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Elucidating chemical reactivity and transition state of mononuclear rearrangement of heterocycles through the use of compartimentalized micellar media

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ABSTRACT

The present comprehensive kinetic investigation in micellar systems deepens and broadens the knowledge of mononuclear rearrangement of heterocycles (MRH) of *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, reaction already carried out in different reaction media. As a matter of fact the use of four types of micelles different for charge, shape and polarity has allowed us to evaluate the role of micellar systems, as reaction media, on the rate of MRH and to quantify their catalytic effect. Moreover, the data obtained have enabled us to draw some intriguing conclusions on the localization of the substrate in the micelles, the transition state structure and the driving force of the reaction.

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1. Introduction

The chemistry of heterocyclic compounds represents a crucial segment of the today's chemistry, with at least 55% of organic chemistry papers devoted to this field. Heterocycles, especially five and six-membered rings containing nitrogen, play a key role in life processes such as the transfer of hereditary information from DNA to proteins, enzyme activity, storage and transfer of bioenergy, oxygen transport by haemoglobin, chlorophyllian synthesis, and so on [1].

Beside organic chemistry and biochemistry, many other sciences, from medicinal to agricultural and from material science to technology, are in debt to heterocycles. Indeed, several drugs (antibiotics, neurotropics, cardiovascular and anticarcinogenic agents), plant development regulators, pesticides, thermostable polymers, highly durable fibres exploit nitrogen containing heterocyclic systems [1–21].

For these reasons we have addressed our interest to synthetic applications and mechanistic studies of the mononuclear rearrangements of heterocycles (MRHs, Scheme 1) [22–26]. This type of reaction, involving an azole five-membered aromatic heterocycle generally linked to a side chain through a continuous π-electron system, leads to the synthesis of several different heteroaromatic azoles. MRHs are S_{Ni} processes occurring *via* a quasi-aromatic transition state (10 π electrons in a bicyclic structure) characterized by structure and solvent-dependent pathways [2,27–38].

We have previously studied the interconversion of several *Z*-arylhydrazones of 5-substituted-3-benzoyl-1,2,4-oxadiazoles into the relevant 4-acylammino-2-aryl-5-phenyl-1,2,3-triazoles in order to clarify the mechanistic aspects of the reaction by collecting both kinetic [2,27–29] and computational data [30]. More recently the use of micelles (Triton X-100 and C_{14}DMAO) [39,40] and cyclodextrin (β-cyclodextrin) [41,42] as well as ionic liquids [35,36,43] has allowed us to obtain detailed information concerning both the reaction mechanism and the effects of substrate structure on the MRH reaction rates.

The micelles provide interfaces able to modify physico-chemical properties of the investigated compounds [44–49].

The incorporation of 1,2,4-oxadiazoles derivatives in non-preorganized (micelles) [39,40] or in pre-organized (β-cyclodextrin) [41,42] systems has allowed to overcome their poor solubility in

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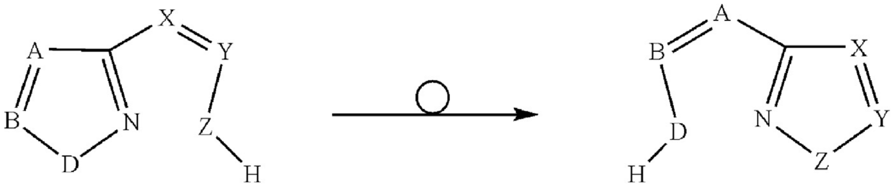


Scheme 1. Azole-into-azole interconversion.

water and, in order to determine proton concentration, to avoid the use of operational scales such as the pS^+ scale [50,51], established by interpolation from known pK_a data in aqueous dioxane.

Moreover the use of an inherently microheterogeneous solvent such as the aqueous micellar solution may offer different advantages over the continuous media. For example reactants in a continuous solvent undergo desolvation in order to approach close enough to react to each other. On the other hand, two reactants of a bimolecular reaction solubilized in the same micelle are forced in close proximity, thereby increasing the rate of reaction at the expense of a substantial loss of freedom of translational motions of the reactant molecules. Indeed, the dimension of the micelles could be critical for the molecular reciprocal orientation in the transition state formation [52].

Besides, in a previous paper, a concerted process was suggested for this MRH, where the magnitude of the activation barrier was determined by the interplay of two opposite factors, that is, the nucleophilicity of the nitrogen atom and the acidity of the nitrogen-bonded proton [30]. Nevertheless, while the former plays a significant role in the micellar aprotic region, the acidity of the nitrogen-bonded proton preferentially manifests itself in the aqueous compartment. Thus, the prevalence of one factor over the other in different micellar systems may highlight their relevant contribution to the MRH process.

Therefore, in order to complete and integrate the results obtained with non-ionic (Triton X-100, polyethylene glycol *tert*-octylphenyl ether) [39] and zwitterionic (C_{14}DMAO, *N*-tetradecyl-*N*,*N*-dimethylamine oxide) [40] micellar systems we have now undertaken a kinetic study in the presence of a wide variety of surfactants (*i.e.* SDS, sodium dodecyl sulfate; CTABr, cetyltrimethyl ammonium bromide; C_{14}DMAO; Triton X-100) in the presence of phosphate buffers at different pH values and temperatures. The S_{Ni} reaction of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2**) was chosen as a model reaction to elucidate mechanistic aspects such as, to name a few, the charge dispersion and timing of chemical bond formation-and-breaking in the transition state (Scheme 2).

The experimental data were fitted into the classical equation based upon Berezin's model [53], *i.e.* the so called pseudophase model, and allowed us to obtain both the reaction rate constants in aqueous and in micellar pseudophase, k_W and k_M respectively, as well as the relevant binding constants (K_S). These results have proven particularly useful and have shown that the four investigated surfactants exhibit some significant differences in catalytic activity due to the prevailing contribution of nitrogen nucleophilicity or of nitrogen-bonded proton acidity in the process.

2. Experimental

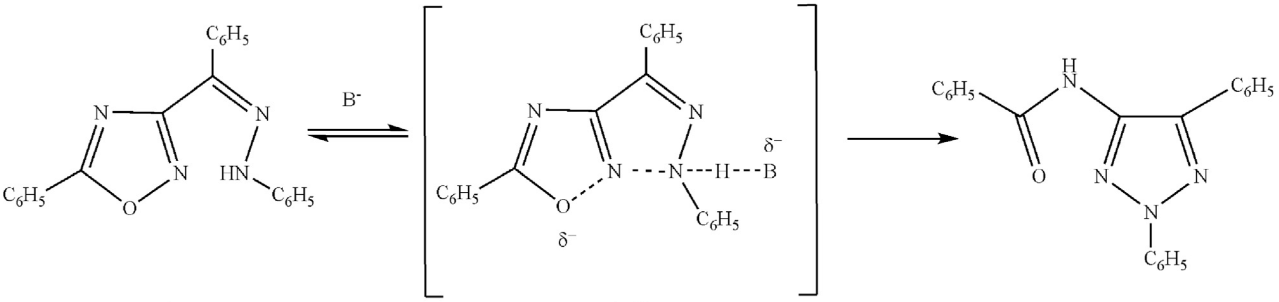
2.1. General

The *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles (**1**) was prepared according to literature methods [55]. The zwitterionic surfactant, C_{14}DMAO, was used as received from Prof. Hoffmann (Bayreuth Centre for Colloids & Interfaces). All other surfactants obtained from commercial suppliers were used without further purification.

Aqueous stock solutions in doubly distilled water of surfactants and phosphate buffer solutions at pH 7.4 ($[H_2PO_4^-]=[HPO_4^{2-}]$) and 11.7 ($[HPO_4^{2-}]=[PO_4^{3-}]$) were prepared by weight and used within few days. The pH measurements were carried out by using a Radiometer PHM 84, calibrated at pH 7.0 and 12.0 (±0.05). The ionic strength of the buffered solutions was kept constant at the value of 0.2 mol dm^{-3} through addition of KCl.

2.2. Critical micellar concentration measurements (c.m.c.)

The surface tensions of the investigated surfactant (SDS, CTABr, C_{14}DMAO and Triton X-100) in the presence and in the absence of **1** (5.0×10^{-5} mol dm^{-3}) were measured with a SensaDyne QC6000 Surface Tensiometer by the maximum bubble pressure method [56]. Dry nitrogen flows into a capillary immersed into the surfactant solution. On gradually increasing the pressure in the capillary, the bubble increases in size and curvature until it becomes hemispherical. Beyond this point the bubble



1 **TS** **2**

Scheme 2. MRH of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2**). B^- is an added base or the solvent.

becomes unstable and eventually escapes from the capillary. Measurements were carried out at different pHs (7.4 and 11.7), temperatures (from 293.1 to 313.1 K) and buffer concentrations. The concentration of additive **1** was kept constant and added, from stock dioxane solution, to surfactant solutions of the elected concentration. The concentration interval of surfactants used in the measurements were: 1.00×10^{-5}–2.20×10^{-3} mol dm^{-3} for Triton X-100, 6.00×10^{-4}–1.00×10^{-2} mol dm^{-3} for SDS, 1.00×10^{-4}–6.00×10^{-3} mol dm^{-3} for C_{14}DMAO and 3.00×10^{-6}–2.00×10^{-3} mol dm^{-3} for CTABr. Surface tension values (dyne cm^{-1}) were plotted *vs.* the decimal logarithm of molar concentration. The graphs are reported in Figs. S1–S5 of the Supplementary data.

It is well known that electrolytes affect the c.m.c. of surfactants. Buffer salts behaves as additional electrolytes. Indeed, the forces of electrostatic repulsion between head groups in a micelle of ionic surfactants are considerably reduced in the presence of electrolytes, enabling micelles to form more easily and at a lower surfactant concentration. The c.m.c. value of SDS is reduced of 15% and 85% at 293.1 and 313.1 K [57], respectively, whereas the c.m.c. of CTABr is reduced of 80% [58] under the adopted experimental conditions. Nevertheless in the presence of substrate **1**, at the highest investigated temperature, the c.m.c. values increase slightly approaching the literature values. La Mesa has already demonstrated that the increase of temperature from 293.1 to 313.1 K causes the increase of the respective c.m.c. values [57]. Moreover, in the present case, the hydrophobicity of the substrate may partially hamper the screening effect of the electrolytes thus strengthening the effect of the temperature.

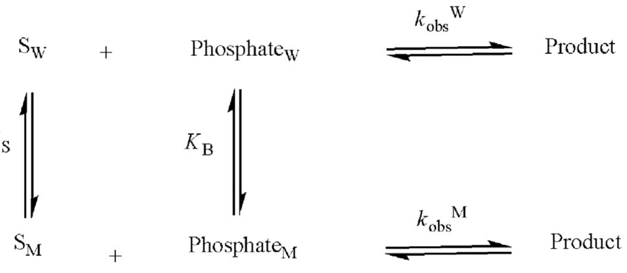
On the other hand, the effect of electrolytes on non-ionic surfactants is not straightforward. Salting-out electrolytes, such as phosphate and Na^+, are known to strongly compete with surfactant polyoxyethylene chains for water of hydration [59]. Nevertheless it has been demonstrated [60] that this decrease of water molecules hydrogen bonded to the surfactant is associated to a progressive increase in the micellar aggregation number and a rise of associated water which is non-specifically bound with the micelle. Indeed, polyoxyethylene chains demonstrated to perfectly interact with hydrophobic surfaces [61] and may thus easily, once dehydrated, deepen in the micellar core rather than expose themselves to the bulk water. These competing effects appear to disfavour, in the present case, Triton X-100 micellization (*i.e.* c.m.c. in water 3.6×10^{-4} mol dm^{-3}) [62].

C_{14}DMAO is known to partially protonate at acidic pH (pK_a of C_{14}DMAO in the micelle is 6.30 at 298 K) [63] and the observed relatively high c.m.c. may confirm a high protonation degree [64].

2.3. Kinetic measurements

MRHs of **1** in the presence of the four surfactants were followed at different temperatures (293.1, 303.1, and 313.1 ± 0.1 K) on a Cary 1E spectrophotometer by measuring the disappearance of **1** at the wavelengths of maximum absorption (λ = 373 nm, 375 nm or 390 nm). The reaction mixtures were obtained by mixing equal volumes of surfactant and buffer solutions.

Substrates were firstly dissolved in dioxane and then diluted in water so as to obtain a final solution with <1.0% of organic solvent and 5.0×10^{-5} mol dm^{-3} of **1**. Pseudo-first order conditions were reached by using a large excess of phosphate buffer. Kinetic measurements were carried out at pH 11.7 by keeping the concentration ratio acid/base constant and equal to unity. The investigated concentrations of buffer ions ($[HPO_4^{2-}] = [PO_4^{3-}]$) were 0.010, 0.015 and 0.025 mol dm^{-3}. For the ionic and zwitterionic surfactant kinetics were performed at pH 7.4 ($[H_2PO_4^{-}] = [HPO_4^{2-}] = 0.010$ mol dm^{-3}) as well.



Scheme 3. Reaction of substrate and base partitioned between water and the micellar pseudophase.

3. Results and discussion

Surfactant aggregates can be considered as supramolecular reactors in which the reactants, compartmentalized in the micelles through electrostatic and/or hydrophobic interactions, may acquire physico-chemical properties significantly different from those experienced in the bulk solvents and may interact more easily and effectively than in a homogeneous solvent due to concentration and orientation effects [52]. The study described herein was undertaken with the primary goal of quantitatively evaluate and compare the influence of neutral (Triton X-100), zwitterionic (C_{14}DMAO), positively (CTABr) and negatively charged (SDS) surfactants on the MRHs rate.

The first and meaningful effect consequent to the use of micellar system as the reaction media is the ability of micelles to solubilize the substrate in water. As already observed in previous studies [39,40], the relatively hydrophobic substrate, embedded in the micelles and sequestered from the aqueous bulk, forms clear aqueous solution. Therefore the MRH processes can be carried out in micellar buffered aqueous solutions rather than in pure or mixed organic or aqueous-organic solvents allowing to overcome preferential solvation effects of mixtures.

The data were treated quantitatively by Berezin pseudophase model (Scheme 3) [52,53]. Scheme 3 implies the partitioning of both the substrate (S) and the phosphate ions between the aqueous (W) and the micellar phase (M) with binding constants $K_S = \{[S_M]/([S_W]C)\}$, where $C = ([\text{Surfactant}] - \text{c.m.c.})$ and $K_B = \{[\text{phosphate}_M]/([\text{phosphate}_W]C)\}$, respectively.

Rate constants k_{obs}^{W} and k_{obs}^{M} are pseudo-first order rate constants in water and in the micellar phase, respectively; strictly speaking, they correspond to the sum of the uncatalysed (k_u) and the general base-catalysed processes, *i.e.* catalysed by bases OH^- (k_{OH}) and phosphate (k), in both phases, following Eq. (1):

$$k_{obs} = k_u + k_{OH}[OH] + k[\text{phosphate}] \qquad (1)$$

Therefore, two base-catalysed reaction paths may contribute to the overall rearrangement rate. The observed second order rate constants, k, can be related to the second order rate constants in both phases, k_W and k_M, and to the binding constants K_S and K_B of the substrate and of the base with the surfactant respectively, by using Eq. (2):

$$k = \frac{k_W + (k_M/V)K_B K_S C}{(1 + K_B C)(1 + K_S C)} \qquad (2)$$

where V is a quantity related to the volume element for the reaction in micelles [53,54].

Moreover, $K_B C$ can be considered negligibly small with respect to unity due to the high hydrophilicity of the phosphate ions and second order rate constants can therefore be fitted into the

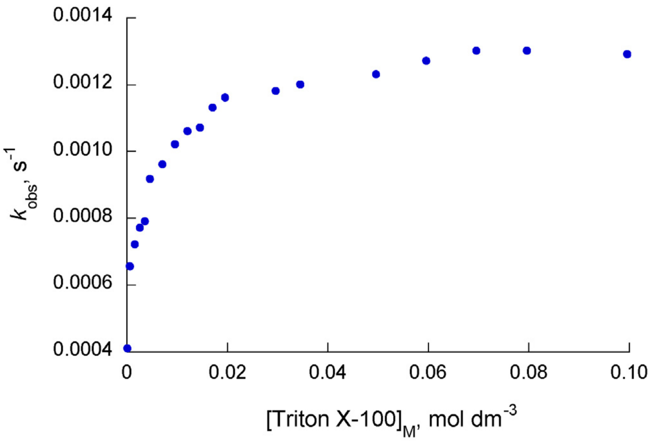


Fig. 1. Dependence of the observed rate constant (k_{obs}, s^{-1}) on micellized Triton X-100 concentration (mol dm^{-3}), *i.e.* [Triton X-100] − c.m.c., in the presence of phosphate buffer (pH 11.7, [acid] = [base] = 0.015 mol dm^{-3}) at 293.1 ± 0.1 K. The c.m.c. in the presence of the substrate is 5.4×10^{-4} mol dm^{-3}.

simplified Eq. (3). This assumption had already been made in previous studies [39,40]

$$k = \frac{k_W + (k_M/V)K_B K_S C}{(1 + K_S C)} \qquad (3)$$

Triton X-100 forms, above the c.m.c. (~5.0×10^{-4} mol dm^{-3}, see also Table S1 and Fig. S1 in the Supplementary data), neutral micelles. This surfactant has already been investigated as MRH promoter, nevertheless, differently from previous measurements, in the present case, MRH of *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole has been investigated in the presence of phosphate rather than in borate buffer (*i.e.* at pH = 11.7 rather than at 9.6) and at different phosphate concentrations (*i.e.* [HPO_4^{2-}] = [PO_4^{3-}] = 0.010, 0.015 and 0.025 mol dm^{-3}) at 293.1 K.

Rate constants were measured over a wide concentration interval of Triton X-100 (5.0×10^{-4}–1.0×10^{-1} mol dm^{-3}). The obtained data are collected in Table S2 of Supplementary data. At constant pH, the k_{obs} values increase with surfactant concentration, levelling off to a maximum plateau value (at ≈5.0×10^{-2} mol dm^{-3} of surfactant; see Fig. 1) presumably corresponding to the complete incorporation of the substrate in the micelles. This kinetic behaviour is similar to what is usually observed for enzymatic catalysis where the rate of catalysis does not show a linear dependence with increasing substrate concentration but, due to enzyme saturation, highlights a levelling to a maximum rate of reaction. At constant Triton X-100 concentration, the k_{obs} values increase linearly with buffer concentration (see Fig. S6 and Table S2 in the Supplementary data). Therefore at each concentration of Triton X-100 a second order rate constant, *k*, related to the observed general base-catalysis for phosphate can be obtained by following Eq. (1). A plot of *k* values *vs.* micellized [Triton X-100] allowed us, by following Eq. (3), to obtain k_W, $k'_M = (k_M/V)K_B$ and K_S (see Table 1 and Fig. S7 in the Supplementary data).

The major contribution to the rate of the process in Triton X-100 is the reaction in the micellar pseudophase ($k'_M/k'_W = 3.4$). This is not surprising because in the micellar pseudophase the MRH may proceed in the outer hydrophilic poly(ethoxy) sheath of the surfactant micelles (*i.e.* in Triton X-100 the Stern layer is much thicker, 25 Å, than that of ionic surfactant such as CTABr and SDS, 6–9 Å) [65] where the anionic base species reside, with the diffusion of the substrate to this region being much more rapid than the time scale of the reaction kinetics. A similar evidence has been previously highlighted [39] in the case of borate buffer at pH 9.6 at 313.1 K, although in the present case the micellar contribution is 7 times higher with respect to that observed in borate buffer, in agreement with a general-base-catalysis from the stronger base PO_4^{3-} {pK_a(HPO_4^{2-}) = 12.38 *vs.* pK_a(H_3BO_3) = 9.23} [66]. The value of the binding constant (K_S) is comparable with that previously calculated (K_S = 120 mol^{-1} dm^3) in borate buffer at pH 9.6 and 313.1 K.

Nevertheless, while in borate buffer the kinetic constants decrease upon increasing Triton X-100 concentration, in the present case the opposite is true. Likely, upon increasing the surfactant concentration, the substrate, diluted in a higher number of micelles, tends to adopt a more superficial localization where the encounter in the micellar sheath with the strong base is favoured. This circumstance may affect the driving force of the MRH process [30], *i.e.* the prevalence of the acidity of the nitrogen-bonded proton contribution over the nucleophilicity of the nitrogen contribution can be hypothesized. Therefore, in the presence of the weak basic borate the prevailing contribution to the rearrangement process is the nucleophilicity of the nitrogen in the micellar aprotic phase, whereas in the presence of the strong basic phosphate the acidity of the nitrogen-bonded proton prevails allowing the acceleration of the rearrangement until the maximum distribution of the substrate on the micellar surface has been reached.

The absorption maximum of **1** undergoes a significant bathochromic shift from 373 nm (at surfactant concentrations ≤5.0×10^{-4} mol dm^{-3}) to 390 nm (at surfactant concentrations ≥5.0×10^{-4} mol dm^{-3}). The observed shift associated to the formation of micelles in the solution is a clear evidence of specific binding interactions of the substrate to micelles. The associated high binding constant of the substrate for these micelles allows to confirm the localization of the substrate at the interface of the hydrophobic micellar core and the polyoxyethylene corona-forming chains of the micelle, region in which **1** favourably interacts with Triton X-100 through π-interactions between the aromatic moiety of Triton X-100 and both the phenyl moiety and the heterocyclic ring of the substrate. The solubilization of the substrate in this portion of the micellar aggregate does also support and explain the prevailing contribution of micellar over aqueous phase [39] and the scarce variation of Triton X-100 c.m.c. on addition of **1**.

Table 1
Second order rate constants in water (k_W) and micellar phase (k'_M) and binding constants (K_S) for the investigated rearrangement in phosphate buffer at different temperature and pH values.

Surfactant	*T*, K	pH	10^2k_W, dm^3 mol^{-1} s^{-1}	K_S, mol^{-1} dm^3	[$10^2k'_M$, dm^3 mol^{-1} s^{-1}][a]
Triton X-100	293.1	11.7	1.11 (±0.37)	133 (±63)	3.75 (±0.17)
	[313.1][b]	[9.6][b]	[0.24 (±0.07)][b]	[120 (±80)][b]	[0.58 (±0.06)][b]
SDS	293.1	11.7	0.0050 (±0.0012)	9.9 (±10.2)	−0.015 (±0.022)
SDS	313.1	7.4	0.56 (±0.70)	88 (±152)	0.049 (±0.009)
CTABr	313.1	7.4	12.2 (±0.1)	50 (±15)	3.25 (±0.49)
C_{14}DMAO	313.1	7.4	0.52 (±0.02)	12 (±4)	2.75 (±0.39)
	[313.1][c]	[9.6][c]	[27.4 (±0.08)][c]	[155 (±28)][c]	[39.2 (±0.2)][c]

[a] $k'_M = (k_M/V)K_B$.
[b] Data from Ref. [39].
[c] Data from Ref. [40].

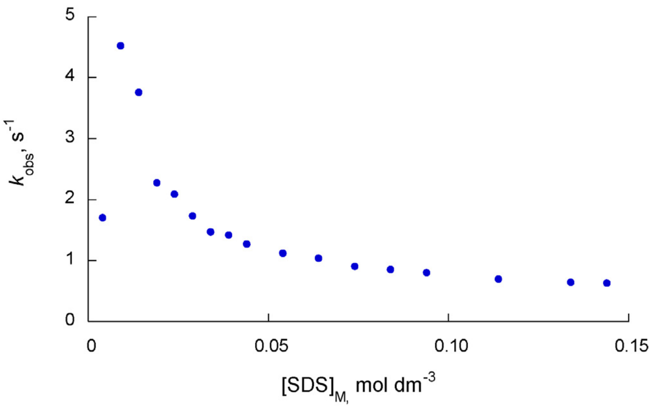


Fig. 2. Dependence of the observed rate constant (k_{obs}, s^{-1}) on SDS micellized concentration (mol dm^{-3}), *i.e.* [SDS] – c.m.c., in the presence of phosphate buffer (pH = 11.7, $[HPO_4{}^{2-}] = [PO_4{}^{3-}] = 0.015$) at 293.1 ± 0.1 K. The c.m.c. in the presence of the substrate is 4.4×10^{-3} mol dm^{-3}.

The rearrangement of **1** into **2** has been hence performed in the negatively charged SDS micelles at various temperatures (293.1 and 313.1 K) and at different pH values (7.4 and 11.7, in the latter case phosphate buffers $[HPO_4{}^{2-}] = [PO_4{}^{3-}] = 0.010$, 0.015 and 0.025 mol dm^{-3} have been investigated). The choice of this micellar environment has been made in order to gain further information on the mechanism of the reaction from the influence of a negatively charged micellar compartment on the formation of the transition state. As a matter of fact the reactivity of the substrate in SDS is strongly reduced compared to that observed in neutral micelles so that only the obtained k_W at pH 11.7 and k'_M at pH 7.4 have a real physical meaning, being the other kinetic or equilibrium values negative or characterized by a high error.

The plot of k_{obs} values *vs.* [SDS] shows a prevailing rate decrease with increasing the concentration of the surfactant thus highlighting the unfavourable role of anionic micelles on the MRH process (Fig. 2 and Table S3 in the Supplementary data), the only exception being data close to the c.m.c. The inhibitory effect can be explained by considering both electrostatic and hydrophobic interactions which operates simultaneously in this reaction system. In particular the effect is twofold: (1) the approach of negatively charged base to negatively charged micelles is limited thus decreasing the encounter of the micellized substrate with the catalyst; and (2) negatively charged micellar environment unfavourably affects the formation of the incipient negatively charged transition state.

At pH = 11.7 and T = 293.1 K, a second order rate constant, k, has been calculated at each SDS concentration following Eq. (1) (see Fig. S8 in the Supplementary data). A plot of k values *vs.* $[SDS]_M$ allowed us, by using Eq. (3), to obtain k_W (see Table 1 and Fig. S9 in the Supplementary data), the negatively $k'_M = (k_M/V)K_B$ and the K_S, characterized by a large error, having no physical meaning. It is plausible to hypothesize that the substrate solubilized in a negatively charged and polar micellar system is not able to encounter the base except in the aqueous phase beyond the negatively charged micellar region. Therefore, by recalling the previously mentioned paper [30] and the interplay of the nucleophilicity of the nitrogen atom and the acidity of the nitrogen-bonded protons in controlling the MRH process, in this micellar system only N—H acidity, although with scarce base assistance, drives the process.

The increase of the temperature to 313.1 K highlights, despite the reduction of the pH from 11.7 to 7.4 ($[H_2PO_4{}^{-}] = [HPO_4{}^{2-}] = 0.010$ mol dm^{-3}) (see Fig. S10 in the Supplementary data), a slight increase of the reactivity. Due to the reduced pH and the consequent absence of any significant base catalysis from OH$^-$, the second order rate constants for each SDS concentrations were calculated by following the simplified Eq. (4) [39]

$$k_{obs} = k[\text{phosphate}] \tag{4}$$

In this case, k'_M obtained according to Eq. (3), although particularly small, was not negligible but significantly lower than the corresponding k'_M values obtained at the same temperature and pH for other surfactant systems (see below).

CTABr, being a positively charged surfactant, is expected to accelerate the MRH. Therefore the rearrangement was investigated only at pH = 7.4 ($[H_2PO_4{}^{-}] = [HPO_4{}^{2-}] = 0.010$ mol dm^{-3}) and 313.1 K. Second order rate constants obtained by following Eq. (4) have been fitted into Eq. (3). As a matter of fact the reactions appear faster in CTABr rather than in SDS or Triton X-100 (see Table in Fig. S11 in the Supplementary data and compare it with Tables in Fig. S10 and Table S2) with k'_M 65 times higher than that determined at the same temperature and pH in SDS (see Table 1 and Fig. S11 in the Supplementary data) and k_W four times higher than k'_M. This evidence is in agreement with the capability of the positively charged CTABr to favour both the approach of the negatively charged base with the micellized substrate and to assist the formation of the negatively charged transition state (see Scheme 2). *Vice versa* the affinity of the substrate with this surfactant is not particularly high and, although data are characterized by a high standard error, comparable with those determined in other micellar systems, highlighting that the micellization of the substrate is hydrophobically rather than electrostatically driven, as expected for a neutral substrate.

The major contribution of the reaction in the aqueous phase ($k_W/k'_M = 3.8$) is not surprising because of the thinness of the Stern layer of cationic micelles. Likely, the micellized substrate is oriented with the reaction site towards the micellar/water interface in order to favour the encounter with the base present in the bulk. Because it has been reported that when base-catalysed conditions prevail, the acidity of the proton bound to the nitrogen of the hydrazone moiety should become the dominant factor, it is likely that in CTABr the role of nitrogen atom nucleophilicity is hampered by the nitrogen-bound proton acidity [30]. Indeed, in this positively charged micellar system, some of the negatively charged hydrogen phosphate ions are located in the proximity of the surfactant headgroup region and comprise the micellar Stern layer. Therefore micellar catalysis could benefit of the presence of the base resulting in a k'_M 60 times higher than that in SDS, where hydrogen phosphate ions are *vice versa* repelled from the Stern layer by negatively charged surfactant headgroups.

Eventually, kinetics in phosphate buffer ($[H_2PO_4{}^{-}] = [HPO_4{}^{2-}] = 0.010$ mol dm^{-3}, see data reported in Fig. S12 in the Supplementary data) at pH = 7.4 and 313.1 K in the presence of zwitterionic micelles of C_{14}DMAO (*N*-tetradecyl-*N*,*N*-dimethylamineoxide) were carried out. The choice felt on C_{14}DMAO because it behaves as a cationic or zwitterionic surfactant depending on the solution pH, it forms spherical aggregates or short rod-like micelles depending on the concentration and finally is characterized by a potential basic site that by itself may promote the rearrangement and thus replace an eventual external base [40]. The evidence of structural changes of the aggregates on increasing the concentration of surfactant is evidenced also in the plots used for c.m.c. determination, *i.e.* it is possible to evidence two different breaks in the surface tension *vs.* logarithmic surfactant concentration (see Fig. S5 in the Supplementary data).

The plot of k values *vs.* $[C_{14}DMAO]_M$ (see Fig. S12 in the Supplementary data) shows a rate constant increase with surfactant concentration analogously to those observed in the presence of Triton X-100 (Fig. S7 in the Supplementary data) and to that recently published for the MRH of **1** in C_{14}DMAO in borate buffer at pH 9.6 [40]. Second order constant separated for both the two phases, k_W

and k_M, following Eq. (3), are reported, and compared to corresponding values in borate buffer at pH 9.6, in Table 1.

The reaction of MRH of **1** in zwitterionic micelles in the presence of phosphate buffer highlight, as yet observed in the presence of Triton X-100, $k'_M > k_W$. It is therefore interesting to note that the micellar systems in which the major contribution to the observed rearrangement rate constants is the reaction in micelles do take advantage, on increasing the surfactant concentration, of the already mentioned maximum distribution of the substrate on micellar surface and consequent increased reactants encounter associated to increased surfactant concentration.

As far as the second rate constants in both phases are concerned, they are much lower than those obtained in borate buffer according to the weaker base catalyst hydrogen phosphate as compared to borate [$pK_a(H_2PO_4^-) = 7.20$ *vs.* $pK_a(H_3BO_3) = 9.23$] [66]. It appears noteworthy that the decrease of k'_M parallels that in K_S (*i.e.* $K_{S(pH=9.6)}/K_{S(pH=7.4)} = 14$), in agreement with a reduced contribution of the micellar pseudo-phase due to a reduced affinity of the substrate for the micelles. The more than 10-fold decrease in the binding constant may be imputable to partial surfactant protonation at the lowest investigated pH and a consequent variation of micellar structure [63]. Indeed, the high c.m.c. measured under the adopted experimental conditions confirms the partly occurred protonation [63]. Maeda and Kakehashi [63] have shown that short-range attractive interactions between the headgroups of the non-ionic (deprotonated) and the cationic species could affect the aggregation type favouring the transformation of rod into infinitely and long cylinder micelles. This transformation confers viscoelastic properties to the solution and could affect the affinity for the sterically hindered **1** [67]. The absence of any evidence of catalysis by the potential basic site of the nitroxide is a further confirmation of the occurred surfactant partial protonation.

4. Conclusions

The data obtained by studying the MRH in different micelles and at different proton concentrations allow to draw some interesting conclusions. The reactivity, at the same pH and temperature and considering the same base catalyst concentration, follows the order $CTABr > C_{14}DMAO \gg SDS$ at pH = 7.4 and 313.1 K and Triton X-100 ≫ SDS at pH = 11.7 and 293.1 K. Similarly, when second order rate constants are compared, the reactivity follows the order $k_{W(CTABr)} > k_{W(C14DMAO)} \gg k_{W(SDS)}$ in micellar pseudo-phase and $k_{M(CTABr)} \gg k_{M(C14DMAO)} \approx k_{M(SDS)}$ in aqueous pseudo-phase, respectively; whereas the second order rate constant are much higher in Triton X-100 than in SDS in both pseudo-phases. Therefore it appears that surfactants able to create aprotic micellar compartments which favour nitrogen nucleophilicity and N—N bond formation, such as Triton X-100 and $C_{14}DMAO$, strongly enhance the MRH. Indeed, in these systems, it has been demonstrated that the observed rate constants increase with surfactant concentration, the reaction in the micellar phase controlling the rate of the process and prevailing over the reaction in the aqueous phase. Triton X-100 is particularly effective because it favours both the nucleophilic contribution in the aprotic micellar core and the encounter of the base with the substrate in the micellar sheath formed by the dangling hydrophilic polyoxyethylene chains.

Vice versa in micelles from more polar surfactants, the contribution of the aqueous pseudo-phase cannot be neglected and rather controls the MRH process. Therefore the rearrangement appears particularly effective in those micellar systems that electrostatically favour the encounter of the substrate with the negatively charged base catalyst at the micellar surface (*i.e.* CTABr) or assist the formation of the negatively charged transition state. It appears quite awkward that in both positively and negatively charged micellar systems the observed rate constant decreases upon increasing the surfactant concentration. This effect is imputable to a persistent competition of the aqueous and micellar contributions to the MRH process. The initially insignificant micellar contribution shows itself when the majority of the substrate is perfectly solubilized in the micellar core and the base-substrate interactions decreases. This is especially true when one considers the high K_s of **1** in SDS.

The ability of the micelles in favouring the reaction depends therefore on the feature of the surfactant and could be tuned by promoting the nitrogen nucleophilicity in the aprotic micellar microenvironment or the N-H acidity in the aqueous rich phase. Indeed, CTABr micelles do exert the greatest catalytic effect in both pseudo-phases because positively charged headgroups stabilize the negatively charged transition state and favour the encounter with the phosphate ions at the micellar surface. Analogously but for opposite reasons, SDS is the less effective micellar system notwithstanding, but because, the high affinity that **1** has for this micellar system.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2013.11.029.

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