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Reactive micelles: nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide to amphiphilic amines†

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ABSTRACT: The reactivity of *N*-methyl-*N*-nitroso-*p*-toluene sulfonamide (MNTS) towards n-alkylamines in water and in micellar aggregates was studied. Kinetic constants in both media were obtained. The pseudophase micellar model allows a satisfactory prediction of the experimental behaviour in all cases. The value obtained for the micellar pseudophase rate constant, k_2^i, is lower than that in bulk water. The increase in the observed rate constant, k_o, with n-alkylamine concentration is due to an increase in the local concentration of reactants in the micellar surface. The differences between k_w and k_2^i values is due to the polarity of micellar pseudophase being lower than that in bulk water. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: alkylamine; micelle; nitrosation; transnitrosation; catalysis

INTRODUCTION

The chemistry of the nitroso compounds is of great interest due to their toxic, carcinogenic, mutagenic and teratogenic properties[1,2] in many animal species.[3] In particular, since the discovery that *N*-nitrosamines are powerful carcinogenic agents in all the animal species in which they have been tested, the nitrosation of secondary and tertiary amines has been widely studied. From this point of view, the transfer of the nitroso group from nitroso group donors to nitroso group acceptors is of great relevance because non-carcinogenic nitroso compounds are able to generate the more dangerous nitrosamines. Under physiologic conditions where these reactions can be catalysed or inhibited transnitrosation reactions are the most important processes.

An interesting use of micellar aggregates is the modulation of chemical reactivity. The reaction rates and equilibrium constants in micellar media can differ from the values in bulk water. These differences in reactivity can be attributed to the solubility of reactants and products, distribution of reactants in different regions at the microheterogeneous medium and different physicochemical properties in the *loci* of reaction as compared with bulk water. Kinetic studies in these systems are interpreted on the basis of the pseudophase model.[4] This model assumes that the different components of the reaction media (bulk water and micellar aggregates) are distributed among different pseudophases in which the reaction takes place. Such a model allows us to explain a large number of kinetic experiments,[5] with the simply assumption of reactive distribution between the pseudophases.

The long chain alkylamines are able to form micellar aggregates in aqueous solutions. This property allows us to study the reactivity of a chemical system where the surfactant is one of the reagents. The alkylamines studied were *N*-methylethylamine (MEA), *N*-methylbutylamine (MBA), n-hexylamine (HA), *N*-methylhexylamine (MHA), *N*,*N*-dimethylhexylamine (DMHA), n-octylamine (OA), *N*-methyloctylamine (MOA), *N*,*N*-dimethyloctylamine (DMOA) and *n*-decylamine (DA).

RESULTS AND DISCUSSION

Critical micelle concentration of n-alkylamines

The critical micelle concentration (*cmc*) of n-alkylamine solutions has been determined using electrical conductivity. Figure 1 shows a typical plot of electrical conductivity vs [amine]. Table 1 shows the *cmc* values obtained for primary, secondary and tertiary amines studied. The *cmc* value decreases by increasing the chain length of alkylamine. In the same way, the *cmc* value decreases by increasing the number of methyl groups in the head group (amine group) with a constant chain length. It is

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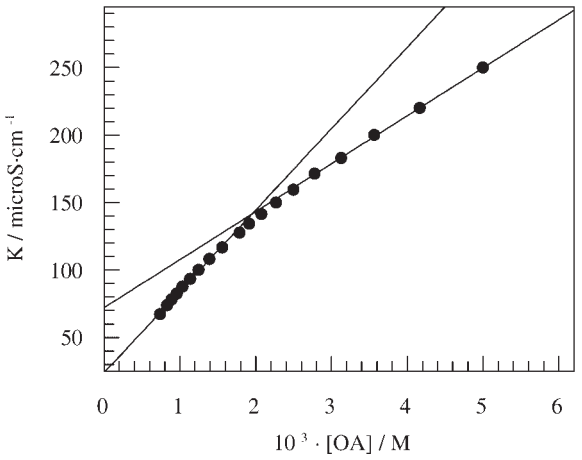
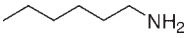
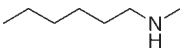
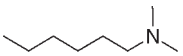
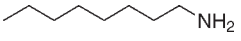
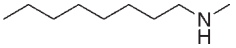
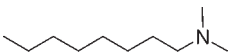
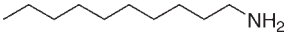
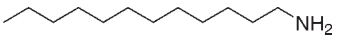
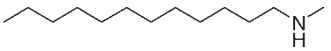
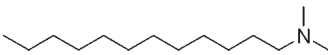


Figure 1. Determination of the *cmc* of OA. Plot of [OA] vs specific conductivity

Table 1. Critical micelle concentration and ΔG_m^0 values of n-alkylamines

Amine	Structure	*Cmc* (m mol)	ΔG_o^m/ (kJ · mol^{-1})
HA		6.36	−22.5
MHA		5.97	−22.6
DMHA		3.73	−23.8
OA		1.94	−25.4
MOA		1.61	−25.9
DMOA		0.54	−28.6
DA		0.97	−27.1
LA		0.81	−27.6
MLA		0.33	−29.8
DMLA		0.27	−30.3

known that the geometry of micellar aggregates is related to a critical packing parameter,[6] $f = v/a_o l_c$, where a_o is the head group area, v is the volume of the surfactant molecule and l_c is the length of the extended hydrocarbon chain. If $f < 0.3$ the resultant aggregate would be spherical micelles. In the case of $f = 0.3$–0.5 it would be non-spherical micelles. Values of f in the range $f = 0.5$–1 would imply the formation of vesicles and bilayers. The aggregate would be reverse micelles if $f > 1$. The decrease in *cmc* by increasing the chain length implies an increase in the value of l_c without significant changes in the volume of the surfactant. This increase in l_c implies a decrease in $v/a_o l_c$. A lower value of f results in a more stable micellar aggregate and hence a lower *cmc* value. The decrease in *cmc* by increasing the number of methyl groups in the head group, keeping the chain length constant, results in a decrease in the f value (a_o increases), and hence, the surfactant packing geometry is more conic. This fact implies that the micellar aggregate is more stable and that the *cmc* decreases.

From *cmc* values ΔG_m^0 of amine micelles can be calculated using Eqn (1)[7]:

$$\Delta G_m^0 = RT \ln X_{cmc} \quad (1)$$

where X_{cmc} is the *cmc* expressed as a molar fraction. The values of ΔG_m^0 are shown in Table 1.

Reactivity in aqueous media

The nitroso group transfer in aqueous media between *N*-methyl-*N*-nitroso-*p*-toulene sulfonamide (MNTS) and various primary, secondary and tertiary amines has been studied. In the previous section it was demonstrated that micellar aggregates are formed by long chain amines ($n_c \geq 6$). For this reason the amine concentration must always be kept below the *cmc* value. The reaction between MNTS and amines goes through the non-protonated form of the amine, without basic or acid catalysis[6,8] (Scheme 1).

Linear relationships between k_o and [amine] can be observed in Figs 2 and 3. The rate equation can be written as

$$k_o = k_{OH}[OH^-] + k_w[\text{amine}] \quad (2)$$

Scheme 1

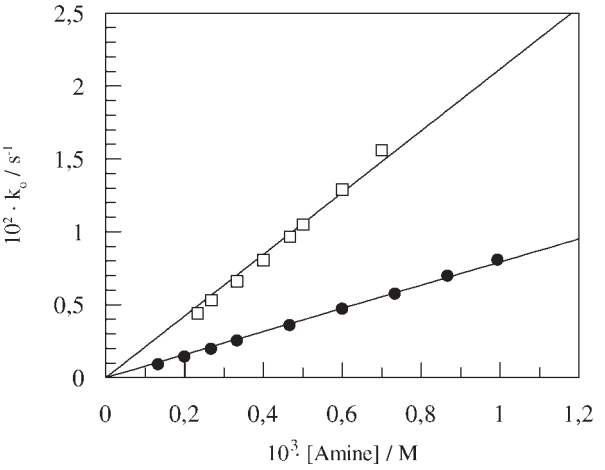


Figure 2. Influence of total amine concentration [MEA (•) and MBA (□)] on the observed first-order rate constant for the reaction with MNTS

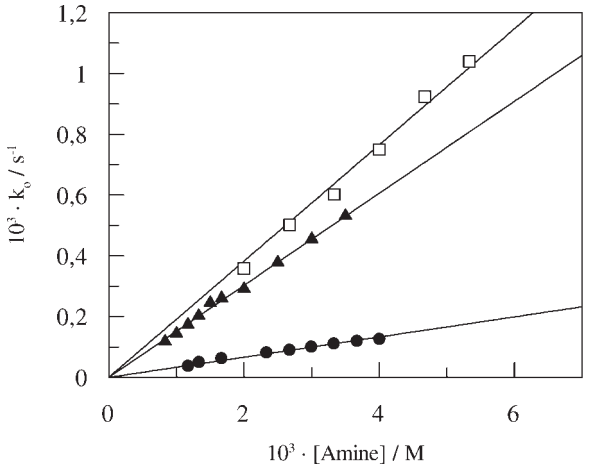


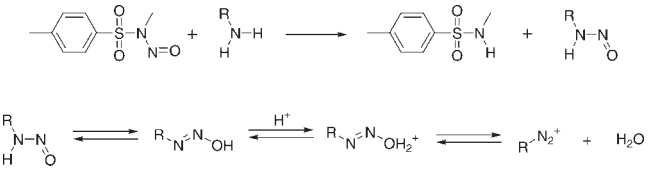
Figure 3. Influence of total amine concentration [HA (•), MHA (▲) and DMHA (□) on the observed first-order rate constant for the reaction with MNTS

where k_{OH} and k_w are the rate constants for MNTS hydrolysis[8] and nitroso group transfer reactions, respectively. The fact that the intercept of k_o vs [amine] is zero proves that MNTS hydrolysis is non-competitive under the experimental conditions used. From the slope of k_o vs [amine], the value of k_w can be obtained (Table 2).

Primary amines react with nitrosating agents to give deamination products (Scheme 2). The first step corresponds to *N*-nitrosation yielding a primary nitrosamine (RNHNO). In many cases, these nitrosamines are unstable and in various fast steps (including a proton transfer process and the loss of a water molecule) yields diazonium ions RN_2^+.

The corresponding reaction of secondary amines stops at the *N*-nitrosamine stage, since in this case there is no α-hydrogen available for the proton transfer reaction that leads to the formation of the diazonium ion.

As Table 2 shows, the primary amines react slower than secondary and tertiary amines. The reaction sequence is: MBA > MHA > DMHA > MOA > DMOA ≈ MEA > DA > OA > HA. Rate constant ratios for these amines are 7.0:6.3:5.0:4.2:2.6:2.6:1.7:1.4:1, respectively. Comparing the rate constant in water with amines pK_a, a good linear relationship between basicity and reactivity can be obtained (Fig. 4). The slope of the Bronsted plot, β_{nuc}, yields



Scheme 2

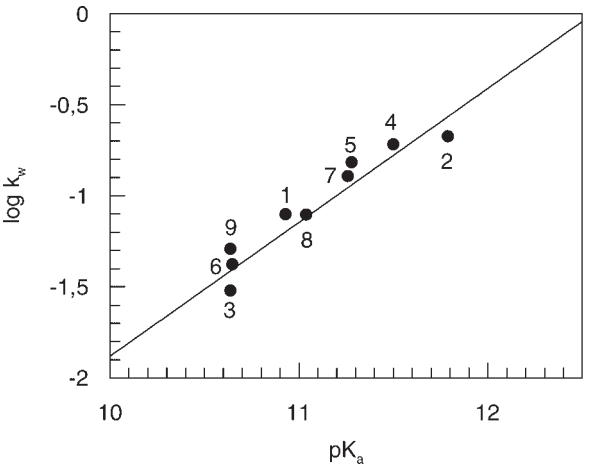


Figure 4. Plot of log k_w vs pK_a for the nitroso group transfer from MNTS to alkylamines. Numbers correspond to amines of Table 2

a value of $\beta_{nuc} = 0.7$, which is compatible with previous results.[9]

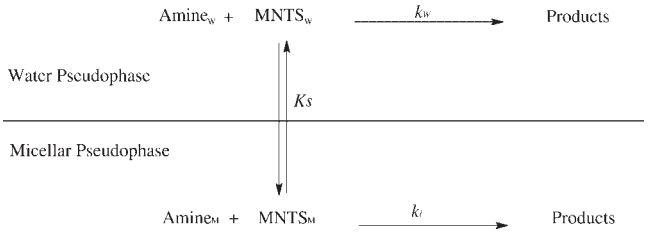
Reactivity in *N*-alkylamine micelles

Under normal conditions, the kinetic studies in micellar media are carried out for reactions where the reactants can be bonded to a micellar surface as a result of their hydrophobicity. One of the most interesting properties of micelles is their capacity for compound solubilization. They act, hence, as reaction media. In the present work, the micelle-forming surfactant (the n-alkylamine) is also one of the reactants in the transnitrosation process. The n-alkylamines used were HA, MHA, DMHA, OA, MOA, DMOA and DA.

In this case, for an amine concentration lower than the *cmc* value, k_o increases by increasing [amine] as

Table 2. Kinetic values for the transnitrosation between MNTS and n-alkylamines from Eqns (2) and (4)

	Amine	p$K_a^{R_3NH^+}$	$k_w/M^{-1}s^{-1}$	K_s/M^{-1}	k_i/s^{-1}	$k_2^i/M^{-1}s^{-1}$
1	**MEA**	10.93	$(7.93 \pm 0.08) \times 10^{-2}$	—	—	—
2	**MBA**	11.79	$(2.12 \pm 0.04) \times 10^{-1}$	—	—	—
3	**HA**	10.64[12]	$(3.02 \pm 0.12) \times 10^{-2}$	5.7 ± 0.8	$(3.84 \pm 0.35) \times 10^{-3}$	$(3.34 \pm 0.30) \times 10^{-4}$
4	**MHA**	11.50	$(1.91 \pm 0.03) \times 10^{-1}$	2.2 ± 0.2	$(1.10 \pm 0.10) \times 10^{-1}$	$(1.14 \pm 0.10) \times 10^{-2}$
5	**DMHA**	11.28	$(1.52 \pm 0.03) \times 10^{-1}$	5.6 ± 0.4	$(2.94 \pm 0.19) \times 10^{-2}$	$(3.59 \pm 0.23) \times 10^{-3}$
6	**OA**	10.65[10]	$(4.19 \pm 0.11) \times 10^{-2}$	11.1 ± 1.7	$(1.89 \pm 0.25) \times 10^{-3}$	$(1.64 \pm 0.22) \times 10^{-4}$
7	**MOA**	11.26	$(1.28 \pm 0.04) \times 10^{-1}$	5.8 ± 1.2	$(2.98 \pm 0.59) \times 10^{-2}$	$(3.09 \pm 0.61) \times 10^{-3}$
8	**DMOA**	11.04	$(7.87 \pm 0.57) \times 10^{-2}$	31.8 ± 6.3	$(3.48 \pm 0.66) \times 10^{-3}$	$(4.25 \pm 0.81) \times 10^{-4}$
9	**DA**	10.64[10]	$(5.10 \pm 0.10) \times 10^{-2}$	14.2 ± 3.0	$(2.24 \pm 0.40) \times 10^{-3}$	$(1.95 \pm 0.35) \times 10^{-4}$



Scheme 3

described above. At amine concentration values higher than the *cmc*, an increase in k_o is observed, whereas a significant change of the slope is observed under these conditions. This change of slope takes place at the *cmc* value. The kinetic *cmc* value is the same as that obtained using electrical conductivity measurements (*vide supra*). This change of slope is due to the appearance of a new reaction path at the micellar surface.

To rationalize the experimental behaviour, Scheme 3 has been proposed on the basis of a pseudophase micellar model.

Subscripts i and w correspond to micellar phase and aqueous phase, respectively, and k_i and k_w are the rate constants in each pseudophase.

Following Scheme 3, n-alkylamine concentration can be written as Eqn (3):

$$[D_n] = [\text{amine}]_T - cmc_{\text{amine}} = [\text{amine}]_M \qquad (3)$$

From the pseudophase formalism the following rate equation can be obtained:[5]

$$k_o = \frac{k_w [\text{amine}]_w + k_i K_s [D_n]}{1 + K_s [D_n]} \qquad (4)$$

where k_w is the rate constant in the bulk water, k_i is the rate constant at the micellar pseudophase, and K_s is the binding constant of MNTS to the micellar surface.

From the fit of Eqn (4) to the experimental data (Figs 5 and 6), the rate constant in the micellar pseudophase, k_i, and MNTS binding constant, K_s have been obtained (Table 2).

For comparison of reactivities in the surfactant interface with the corresponding reactivities in bulk water, the k_i (defined in terms of mole per mole concentrations and expressed in s^{-1}) must be converted into conventional reaction rates expressed in $1\,mol{-}^1\,s^{-1}$. We accordingly define a 'conventional' bimolecular rate constant, k_2^i for the reaction at the micellar pseudophase by:

$$k_2^i = k_i \overline{V} \qquad (5)$$

The application of this definition requires some knowledge of the molar volume ($\overline{V}$) of the micellar pseudophase. This volume is generally identified as the Stern layer volume. The range of $\overline{V}$ values is normally between

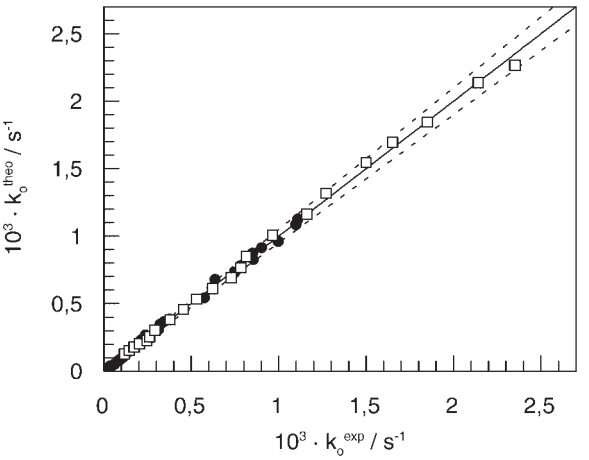


Figure 5. Experimental and theoretical values of k_0 for amines HA (•) and DMHA (□) for the transnitrosation reaction with MNTS. Dotted lines represent an error of 5%

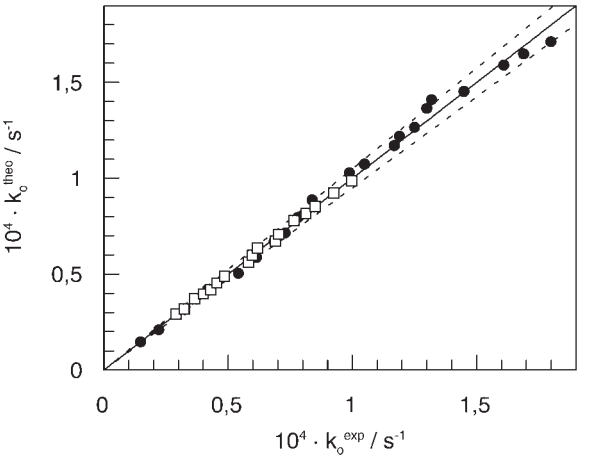
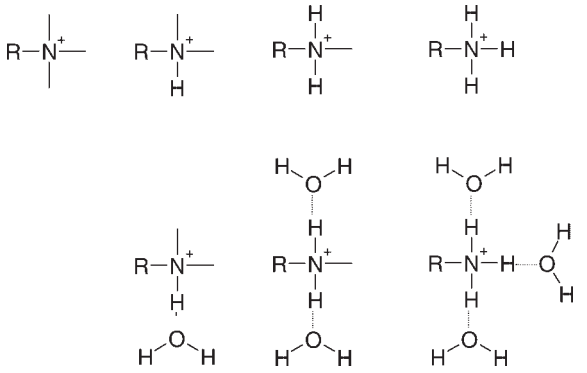


Figure 6. Experimental and theoretical values of k_0 for amines OA (•) and MOA (□) for the transnitrosation reaction with MNTS. Dotted lines represent an error of 5%

0.14 and $0.37\,l\,mol^{-1}$,[10] whereas the molar volume can be related to the nature of the head group (for large head groups[11] this value can be $0.5\,l\,mol^{-1}$). If we consider $0.14\,l\,mol^{-1}$ as the molar volume for *tert*-methylammonium group and $0.37\,l\,mol^{-1}$ for *tert*-butylammonium, the molar volume of the R—NH_3^+ group can be estimated as $0.087\,l\,mol^{-1}$. We must take into account that this value can be increased by the hydration of the NH_3^+ group. This value would become 0.14–$0.20\,l\,mol^{-1}$ (Scheme 4).

Analogously, for methylammonium and dimethylammonium groups the corresponding values are 0.104 and $0.122\,l\,mol^{-1}$, respectively (Fig. 7). Similar considerations about hydration can be made for these groups.

Table 2 shows the values of k_2^i. In all cases, the value of the rate constant at the micellar pseudophase, k_2^i, is lower than in bulk water. In fact, the rate changes in the presence of colloid aggregates are not proper catalytic process according to the traditional definition of catalysis.



Scheme 4

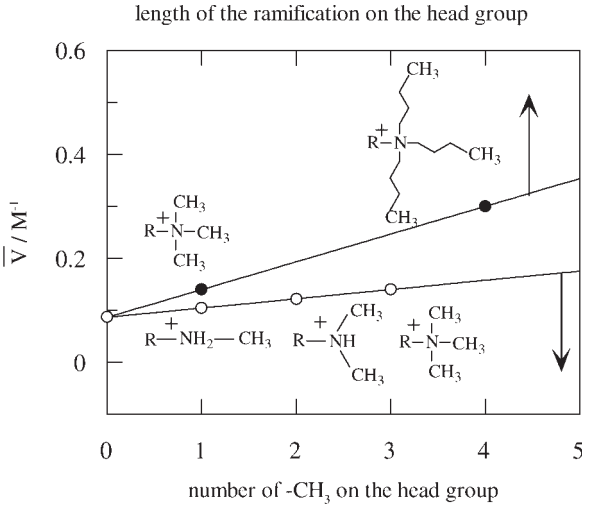


Figure 7. Molar volumes of various surfactants vs length of the ramification of the head group (•) and molar volumes calculated for n-alkylamines as a function of the number of methyl groups (○)

Micellar aggregates do not imply changes to the intrinsic barrier of reaction. In this case, the modification to the observed rate constant is due to changes in the local concentration of reactants at the various pseudophases of the microheterogeneous media.

Even though the reactivity sequence at micellar aggregates is the same as that in bulk water (see Table 2), there are significant differences with respect to the ratios between the constants. Considering the reactivity sequence of primary alkylamines (HA, OA and DA), in all cases the pK_a values are approximately 10.64, while the ratio k_w/k_2^i is, respectively, 90, 250 and 260. Changes in the molar volume of the Stern layer associated with the hydration of the head groups have no influence on the relative values of this sequence. The most unfavourable value affects the three ratios in the same proportion and yields the sequence 45, 125 and 130. This sequence corresponds to the *cmc* values for these amines: the *cmc* values are 6.36, 1.94 and 0.97 mM, respectively (*vide supra*).

Analogous behaviour has been observed for secondary and tertiary amines.

By increasing the hydrophobic character of the surfactant, the differences in reactivity in the aqueous medium and the micellar medium are increased. This phenomenon is due to the decrease in reactivity with the decrease in the medium polarity.

For this reason, the rate k_w/k_2^i constitutes a valuable tool that allows us to evaluate the changes in polarity at a micellar phase as a function of changes in the nature of the surfactant monomer. In this way, some interesting conclusions can be obtained taking into account the observed changes when chain length or head group nature is varied.

By increasing the number of carbons in the hydrocarbon chain, keeping the nature of the head group constant, an increase of the inhibition of the transnitrosation reaction is observed. This means that by increasing the chain length (and hence its hydrophibicity) the Stern layer is less polar, yielding a larger kinetic effect upon the transnitrosation process. This effect is parallel to that observed on the MNTS binding constant ($K_s^{HA} = 5.7$, $K_s^{OA} = 11.1$, $K_s^{DA} = 14.2$). The differences in reactivity between HA, MHA and DMHA are not discussed because the differences of hydration result in different Stern Layer volumes. At this point it must be added that the steric hindrance at the micellar surface could be different to that in bulk water due to the restrictions of mobility at the micelle.

CONCLUSIONS

In the present study, the pseudophase micellar model allows a satisfactory prediction of the experimental behaviour in all cases. From the experimental results we can conclude that the value of micellar pseudophase rate constant, k_2^i, is lower than that in bulk water. The increase in the observed rate constant, k_o, with n-alkylamine concentration can be attributed to an increase in the local concentration of reactants in the micellar surface. The differences between k_w and k_2^i values is due to a medium effect (the lower polarity of micellar pseudophase than bulk water).

EXPERIMENTAL

All reactants were purchased from Aldrich. The low solubility of the *N*-methyl-*N*-nitroso-*p*-toluene sulfonamide (MNTS) in water necessitated the use of acetonitrile as a cosolvent in a proportion never exceeding 1% (v/v) in the reaction mixture.

Reactions were followed by monitoring the UV absorbance of substrate solutions using an HP 8453 spectrophotometer fitted with thermostated cell holders at 25.0 ± 0.1 °C. The wavelength used for the kinetic studies was 250 nm. In all cases kinetic experiments were carried out under pseudo- first-order conditions ([MNTS] ≪ [amine]). The integrated first-order rate expression [Eqn (6)] was fitted to the absorbance–time

data by linear regression ($r > 0.999$) in all cases. The observed rate constants, k_0, could be reproduced with an error of $\pm 5\%$. In each instance, it was observed that the final spectrum of the product of the reaction coincided with one obtained in pure water, guaranteeing that the presence of micellar aggregates would not alter the product of the reaction.

$$\ln|A_t - A_\infty| = \ln|A_0 - A_\infty| - k_0 t \qquad (6)$$

The electrical conductivity (κ) was measured with a Crison conductivimeter calibrated using two KCl conductivity standard solutions supplied by Crison ([KCl] = $0.0100\,\text{mol dm}^{-3}$, $\kappa = 1413\,\mu\text{S cm}^{-1}$ at $25\,^\circ\text{C}$ and [KCl] = $0.100\,\text{mol dm}^{-3}$, $\kappa = 12.88\,\text{mS cm}^{-1}$ at $25\,^\circ\text{C}$). The error in the accuracy of these measurements was $\pm 0.5\%$. During the measurements of electrical conductivity the temperature was regulated using a thermostat-cryostat Teche TE-8D RB-5, with a precision of $\pm 0.1\,^\circ\text{C}$. The container with the sample was immersed in an ethanol–water-bath, and the temperature was measured together with the conductivity inside the sample container. The water used for the solution was distilled–deionised ($\kappa = 0.10\text{-}0.50\,\mu\text{S cm}^{-1}$). The pH value of the reaction media corresponded to that of the amine solution, and it was not buffered. Under these conditions a large amount of amine is in the protonated form. For these reason, electrical conductivity was used for *cmc* value determinations. Surface tension measurements (Kruss K9 tensiomenter) were also carried out. Values of *cmc* obtained by electrical conductivity measurements and by surface tension measurements were compatible.

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