannot be calculated accurately, but it seems that ρ^+ is twice that for vesicles than for water), as we mentioned above, the development of negative charge at the reaction center increases as substituents become more electron-withdrawing, and then the interaction with the cationic headgroups of the DPPC vesicles plays an important role increasing the reaction rate and leading to a higher Hammet slope than that in water.

Conclusions

A study has been carried out on the solvolysis of substituted benzoyl chlorides in DPPC vesicles. Kinetic effects on the observed rate constant have been explained by means of the pseudophase model which allowed us to obtain the association constants and the rate constants at the vesicular and aqueous pseudophases.

The reaction takes place simultaneously through dissociative and associative mechanisms on which the DPPC vesicles exert opposite effects. For benzoyl chlorides with electron-donating groups (from 4-MeO to 3-Cl), the rate constants decrease as the vesicle concentration increases. These substrates react predominantly via a dissociative mechanism which is strongly affected by medium properties. The vesicular interface provides a less polar environment for reactions, having the interface water molecules lower electrophilic character than bulk water, and consequently, the medium has a lower capability to solvate the leaving group. On the other hand, for substituents with higher electron-withdrawing character (4-CF_3 and 4-NO_2), which react mainly via an associative mechanism, the formation of the transition state is more favored by vesicles, probably because of the development of negative charge in the organic residue. This negative charge development is favored by the cationic headgroups of the vesicles, and consequently, DPPC catalyses the reaction. In vesicles, just like in water, Hammet plots show a sharp change in slope pointing toward a modification of the solvolysis mechanism. Finally, we found a larger catalytic or inhibiting efficiency in these vesicular systems when compared with that of micellar aggregates.

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