Comparative study of nitroso group transfer in colloidal aggregates: micelles, vesicles and microemulsions

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A kinetic study was carried out on nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) to different secondary amines: morpholine (MOR), piperazine (PIP), dimethylamine (DMA) and piperidine (PIPER) in micelles of dodecyltrimethylammonium bromide (LTABr) and in vesicles of dioxadecyltrimethylammonium chloride (DODAC). Amine nucleophiles were chosen on the basis of their hydrophobicity and basicity. The observed rate constant, k_{obs}, shows opposite behavior in micelles and vesicular systems. k_{obs} for micelle systems decreases as the surfactant concentration increases. This behavior can be interpreted according to the distribution of the reagents among the different pseudophases of the system and the physicochemical properties of the latter. It has been observed that the product of the rate constant in the micellar pseudophase and the distribution constant of the amine, $k_2^{m}K_m^{R_2NH}$, retains a sequence similar to the reactivity observed in water. The differences observed can be explained on the basis of the different hydrophobicity of the amines and consequently different values of $K_m^{R_2NH}$. In all cases a catalytic effect on the addition of vesicles was observed reaching a limiting value of k_{obs}. The kinetic behavior can be explained quantitatively on the basis of a single pseudophase model. $k_2^{v}K_v^{R_2NH}$ in the vesicular systems of DODAC displays a variation which is analogous with the micellar systems but approximately 35 times greater, which in turn indicates the greater hydrophobic character of the vesicles of DODAC by comparison with the micelles of LTABr. In AOT/isooctane/water microemulsions we have found similar behavior where the product is approximately 22 times lower than in vesicles, indicating that the polarity of the interface of the microemulsions is greater than that of the micelles of LTABr and smaller than that of DODAC vesicles. The comparative analysis of the reactivities in the interface of the microemulsion and in an aqueous medium shows that the reactive position in the interface changes as the hydrophobic character of the amine varies.

Introduction

Surfactants, or amphiphiles, are surface-active nonionic molecules or organic salts which, either alone or in combination with a wide variety of other ionic and nonionic solutes, aggregate spontaneously and with a high degree of cooperativity in solution to form a variety of assemblies (or association colloids) whose structures depend both on the solution composition and on the structures of the components, primarily the surfactant.[1,2]

Micelles are highly dynamic, often polydisperse aggregates formed from single-chain surfactants[3] beyond the critical micelle concentration, cmc. Micellization is primarily driven by bulk hydrophobic interactions between the alkyl chains of the surfactant monomers and usually results from a favorable entropy change.[4] The overall Gibbs energy of the aggregate for ionic surfactants[5] is a compromise of a complex set of interactions, with major contributions from headgroup repulsions and counterion binding. It has long been known that aqueous micelles can influence chemical reaction rates and equilibria. Early studies of micellar effects on reaction rates and equilibria are described in extensive monographs.[1b,6] Much of the impetus for the study of reactions in micelles is that they model, to a limited extent, reactions in biological assemblies, and the term "biomimetic chemistry" has been coined to describe this general area of study.

Micellar catalysis of organic reactions has been extensively studied.[7] This type of catalysis is critically determined by the ability of micelles to take up all kinds of molecules. The binding is generally driven by hydrophobic and electrostatic interactions. The take-up of solutes from the aqueous medium into the micelle is close to diffusion controlled, whereas the residence time depends on the structure of the surfactant molecule and the solubilizate and is often of the order of 10^{-4}–10^{-6} s.[8] Solubilization is usually treated in terms of a pseudophase model in which the bulk aqueous phase is regarded as one phase and the micellar pseudophase as another. The time-averaged location of different solubilizates in or at a micelle has been a topic of contention.[9] Apart from saturated hydrocarbons, there is usually a preference for binding in the interfacial region, that is, at the surface of the micelle.[10] Such binding locations offer possibilities for hydrophobic interactions and avoid unfavorable disturbances of the interactions between the alkyl groups of the surfactant molecules in the core of the aggregate. The preferential binding of aromatic molecules at the micellar surface has been explained at least in part by the ability of the π-system of the molecule to form a weak hydrogen bond with water.[11]

Surfactant vesicles, like the systems based on spherical double layers, constitute a rather more realistic model of biological membranes than closed single-layer surfaces.[12] In fact, vesicles (or liposomes) have the bilayer structure of biological membranes and they have been proposed as possible precellular systems.[13] Vesicles share the ability of micelles to accelerate certain chemical reactions by trapping and concentrating the

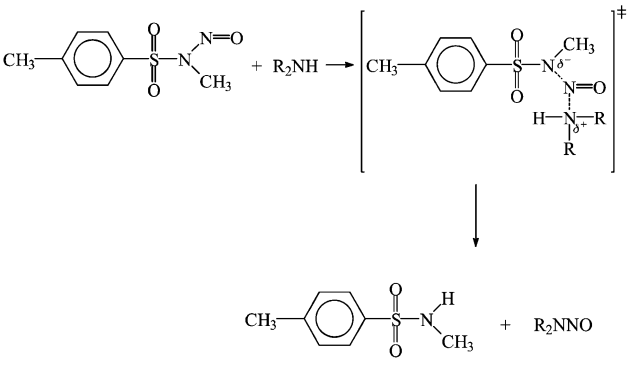
reagents.[6a,d] Vesicles are thermodynamic metastable aggregates and they can be obtained by different preparation methods.[14] The most widely used choices in this respect are sonication and ethanol injection methods, which yield small vesicles (diameter approximately in the range 30–50 nm).[15] Also extrusion methods[16] are used for the production of large unilamellar vesicles. Salt concentration and pH significantly control the degree of vesicle packing and hence vesicle size.[17] Vesicles formed by sonicating dialkylmethylammonium salts are stable over the range pH 1–13.[18]

The vesicles can inhibit chemical reactions encapsulating one of the reagents in the internal compartment,[19] or can catalyze reactions concentrating the reagents in the water–bilayer interface, acting as microreactors.[19,20] The catalytic capacity of the vesicles is greater than that of the micelles,[21] and depends on the size of the aggregate, which is greater for the small vesicles prepared by sonication than for the large vesicles prepared by chloroform injection.[22] The reason for this influence of the size of the vesicle on its catalytic activity is fundamentally that the degree of dissociation of the counterion of the vesicle[15b,21b] and its capacity to solubilize reagents[22] are affected by the size of the aggregate. In addition an adequate selection of the vesicular surfactant and the reagents enables us to find different reactivities in the internal and external interface,[19,23] observing in these cases biphasic kinetic behavior in which the permeation through the bilayer of one of the reagents is the determining stage of the reaction.

The influence of microemulsions on chemical reactivity has been studied to a lesser extent, mainly in those cases in which the reagents can be distributed throughout the different pseudophases of the system. In our laboratory we have developed a kinetic model based on the formalism of the pseudophase which has been applied satisfactorily to nitroso group transfer in microemulsions of AOT/isooctane/water.[24,25]

In the literature there exist doubts about the existence of a parallelism between the behavior observed in micelles and in microemulsions. The results obtained on studying the formation of 5-hexadecyl-7-methylindazole from 2,6-dimethyl-4-hexadecylbenzenediazonium tetrafluoroborate indicate that the interfacial basicity of cationic microemulsions is less than that which corresponds with the micellar systems of the same sign, considering that this property is due to the high concentration of counterions present in the interfacial zone in the microemulsions.[26] In the same way the studies carried out on micellar and vesicular systems indicate that the vesicular interface has a more hydrophobic character.[27] However this greater hydrophobic character does not always constitute a greater catalytic or inhibiting efficiency in these systems when they are compared with the micellar aggregates. Engberts and Rispens[28] observed greater catalytic efficiency for Diels–Alder reactions when micelles of $Cu(DS)_2$ were used than when vesicles of $Cu(dDP)_2$ were used. However the catalysis was observed for metallovesicles at lower concentrations than for metallomicelles, which is due to the lower critical vesicular concentration of $Cu(dDP)_2$ in comparison with the critical micellar concentration of $Cu(DS)_2$. As a result, hydrophobic microdomains are present at lower concentrations, to which both the diene and the dienophile can bind efficiently.

This article presents a comparative study of the reactivity in strongly differentiated three colloidal media: dodecyltrimethylammonium bromide micelles, microemulsions of sodium bis(2-ethylhexyl)sulfosuccinate (AOT)/isooctane/water and vesicles of dioctadecyldimethylammonium chloride (DODAC). For this study we have used a reaction of which we have wide experience, the nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) to secondary amines (Scheme 1). This reaction has been studied in our laboratory in an aqueous medium,[29] a micellar medium,[30] in non-aqueous solvents[31] and in microemulsions of AOT/isooctane/water.[24,25,32] The amines used, namely: morpholine (MOR),



Scheme 1

piperazine (PIP), dimethylamine (DMA) and piperidine (PIPER) were chosen on the basis of their hydrophobicity, basicity and reactivity in water against the nitroso group.[29a] Given that this reaction had already been studied previously in our laboratory in microemulsions of AOT/isooctane/water all we need do is reanalyze the results obtained to make them compatible with the distribution constants and reactivity constants obtained in the micellar systems.

The aim of the study will be to compare the sequences of reactivity observed in different colloidal systems. In this way we can obtain information about the specific properties presented by the interfaces of these three colloidal aggregates. The results obtained have shown parallel behavior in the different colloidal media studied.

Experimental

All reagents were Merck or Sigma-Aldrich products of the maximum commercially available purity. Amines (Aldrich) were purified by distillation under an argon atmosphere prior to use. DODAC (Fluka) was used as supplied. All aqueous solutions were prepared by weight using double-distilled water.

Reaction kinetics were recorded at 25 °C in a MILTON ROY SPECTRONIC 3000 diode array spectrophotometer equipped with thermostated cell carriers. The disappearance of the absorbance at 270 nm due to MNTS consumption was followed. The MNTS concentration (approximately 4×10^{-5} M) was always very much lower than the concentration of amine (0.1 M). The kinetic data always fitted the first-order integrated rate equation satisfactorily ($r > 0.999$), eqn. 1; in what follows, k_{obs} denotes the pseudo first order rate constant. For the reactions in vesicles, reagents were always added to the reaction cell in the same order: first the presonicated DODAC, followed by the solution providing MNTS, and finally the amine.

$$\ln(A_t - A_\infty) = \ln(A_o - A_\infty) - k_{obs}t \qquad (1)$$

DODAC vesicles were prepared by sonication.[18] Typically, 70–90 mg of solid DODAC were dispersed in 12–15 mL of water, sonicated for 25 min at 53–60 °C with a Branson 250 sonicator, centrifuged, and passed through a 0.45 μm filter to remove tip debris. Since the age of the vesicle preparations was found to affect the observed reaction kinetics, all reactions were carried out in vesicular media prepared within the preceding 6 hours. The effect of the age of the vesicle on kinetics is attributed to a gradual increase in the average size and polydispersity of the vesicle populations, a process which is accelerated by the presence of salts.[33]

The size and shape of vesicles depends on the duration of sonication and the temperature at which it is carried out. Turbidity measurements have shown that below 36 °C the DODAC double layer forms a continuous macroscopic sheet

at the surface of the aqueous medium rather than a dispersion of vesicles.[34] Sonication at higher temperatures gives rise to multicompartment vesicles which, if sonication is continued, split into smaller single-compartment vesicles. We characterized our preparations at 25 °C by performing dynamic light scattering measurements at scattering angles of 90° and 120° using Ar^+ laser irradiation ($\lambda = 514.5$ nm) and an ALV-5000 digital correlator. Correlation functions fitted by the CONTIN and cumulant methods[35] afforded hydrodynamic radius values of 200 Å at 90° and 120° and polydispersity values of 0.1–0.2; these values are in keeping with those reported by Fendler[20d] for single-compartment vesicles.

Turbidity measurements were carried out at 25 °C in a MILTON ROY SPECTRONIC 3000 diode array spectrophotometer equipped with thermostated cell carriers. The turbidity was monitored as a function of time following the changes in absorbance at $\lambda = 400$ nm.

Results and discussion

Nitroso group transfer in LTABr micelles

We studied the nitrosation reaction of various aliphatic amines: morpholine (MOR), piperazine (PIP), dimethylamine (DMA) and piperidine (PIPER), by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in the presence of micelles of LTABr (0–0.25 M) keeping constant the total amine concentration ($[R_2NH] \approx 0.25$ M). The addition of the surfactant in concentrations which are higher than its critical micellar concentration gives rise to an inhibition of the reaction (see Fig. 1). The influence of cationic micelles on the reaction rate can be quantitatively analyzed according to the model of the micellar pseudophase.[6,36] We assume that the presence of cationic micelles does not change the base ionization equilibria of the amine in water as we have done previously.[30c] Under these experimental conditions, Scheme 2 can be proposed.

In this scheme subscripts w and m indicate aqueous and micellar pseudophases, respectively, and D_n represents the micellized surfactant, that is $[D_n] = [D_T] - \text{cmc}$, where $[D_T]$ is the stoichiometric surfactant concentration and cmc the critical micelle concentration, obtained under the experimental conditions as the minimum surfactant concentration required to observe any kinetic effect (typical values being $(8–15) \times 10^{-3}$ M).

Scheme 2 considers the distribution of MNTS between the aqueous and micellar pseudophases, K_m^{MNTS}. This association constant has been previously obtained from studies of acid and basic hydrolysis of MNTS[30b] in micellar systems with a value of $K_m^{MNTS} = 132\ M^{-1}$. The distribution of the neutral form

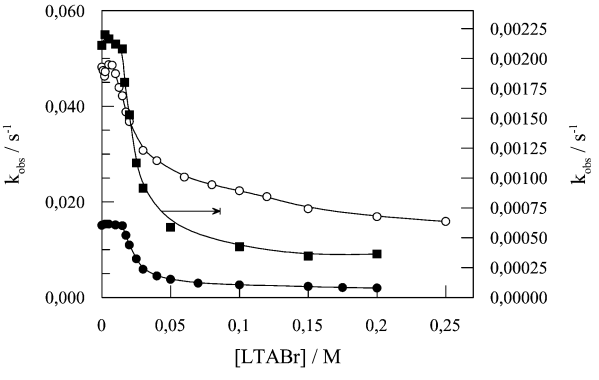
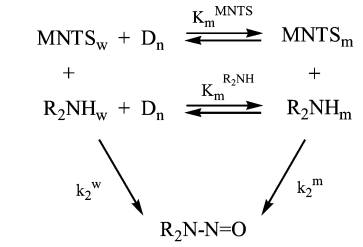


Fig. 1 Influence of LTABr micelles on the observed rate constant of nitrosation of piperidine (○, [PIPER] = 0.26 M, left axis), piperazine (●, [PIP] = 0.25 M, left axis) and morpholine (■, [MOR] = 0.27 M, right axis) by MNTS at 25 °C.



Scheme 2

of the amine, R_2NH, between both pseudophases is considered through the distribution constant $K_m^{R_2NH}$. The different reactivities in the aqueous and micellar pseudophases have been taken into account through the corresponding second order rate constants: k_2^w and k_2^m. The values of k_2^w have been obtained by studying the reaction in the absence of the surfactant and are compatible with those obtained previously in the presence of different quantities of organic cosolvent (acetonitrile or dioxane).[29a]

The amine concentration in the micellar pseudophase has been defined as the local, molar concentration within the micellar pseudophase: $[R_2NH]_m = [R_2NH]_m/[D_n]\bar{V}$, where $\bar{V}$ is the molar volume in $dm^3\ mol^{-1}$ of the reaction region and $[D_n]\bar{V}$ denotes the micellar fractional volume in which the reaction occurs. We assume $\bar{V}$ is equal to the partial molar volume of the interfacial reaction region in the micellar pseudophase, determined by Bunton[37] as 0.14 $dm^3\ mol^{-1}$. Micellar binding of both substrates, MNTS and R_2NH, is governed by hydrophobic interactions, and the equilibrium constants K_m^{MNTS} and $K_m^{R_2NH}$ are expressed by referring these concentrations to the total volume of the reaction mixture. The expression for the observed rate constant, k_{obs}, based on Scheme 1 and on the above considerations, is given by the following equation.

$$k_{obs} = \frac{k_2^w + \frac{k_2^m}{\bar{V}} K_m^{MNTS} K_m^{R_2NH}[D_n]}{(1 + K_m^{MNTS}[D_n])(1 + K_m^{R_2NH}[D_n])}[R_2NH]_T \qquad (2)$$

Second order rate constants at the micellar interface and association constants of the neutral form of the amine to LTABr micelles were obtained by fitting eqn. 2 to the experimental data.

Fig. 2 shows the correspondence of the experimental data to the rate equation rewritten in the following form for the

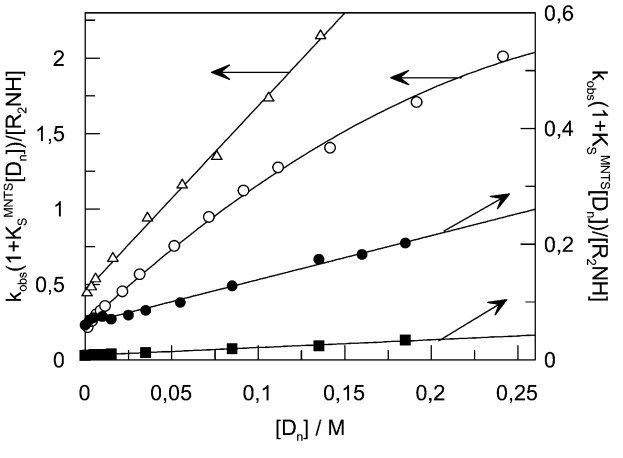


Fig. 2 Fitting of experimental data for nitrosation of piperidine (○, [PIPER] = 0.26 M, left axis), piperazine (●, [PIP] = 0.25 M, right axis), dimethylamine (△, [DMA] = 0.09 M, left axis) and morpholine (■, [MOR] = 0.27 M, right axis) by MNTS in LTABr micelles at 25 °C according to eqn. 3.

nitrosation of piperidine

$$\frac{k_{obs}(1+K_m^{MNTS}[D_n])}{[R_2NH]_T}=\frac{k_2^w+\frac{k_2^m}{V}K_m^{MNTS}K_m^{R_2NH}[D_n]}{1+K_m^{R_2NH}[D_n]} \quad (3)$$

using the value of $K_m^{MNTS}=132\ M^{-1}$ previously obtained. From this fit we obtain a value of $k_2^w=(0.21\pm0.1)\ M^{-1}\ s^{-1}$ which is compatible with the value obtained previously in an aqueous medium.[29a] Likewise we obtain a value of $K_m^{R_2NH}=(2.6\pm0.3)M^{-1}$ for the incorporation of the piperidine into the micelles of LTABr and $k_2^m=5.0\times10^{-3}\ M^{-1}\ s^{-1}$. This value of k_2^m indicates that the reaction rate in the micelle is 42 times lower than in the aqueous medium, a result which is compatible with the expected polarity for the interface of the micelle of LTABr and for the solvent effect on the rate of nitrosation of amines by MNTS.[29a,31b]

The behavior observed for the nitrosation of morpholine, dimethylamine and piperazine is slightly different. As we can observe in Fig. 2 the representation of

$$K_{oi}^A=\frac{[A]_i}{[A]_o}Z \qquad K_{oi}^B=\frac{[B]_i}{[B]_o}Z$$

$$K_{wi}^A=\frac{[A]_i}{[A]_w}W \qquad K_{wi}^B=\frac{[B]_i}{[B]_w}W$$

vs. $[D_n]$ is perfectly linear. In the denominator of rate eqn. 3 the term which corresponds to the association constant of the unprotonated amine to the LTABr micelles, $K_m^{R_2NH}$, does not appear because, as will be seen,[38] the value which can be estimated for that equilibrium constant turns out to be very small. This means that the amount of micellar-bound amine is stoichiometrically negligible with respect to the total amine, although this small amount has kinetic relevance. In this way eqn. 3 can be simplified as:

$$\frac{k_{obs}(1+K_m^{MNTS}[D_n])}{[R_2NH]_T} \quad (4)$$

Fig. 2 shows by way of example the fulfilment of eqn. 4 for the nitrosation of morpholine, dimethylamine and piperazine by MNTS, obtaining the values of $k_2^w=(8.0\pm0.5)\times10^{-3}\ M^{-1}\ s^{-1}$; $k_2^w=(6.3\pm0.2)\times10^{-2}\ M^{-1}\ s^{-1}$ and $k_2^w=(4.5\pm0.1)\times10^{-1}\ M^{-1}\ s^{-1}$ for the nitrosation of morpholine, piperazine and dimethylamine respectively, which are compatible with those obtained previously in an aqueous medium.[29a] Likewise we obtain for the product $k_2^mK_m^{R_2NH}$ the values $k_2^mK_m^{R_2NH}=1.4\times10^{-4}\ M^{-2}\ s^{-1}$; $k_2^mK_m^{R_2NH}=8.1\times10^{-4}\ M^{-2}\ s^{-1}$ and $k_2^mK_m^{R_2NH}=1.3\times10^{-2}\ M^{-2}\ s^{-1}$ for morpholine, piperazine and dimethylamine respectively. Table 1 shows the results obtained for the different kinetic parameters in the nitrosation of amines by MNTS in micelles of LTABr.

The results presented in Table 1 allow us to study the influence of the nature of the amine on the product $k_2^mK_m^{R_2NH}$ for the nitrosation of amines by MNTS in micelles of LTABr. The product $k_2^mK_m^{R_2NH}$ presents the following sequence 93:93:6:1 for piperidine, dimethylamine, piperazine and morpholine respectively. These values present a sequence in parallel with that found in water, however they behave differently from the reactivity sequence in the aqueous medium, k_2^w, 26:56:8:1 for the same amines. Whereas in water the transfer of the nitroso group from the MNTS to the piperidine is 26 times faster than when the least reactive amine is involved, in micelles this difference in reactivity increases by 3.6 times. This increase in reactivity in the micellar medium with regard to the aqueous medium is only 1.6 times that for dimethylamine. However there are no divergences in the case of the piperazine.

Table 1 Kinetic parameters obtained by applying the pseudophase model for the nitroso group transfer from MNTS to different amines in presence of LTABr micelles and DODAC vesicles[a]

Amine	k_2^w/ $M^{-1}\ s^{-1}$	k_2^m/ $M^{-1}\ s^{-1}$	$K_m^{R_2NH}$/ M^{-1}	$k_2^mK_m^{R_2NH}$/ $M^{-2}\ s^{-1}$	$k_2^vK_v^{R_2NH}$/ $M^{-2}\ s^{-1}$
Piperidine	2.1×10^{-1}	5.0×10^{-3}	2.6	1.3×10^{-2}	4.8×10^{-1}
Dimethylamine	4.5×10^{-1}	—	—	1.3×10^{-2}	4.6×10^{-1}
Piperazine	6.3×10^{-2}	—	—	8.1×10^{-4}	2.4×10^{-2}
Morpholine	8.0×10^{-3}	—	—	1.4×10^{-4}	4.9×10^{-3}

[a] $K_m^{MNTS}=132\ M^{-1}$; $K_v^{MNTS}=380\ M^{-1}$.

Stability of vesicles

A very important aspect to take into account when dealing with vesicles as a reaction medium is their stability and the behavior which they will exhibit towards the reagents added to the medium. When an additive is added to a vesicle obtained by sonication, passive transport of water as well as substrates will occur with the purpose of compensating the slopes of the concentration which prevail between the internal water and the external water of the system. In fact it is known that the vesicles obtained from DODAC present ideal osmotic behavior.[39] Due to the osmotic gradient, when a reagent is added which does not have a permeable membrane, there will be a reduction in the vesicular size. This reduction of a medium size constitutes an increase in the turbidity of the system (measured by means of spectrophotometry at $\lambda=400$ nm). Keeping in mind that the membranes of the DODAC are impermeable to molecules such as urea or sucrose,[39] it is possible that this same problem of stability of the vesicle would prevail in our experimental conditions, in which the vesicle is subjected to an important osmotic slope through the addition of appreciable concentrations of amine.

In the presence of amine we have observed an increase in the turbidity of the system. An increase in the turbidity can be attributed to the breakage/rupture of the vesicles or to the fusion of the vesicles or to the possible fragments of bilayer present in the sonicated medium.[39] The increase in turbidity is greater when the concentration of DODAC present in the medium is greater. However in all cases we have observed a period of induction which is greater than or equal to 9–10 minutes, for which no quantifiable variations were observed in the turbidity of the system.

To illustrate the behavior observed, and by way of example, Figs. 3 and 4 show the increase in absorbance at 400 nm which corresponds with vesicles of DODAC in the presence of two amines: dimethylamine (Fig. 3) and piperidine (Fig. 4). Similar behavior has been found for the rest of the studied amines. The

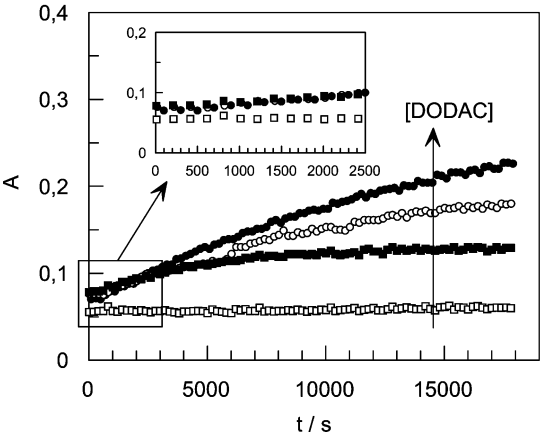


Fig. 3 Turbidity measurements of DODAC vesicles in the presence of dimethylamine, [DMA] = 0.1 M, $T=25.0\,^{\circ}C$. (●) [DODAC] = 7.00×10^{-3} M; (○) [DODAC] = 5.60×10^{-3} M; (■) [DODAC] = 4.00×10^{-3} M and (□) [DODAC] = 2.00×10^{-3} M.

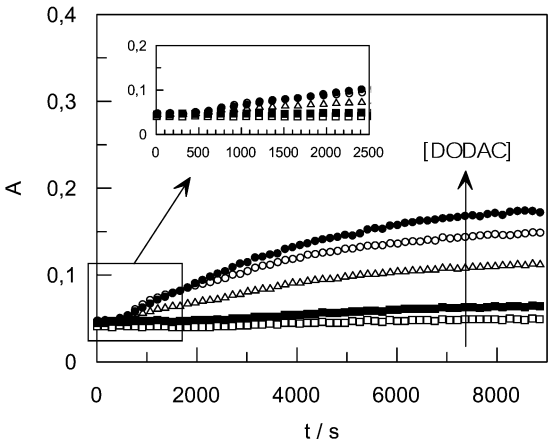


Fig. 4 Turbidity measurements of DODAC vesicles in the presence of piperidine, [PIPER] = 0.1 M, T = 25.0 °C. (●) [DODAC] = 7.00×10^{-3} M; (○) [DODAC] = 6.40×10^{-3} M; (■) [DODAC] = 4.40×10^{-3} M; (△) [DODAC] = 4.00×10^{-3} M and (□) [DODAC] = 3.60×10^{-3} M.

observed results allow us to optimize the conditions of the reaction to obtain a reaction half life at least 5 times shorter that this induction period to ensure that there is no influence of turbidity upon the absorbance/time data.

Nitroso group transfer in DODAC vesicles

The effect of the presence of DODAC vesicles on the nitrosation of amines by MNTS was studied at constant amine concentration (typically $[R_2NH] = 0.10$ M) and DODAC concentrations ranging from 0 to 6.30×10^{-3} M. Unlike the behavior detected in micelles of LTABr, the values of the rate constant observed, k_{obs}, rose with DODAC concentration in all cases (see Figs. 5–6).

To carry out a quantitative interpretation of the experimental results we should take into account the formalism of the pseudophase, while bearing in mind that the rate of transmembrane equilibration of fairly low molecular weight hydrophobic substrates (such as both amine and MNTS) is fast in relation to the time scale of the transnitrosation reaction. This high mobility of both MNTS and amine inside the DODAC bilayer means that the permeation of one of these reagents will never be the rate-determining step of the reaction and hence our system will be under chemical control. In this case, inner and outer reaction (bulk water and intravesicular water) cannot be discriminated. This leads to a pure monophasic chemical process similar to that observed in LTABr micelles.

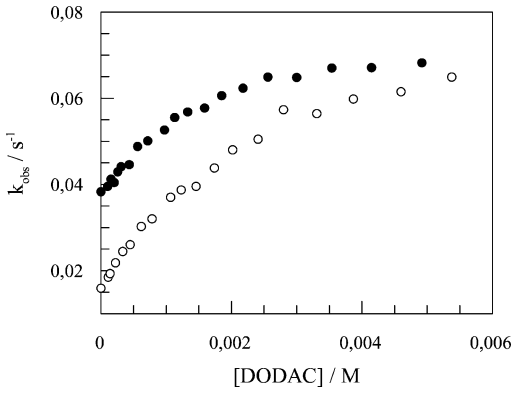


Fig. 5 Influence of DODAC vesicles on the observed rate constant of nitrosation of dimethylamine (○, [DMA] = 0.10 M) and piperidine (●, [PIPER] = 0.10 M) by MNTS at 25 °C.

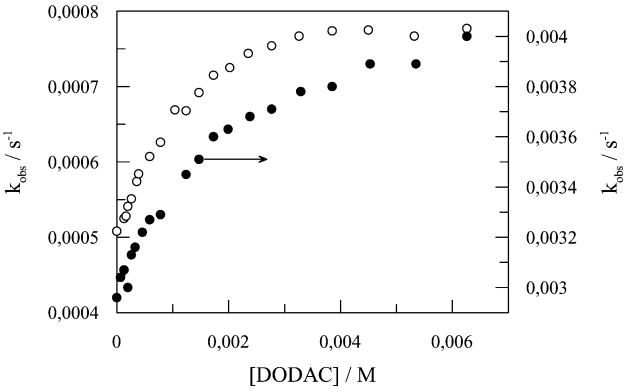


Fig. 6 Influence of DODAC vesicles on the observed rate constant of nitrosation of morpholine (○, [MOR] = 0.10 M, left axis) and piperazine (●, [PIP] = 0.10 M, right axis) by MNTS at 25 °C.

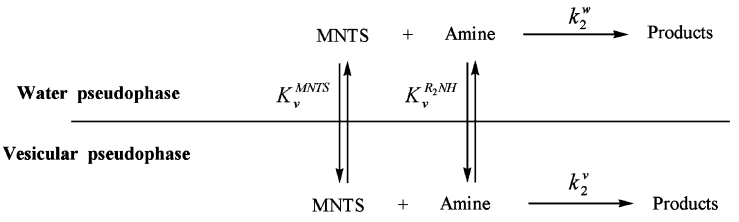
The application of the formalism of the pseudophase in combination with the mass action model (Scheme 3) allows us to obtain the following rate equation which is analogous with that obtained for micelles of LTABr.

$$\frac{k_{obs}(1 + K_m^{MNTS}[D_n])}{[R_2NH]_T} = k_2^w + \frac{k_2^m}{\bar{V}} K_m^{MNTS} K_m^{R_2NH}[D_n] \quad (5)$$

In order to obtain this equation we have assumed that the distribution of the amine between the two pseudophases (DODAC film and both bulk aqueous medium and intravesicular compartment) is governed by the association equilibrium constant, $K_v^{R_2NH}$. The nitrosating agent, MNTS, presents a similar distribution equilibrium k_v^{MNTS}, and the reaction will be able to take place simultaneously in the aqueous pseudophase, k_2^w, and the vesicular pseudophase, k_2^v. The vesicular concentration of the amine has been defined as the local concentration within the vesicular pseudophase: $[R_2NH]_v = [R_2NH]_v/[DODAC]\bar{V}$, where $\bar{V}$ is the molar volume in dm^3 mol^{-1} of the reaction region and $[DODAC]\bar{V}$ denotes the vesicular fractional volume in which the reaction occurs. We assume $\bar{V}$ is equal to the partial molar volume of the interfacial reaction region in the vesicular pseudophase (0.54 dm^3 mol^{-1}).[21b,22]

For the application of eqn. 5 to the experimental results we will consider that all the DODAC in the medium was incorporated in vesicles, although there is a surfactant concentration (critical vesicular concentration, cvc) threshold, somewhere in the range $(4–8) \times 10^{-6}$ M,[40] below which vesicles do not form, much lower than typical values of critical micellar concentration (cmc). Its threshold is not, like the cmc of micellar media, the result of a dynamic equilibrium between free and vesicular surfactant; once formed, vesicles are not destroyed by dilution, and have, in fact, been detected at surfactant concentrations as low as 10^{-8} M,[41] which is far below the concentrations used in this work. For this reason, in the case it would be a good approximation that $[D_n]$ is equal to the total DODAC concentration.

This expression predicts that k_{obs} increases with DODAC concentration until all the reagents are incorporated in the DODAC bilayer, after which the value of the observed rate constant, k_{obs}, will fall due to the dilution of reactive species among an excess of vesicles. Although no clear fall in at high DODAC concentrations was observed experimentally (it was not possible to use DODAC concentrations greater than 7×10^{-3} M because of the appearance of turbidity, due to fusion of vesicles). For the fitting procedure the value of k_v^{MNTS} was kept constant and equal to the value of $k_v^{MNTS} = 380$ M^{-1} obtained in previous works from the basic and acid hydrolysis of MNTS in this medium and



Scheme 3

by spectroscopic techniques.[42] In this way eqn. 5 can be rewritten as:

$$k_{obs} = \frac{k_2^w + \frac{k_2^v}{V} K_v^{MNTS} K_v^{R_2NH}[DODAC]}{(1 + K_v^{R_2NH}[DODAC])(1 + K_v^{MNTS}[DODAC])}[R_2NH]_T \quad (6)$$

The representation of $k_{obs}(1 + K_v{}^{MNTS}[DODAC])/[R_2NH]_T$ *vs.* [DODAC] presents a perfectly linear dependence for all the amines studied (see Figs. 7 and 8). The existence of this linear dependence is a consequence of the fact that $1 \gg K_v{}^{R_2NH}$ [DODAC], in such a way that eqn. 6 can be simplified to:

$$\frac{k_{obs}(1 + K_v^{MNTS}[DODAC])}{[R_2NH]_T} = \frac{k_2^w + \frac{k_2^v}{V} K_v^{MNTS} K_v^{R_2NH}[DODAC]}{(1 + K_v^{R_2NH}[DODAC])} \quad (7)$$

From the fit of eqn. 7 to the experimental data we obtain the values of $k_2{}^w$ and of the product $k_2{}^v K_v{}^{R_2NH}$ which are shown in Table 1. It is important to point out that in all cases the value of $k_2{}^w$ is analogous to that observed previously in an aqueous medium.

The experimental results obtained show the existence of a strong parallelism between the vesicles of DODAC and the micelles of LTABr. The fact that $1 \gg K_v{}^{R_2NH}[DODAC]$ seems contradictory with the results existing in the literature which indicate that the vesicular interfaces are more hydrophobic than the micellar interfaces. In accordance with this observation it is necessary to check that $K_v{}^{R_2NH}$ should be greater than its analogue for the association of amines to micelles, $K_m{}^{R_2NH}$. This result seems to contradict the fact that for the nitrosation of piperidine in vesicles it follows that $1 \gg K_v{}^{R_2NH}$ [DODAC], whereas in micellar systems this approximation is not correct (see previous discussion and Fig. 2). The behavior observed experimentally in this study is justified on the basis of the lowest concentration of DODAC which can be reached in comparison with [LTABr]. In fact we have previously obtained for the association constant of piperidine at micelles of LTABr a value of $K_m{}^{R_2NH} = (2.6 \pm 0.3)\ M^{-1}$. The more hydrophobic character of DODAC must cause an increase in $K_v{}^{R_2NH}$ in comparison with $K_m{}^{R_2NH}$, in such a way that we could suppose that $K_v{}^{R_2NH} \approx 10\ M^{-1}$. However, even with this value of $K_v{}^{R_2NH}$ we would have $1 \gg K_v{}^{R_2NH}[DODAC]$ since the maximum [DODAC] which we can reach is [DODAC] $\approx 6.0 \times 10^{-3}$ M.

We have obtained the following values for the product $k_2^v K_v{}^{R_2NH}$ for nitroso group transfer from MNTS to piperidine, $k_2{}^v K_v{}^{R_2NH} = 0.48\ M^{-2}\ s^{-1}$; dimethylamine, $k_2{}^v K_v{}^{R_2NH} = 0.46\ M^{-2}\ s^{-1}$; piperazine, $k_2{}^v K_v{}^{R_2NH} = 2.4 \times 10^{-2}\ M^{-2}\ s^{-1}$ and morpholine $k_2{}^v K_v{}^{R_2NH} = 4.9 \times 10^{-3}\ M^{-2}\ s^{-1}$. If we compare the relative values of the rate of nitrosation of these amines by MNTS in water we obtain a reactivity sequence: PIPER:DMA:PIP:MOR (reactivity sequence 26:56:6:1), while on comparing the product $k_2{}^v K_v{}^{R_2NH}$ we obtain 98:95:4.8:1 for the same amines. The absence of parallelism must be due to the different association constants of the amines at the DODAC vesicle, in such a way that piperidine will present a value of $K_v{}^{R_2NH}$ superior to that of DMA while piperazine will present a value of $K_v{}^{R_2NH}$ which is slightly lower. This sequence of association constants must be parallel to the hydrophobicity of the amines such as we observe in micelles of LTABr and in microemulsions of AOT/isooctane/water.

The values of $k_2{}^v K_v{}^{R_2NH}$ obtained in vesicles of DODAC can be compared with the analogous values obtained in micelles of LTABr, $k_2{}^m K_m{}^{R_2NH}$. The values obtained for the quotient $k_2{}^v K_v{}^{R_2NH}/k_2{}^m K_m{}^{R_2NH}$ for the nitrosation of piperidine, dimethylamine, piperazine and morpholine are 37:35:29:35 respectively. These values indicate that there exists a parallelism between the behavior in micellar systems and vesicular systems. The difference in behavior can be attributed for the most part to the difference between the values of the

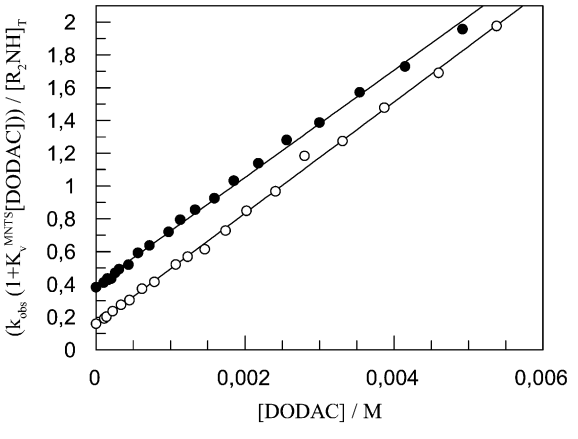


Fig. 7 Fitting of experimental data for nitrosation of piperidine (○, [PIPER] = 0.10 M) and dimethylamine (●, [DMA] = 0.10 M) by MNTS in DODAC vesicles at 25 °C according to eqn. 7.

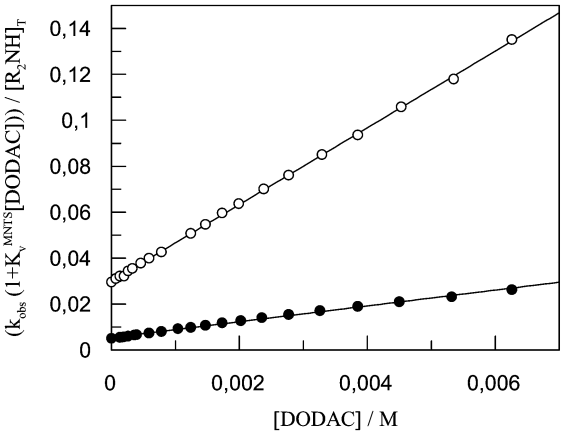


Fig. 8 Fitting of experimental data for nitrosation of piperazine (○, [PIP] = 0.10 M) and morpholine (●, [MOR] = 0.10 M) by MNTS in DODAC vesicles at 25 °C according to eqn. 7.

association constants of the amines at the vesicular and micellar interphases. It is to be expected that $K_v^{R_2NH}$ in vesicles of DODAC would be greater than $K_m^{R_2NH}$ in micelles of LTABr, due to the greater length of the hydrocarbon chain of DODAC (18 carbon atoms) *vs.* LTABr (12 carbon atoms). In fact in micellar systems it can be observed that the association constant of MNTS at the micelles increases three times as the length of the hydrocarbon chain of the tensioactive increases from 12 carbon atoms (LTABr) to 18 carbon atoms (OTACl). Likewise this difference should increase as a consequence of the existence of a double hydrocarbon chain in DODAC against the simple chains present in micellar systems based on quaternary ammonium salts. The existence of parallel behavior for $k_2^v K_v^{R_2NH}/k_2^m K_m^{R_2NH}$ indicates that the properties of the micellar interphase of LTABr and the vesicular interphase of DODAC are parallel.

Nitroso group transfer in AOT/isooctane/water microemulsions

The nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) to several amines has been studied previously in AOT/isooctane/water microemulsions.[24] However, and for the purpose of comparison, it is necessary to recalculate the distribution constants of the amines between the different pseudophases. The application of the formalism of the pseudophase allows us to explain the reactivity in microemulsions considering the existence of three well differentiated microenvironments: a continuous medium formed by the alkane, an aqueous microdroplet and an interphase or tensioactive film which separates both microenvironments. For any general reaction, A + B → Products, we can obtain a reaction scheme like that which is shown below (Scheme 4) for which we assume that the distribution of the reagents throughout the different pseudophases is governed by distribution constants for the incorporation of the reagents from the continuous medium, oil, to the interphase: K_{oi}^A and K_{oi}^B, and by distribution constants for the incorporation of the reagents from the aqueous medium to the interphase: K_{wi}^A and K_{wi}^B. If the reagents are distributed throughout the different pseudophases of the system we can assume that the reaction can occur simultaneously in the continuous medium, the interphase and the aqueous medium with rate constants: k_2^0, k_2^i and k_2^w respectively. From these considerations we can obtain the following expression for the rate of the reaction assuming that $\bar{V}_o$, $\bar{V}_i$ and $\bar{V}_w$ are the molar volumes of the oil, the interphase and the water respectively:

$$\frac{k_{obs}(1+K_v^{MNTS}[DODAC])}{[R_2NH]_T} = k_2^w + \frac{k_2^v}{\bar{V}} K_v^{MNTS} K_v^{R_2NH} [DODAC] \quad (8)$$

where W and Z are the molar relationships $W = [H_2O]/[AOT]$ and $Z = [\text{isooctane}]/[AOT]$ and where the distribution constants have been defined thus:

$$\text{rate} = \frac{\frac{k_2^i}{\bar{V}_i} + \frac{\frac{k_2^w}{\bar{V}_w} W}{K_{wi}^A K_{wi}^B} + \frac{\frac{k_2^o}{\bar{V}_o} Z}{K_{oi}^A K_{oi}^B}}{\left(1 + \frac{W}{K_{wi}^A} + \frac{Z}{K_{oi}^A}\right)\left(1 + \frac{W}{K_{wi}^B} + \frac{Z}{K_{oi}^B}\right)} \frac{[A]_T[B]_T}{[AOT]}$$

Therefore, although the rate constants in the pseudophases of the microemulsion are directly comparable with the rate constants in an aqueous, micellar or vesicular medium, the distribution constants between the pseudophases of the microemulsion and the micellar or vesicular systems are not. To make these constants compatible we must take into account that

$$K_{wi}^A = \frac{[A]_i}{[A]_w} \frac{[H_2O]}{[AOT]}$$

and that

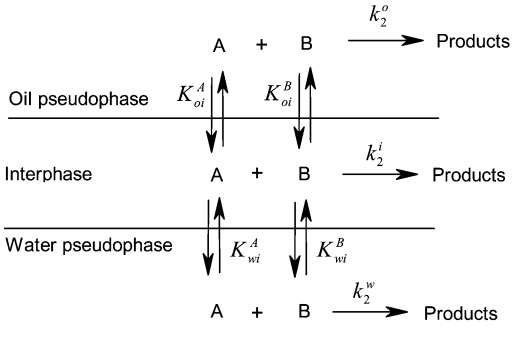
$$K_m^A = \frac{[A]_m}{[A]_w} \frac{1}{[LTABr]}$$

in such a way that for the purpose of comparison we could write[43] $K_{wi}^A = [H_2O]K_m^A$. The values of the equilibrium constants are not directly comparable since the tensioactives do not have the same structure (LTABr, DODAC and AOT) and the properties of the microenvironments of a microemulsion, whether micellar or vesicular, are the same. However, it would be interesting to compare sequences of rate constants as the nature of the amine varies and so determine its possible repercussions on the rate constants of the interphases.

Table 2 shows the equilibrium constant for the distribution of the different amines and MNTS written in the form $K_{wi}^A/[H_2O]$ and $K_{oi}^A/[\text{isooctane}]$, as well as the rate constants obtained for nitroso group transfer in the interphase. Likewise the said table also shows the values of the product $K_{wi}^A k_2^i/[H_2O]$ with the aim of comparing it with $K_m^{R_2NH} k_2^m$ and $K_v^{R_2NH} k_2^v$.

We can obtain the quotient $K_v^{R_2NH} k_2^v/(K_{wi}^{R_2NH}/[H_2O])k_2^i$ for the nitrosation of dimethylamine, piperazine and morpholine as 20:26:24 respectively. Likewise as the analogous quotient for comparing the reactivity between microemulsions and micelles, $K_m^{R_2NH} k_2^m/(K_{wi}^{R_2NH}/[H_2O])k_2^i$ allows us to obtain values of 0.5:0.9:0.7 for these same amines respectively. The results obtained indicate that the greatest kinetic effect is observed for the vesicles of DODAC, and the effect produced by the LTABr micelles and the microemulsions of AOT/isooctane/water is very similar.

The existence of a parallelism between the quotients $K_v^{R_2NH} k_2^v/(K_{wi}^{R_2NH}/[H_2O])k_2^i$; $K_m^{R_2NH} k_2^m/(K_{wi}^{R_2NH}/[H_2O])k_2^i$ and $K_v^{R_2NH} k_2^v/K_m^{R_2NH} k_2^m$ indicates that the effect produced by the micellar interphases of the LTABr, vesicles of DODAC and microemulsions of AOT on the transfer reactivity of the nitroso group to/at amines is similar. As has been discussed previously the experimental conditions have not allowed us to obtain the values of the bimolecular rate constants in the micellar and vesicular interphases, but to obtain its product with the association constant of the amine to/at the said interphases. In the case of the microemulsions of AOT/isooctane/water the experimental conditions have allowed us to obtain the values of k_2^i which can be compared with the values obtained for the same reaction in an aqueous medium, k_2^w. The conclusions reached on the basis of this comparison will be able to be extrapolated to the micellar and vesicular systems since the constancy of comparing values of the products of $k_2^m K_m^{R_2NH}$; $k_2^v K_v^{R_2NH}$ and $k_2^i K_{wi}^{R_2NH}/[H_2O]$ has been verified. The relationship k_2^w/k_2^i is the same at 20; 70; 27; 12; 41 and 33 for the nitrosation of pyrrolidine, piperidine, dimethylamine, piperazine, *N*-methylbenzylamine



Scheme 4

Table 2 Kinetic parameters obtained by applying the pseudophase model for nitroso group transfer from MNTS to different amines in AOT/isooctane/water microemulsions. Data from ref. 24

Amine	$k_2^w/M^{-1}\ s^{-1}$	$K_{wi}^A/[H_2O]^a$	$K_{oi}^A/[isooctane]^a$	$k_2^i/M^{-1}\ s^{-1}$	$K_{wi}^A k_2^i/[H_2O]^b$
Pyrrolidine	0.83	0.15	20.7	4.22×10^{-2}	6.33×10^{-3}
Piperidine	2.1×10^{-1}	—	4.25	3.0×10^{-3}	
Dimethylamine	4.3×10^{-1}	1.5	13.8	1.6×10^{-2}	2.4×10^{-2}
N-Methylbenzylamine	4.1×10^{-2}	—	4.23	1.00×10^{-3}	
Piperazine	6.3×10^{-2}	0.17	—	5.33×10^{-3}	9.06×10^{-4}
Morpholine	8.0×10^{-3}	0.84	33.1	2.4×10^{-4}	2.02×10^{-4}

[a] M^{-1}. [b] $M^{-2}\ s^{-1}$.

and morpholine respectively. Within this reactivity sequence we can distinguish three types of behavior: piperazine (the least hydrophobic amine) presents an inhibition of 12 times, *N*-methylbenzylamine and piperidine (the most hydrophobic amines) present an inhibition of 41 and 70 times respectively, while for the amines with intermediate hydrophobicity (pyrrolidine, dimethylamine and morpholine) the inhibition observed is approximately 25 times in all cases.

This hydrophobic/hydrophilic balance with the distribution of the amines is found throughout the different pseudophases of the microemulsion. In this way the piperazine is distributed solely between the aqueous microdroplet and the interphase, whereas piperidine and *N*-methylbenzylamine will be found to be distributed between the continuous medium and the interphase of the microemulsion. The other three amines are found to be distributed throughout the three pseudophases of the system. The different distributions of the amines throughout the system will give rise to different zones of residence within the interphase of the microemulsion: the most hydrophobic amines will be in nearer to the head groups in a more hydrated medium, and therefore the decrease in the rate with respect to the aqueous medium will be small. The most hydrophobic amines (*N*-methylbenzylamine and piperidine) will be found in an interfacial zone nearer to the continuous medium where the hydration will be less. Consequently the inhibition with regard to the aqueous medium will be lower. The amines with intermediate hydrophobicity will be distributed between the former in such a way as to make their kinetic behavior intermediate.

Conclusions

The behavior observed for nitroso group transfer from MNTS to different secondary amines in micelles of LTABr has been explained by means of the application of the formalism of the micellar pseudophase. The obtained values for the product of the rate constant in the micellar pseudophase with the association constant of the amines at the micelle, $k_2^m K_m^{R_2NH}$, do not present the same sequence of behavior as for the reactivity in an aqueous medium, k_2^w. This apparent anomaly may be due to the different values of $K_m^{R_2NH}$. If we suppose that the inhibiting effect caused by the polarity between the micellar interphase and the aqueous medium is constant for all the amines studied, we would find a sequence of values of $K_m^{R_2NH}$ 3.5:1.6:0.7:1 for piperidine, dimethylamine, piperazine and morpholine. This behavior would be parallel to the hydrophobicities, where piperidine is the most hydrophobic amine of those studied and piperazine is the most hydrophilic, with dimethylamine and the morpholine possessing similar hydrophobicities.

The study of nitroso group transfer in DODAC vesicles shows different experimental behavior in which the observed rate constant increases as the concentration of DODAC increases until a limit value is reached. This experimental behavior has been explained by means of the application of the formalism of the pseudophase in an analogous way to that obtained in LTABr micelles. The obtained values for $k_2^v K_v^{R_2NH}$ show different behavior which is parallel with that obtained in micelles of LTABr. In fact the quotient $k_2^v K_v^{R_2NH}/k_2^m K_m^{R_2NH}$ is practically constant and independent of the nature of the amine, with a value in the region of 35. This behavior is consistent with the interphase of the vesicle being more hydrophobic than that of the micelles.

To compare these experimental results with those obtained previously in microemulsions of AOT/isooctane/water it is necessary to obtain the product of the bimolecular rate constant at the interphase of the microemulsion with the distribution constant of the reagents from water to the interphase, which has been defined in the same way as in micellar systems: $k_2^i K_{wi}^{R_2NH}/[H_2O]$ (analogous with the product $k_2^m K_m^{R_2NH}$ in micellar systems or $k_2^v K_v^{R_2NH}$ in vesicular systems). The relative values of $K_v^{R_2NH} k_2^v/(K_{wi}^{R_2NH}/[H_2O])k_2^i$ for the nitrosation of dimethylamine, piperazine and morpholine are approximately constant and in the region of 23. These values indicate than the interphase of the microemulsion will be less hydrophobic than the vesicular interphase and more hydrophobic than that of the micelles of LTABr. The comparison of the bimolecular rate constants at the interphase of the microemulsion and in the aqueous medium, k_2^w/k_2^i, shows three types of behavior which are well differentiated according to the hydrophobicity of the amines, which reflect the amine localization in different zones of the interphase of the microemulsion. These zones of the interphase of the microemulsion will have different polarities and consequently will give rise to different effects on the rate of the reactions.

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38 If we assume that the quotient k_2^{w}/k_2^{m} takes the same value for the nitrosation of piperidine, piperazine and morpholine by MNTS, we can estimate the value of $K_m^{R_2NH}$ for the last two amines using the values of $k_2^{m}K_m^{R_2NH} = 1.4 \times 10^{-4}$ M^{-2} s^{-1} and $k_2^{m}K_m^{R_2NH} = 8.1 \times 10^{-4}$ M^{-2} s^{-1}. The values obtained for $K_m^{R_2NH}$ are $K_m^{R_2NH} \approx 0.73$ M^{-1} and $K_m^{R_2NH} \approx 0.54$ M^{-1} for morpholine and piperazine respectively. These values mean that the product $K_m^{R_2NH}[D_n]$ is always lower that 0.18 in such a way as for it to be compatible with the simplification of eqn. 3.

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