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Cyclization of 2-(3-Halopropyloxy)phenoxide Ions in Functionalized Surfactants

Giorgio Cerichelli,*[a] Luciana Luchetti,*[b] Giovanna Mancini,[c] Gianfranco Savelli[d]

[a] Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università degli Studi de L'Aquila, Via Vetoio, 67010 Coppito Due (AQ), Italia.

[b] Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma "Tor Vergata", Via della Ricerca Scientifica, 00133 Roma, Italia.

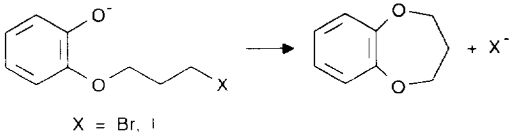
[c] Centro CNR di Studio sui Meccanismi di Reazione, c/o Dipartimento di Chimica, Università degli Studi di Roma "La Sapienza", P.le Aldo Moro 5, 00185 Roma, Italia.

[d] Dipartimento di Chimica, Università degli Studi di Perugia, Via Elce di Sotto, 06100 Perugia, Italia

Abstract: Observed rate constants (k_{obs}) of cyclization of 2-(3-halopropyloxy)phenoxide (halo = bromo, iodo; PhBr7 and PhI7, respectively) in aqueous micelles of N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium bromide (**1**) depend on [**1**] and [NaOH]. The rate profiles go through a maximum and, at high [**1**], the catalytic effect is modest. By contrast, k_{obs} in aqueous micelles of N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium sulfate (**2**) increases monotonically with increasing surfactant concentration and becomes constant at high [**2**]. ^1H, ^{13}C, and ^{14}N NMR spectra of **1** and **2** show that micelles of **1** and **2** do not differ in dimension and shape and that the average conformations of **1** and **2** are similar.

Aqueous micelles exert a medium effect both on spontaneous and non-spontaneous reactions.[1-4] They also accelerate, or inhibit, bimolecular reactions by bringing reactants together at the micellar surface, or by keeping them apart. This concentration effect is independent of the micellar medium effect, so micellar rate effects have to be treated in terms of models that estimate partitioning of the two reagents between water and micelles and second order rate constants in each pseudophase. To apply this model we must estimate the reagent concentration in the micellar pseudophase, despite the fact that the volume available to the reactant is uncertain. Sometimes it is possible to measure reagent partitioning, for example electrochemically or by fluorescence techniques,[5] but often it is calculated by using equations that contain parameters whose values are uncertain.[2,6-9] For these reasons, comparison between second order rate constants that differ by less than an order of magnitude are not very significant and second order rate constants in water and micelles are very similar for many bimolecular reactions. On the other hand, differences in first order rate constants are more significant because they do not depend on reaction volume.

We have overcome the problems caused by uncertainty in reagent partitioning by studying micellar effects on the cyclization reaction,[10] specifically cyclizations of 2-(3-bromopropyloxy)phenoxide and 2-(3-iodopropyloxy)phenoxide (PhBr7 and PhI7, respectively) that give seven member cyclic ethers.



Cyclizations are S_N2 reactions, but first order processes because they are intramolecular reactions and their rate constants only depend on medium effects. Cyclizations have been studied both in homogeneous[11] and in micellar solutions[10] and micellar induced changes in the rate constant of the fully micellar bound substrate give useful information on the properties of micellar surface.

In the absence of micelles, cyclization rate constants increase with the decreasing polarity of the solvent (H_2O, MeOH, EtOH, 2-PrOH), as does the substrate reactivity ratio k_I / k_{Br} that is 0.69 in water and > 1 for reactions in organic solvents.[12] Similar behaviour is shown by cationic micelles in which both rate constants and ratio k_I / k_{Br} increase with the increasing bulk of the surfactant head group.[10a]

Here we report results on the cyclization of PhBr7 and PhI7 in aqueous micelles of N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium bromide (**1**) and sulfate (**2**). The hydroxyethyl group in the head of the surfactants is weakly acidic and, in the presence of NaOH, could also be present in the deprotonated form (**1a** and **2a**, respectively). For this reason we have examined the reaction at different [NaOH].

RESULTS AND DISCUSSION

In a non-functionalized surfactant, as N-hexadecyl-N,N,N-trimethylammonium bromide (CTABr), the overall rate constant (k_{obs}) generally increases monotonically with increasing surfactant concentration and becomes constant when the substrate is fully micellar bound.[10a] k_{obs} is given by Equation 1[13]

$$k_{obs} = \frac{k_w + k_m K_S[D_n]}{1 + K_S[D_n]} \qquad (1)$$

where k_m and k_w are the first order rate constants in micelles and water, respectively, and K_S is the binding constant of substrate (S) to micellized surfactant (D_n). $[D_n]$ is given by Equation 2

$$[D_n] = [D] - \text{cmc} \qquad (2)$$

where D denotes total surfactant and cmc (the critical micelle concentration) is assumed to give the

Table 1. Cyclizations of PhBr7 and PhI7 in Aqueous Solution of 1[a]

	[NaOH] = 0.01			**[NaOH] = 0.05**			**[NaOH] = 0.10**		
$10^3 \times [\mathbf{1}]$, M	PhBr7	PhI7	k_I / k_{Br}	PhBr7	PhI7	k_I / k_{Br}	PhBr7	PhI7	k_I / k_{Br}
0	2.33	1.40	0.60	2.33	1.40	0.60	2.33	1.40	0.60
0.05	2.30	1.60	0.70	3.12	2.16	0.69	2.51	1.83	0.73
0.07	2.30	1.78	0.77	3.26	2.67	0.82	2.67	2.20	0.82
0.10	2.50	2.50	1.00	3.32	3.42	1.03	2.98	3.43	1.15
0.20	2.93	3.61	1.23	3.60	5.29	1.47	3.50	4.98	1.42
0.40				4.00	5.92	1.48	3.91	6.08	1.55
0.70	3.42	4.86	1.42	4.30	6.60	1.53	4.30	6.83	1.59
1.00	3.50	5.00	1.43	4.31	6.29	1.46	4.31	6.81	1.58
4.00				4.19	6.19	1.48	4.43	6.96	1.57
7.00	2.83	4.49	1.59	3.90	5.89	1.51	4.42	6.90	1.56
10.0	2.80	4.31	1.54	3.88	5.74	1.48	4.20	6.50	1.55
20.0	2.55	3.88	1.52	3.60	5.30	1.47	4.01	6.18	1.54
50.0				3.11	4.58	1.47	3.50	5.51	1.57

[a] Values of $10^4 \times k_{obs}$, s^{-1}, at 25.0°C, with 10^{-4} M substrate.

concentration of monomeric surfactant. In the case of high binding constant and at increasing [D], k_{obs} should remain constant provided that the micelle structure does not change, affecting k_m.

In Table 1 we report k_{obs} for the cyclization reaction of PhBr7 and PhI7 in aqueous solution of **1** at 25°C. As shown in Figure 1, the rate profiles go through a maximum. With [NaOH] = 0.01 we observe the maximum catalytic effect at $[\mathbf{1}] = 8 \times 10^{-4}$ and, at high [**1**], the catalytic effect is modest, $k_m / k_w = 1.09$ and 2.77 for PhBr7 and PhI7, respectively.

The extent of deprotonation of the hydroxyethyl group of **1** influences k_{obs} because in its protonated form, **1**, may hydrogen bond with the phenoxide. This interaction stabilises the nucleophile and inhibits the reaction. The extent of deprotonation of **1** at the micellar surface depends on the stoichiometric amount of OH^-,[14] or the measured pH when buffers are used.[15] The ion-exchange model predicts that the amount of OH^- at the micellar surface depends on the relative amounts of Br^- and OH^- in solution.[2a,4,16] Adding **1**, increases the amount of Br^- which decreases the interfacial concentration of OH^-, increasing the extent of protonation of **1**. The percentage of protonated form **1a** increases, the fraction of substrate stabilised by hydrogen bonding increases, and the reaction slows down, as observed.

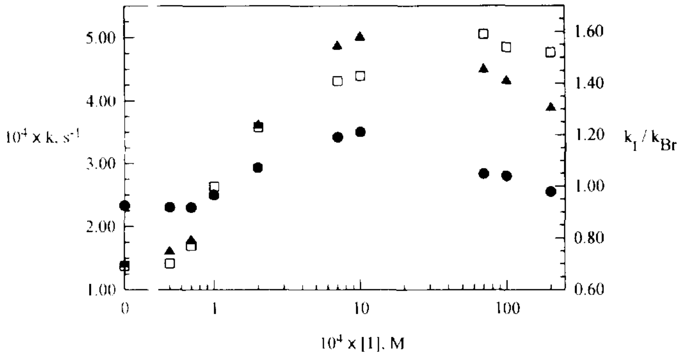


Figure 1. Variation of k_{obs} for the cyclization of PhBr7 (●) and PhI7 (▲) (left axis) and variation of ratio k_I / k_{Br} ( ) (right axis) with [1], [NaOH] = 0.01

The observed rate profiles could also be explained by continuous changes in the aggregate structure. Variation of the percentage of **1** and **1a** changes the surface charge density and possibly micellar structure. If the micelles become opener, the extent of water penetration at the surface increases and, in a more polar reaction site, the cyclization rate is lowered. This explanation is inconsistent with changes in the ratio k_I / k_{Br}. In general, nucleophilic assistance to the leaving group is given by the solvent. In cationic micelles, where the content of water is lower than in bulk water, head groups interact with Br^- and even more strongly with I^-,[2,5] so that they might provide electrophilic assistance to reaction. Ratio k_I / k_{Br} increases with increasing [**1**] and becomes constant and > 1 at high [**1**]. This effect shows that the leaving group are not sensitive to variation properties of the micellar surface, thus decrease in the reaction rate is more consistent with stabilisation of the phenoxide by hydrogen bonding.

The maximum in the rate profile could also be caused by a competing reaction. The alkoxide ion **1a** could react with the halide groups of the substrate in a S_N2 reaction to make a second product which is a phenoxide ion. As before, increasing surfactant concentration transfers the substrate to the lower polarity medium of micellar phase which speeds the reaction. This effect is opposed by decreasing contribution of the competing bimolecular reaction because the interfacial concentration of the alkoxide ions decreases continuously with added surfactant. This effect can be excluded because the absorbance at infinite time is not higher than expected, showing that the product of the reaction is not a phenoxide ion.

The rate constants in **1** are lower than in CTABr. This result is in agreement with the apparent dielectric constant of **1** that is higher than CTABr.[17] This effect overcomes the increasing in the head group size that was observed to speed the cyclization.[10a]

The rate profiles for the cyclization of PhBr7 and PhI7 in **1** with [NaOH] = 0.05 and 0.1 are qualitatively similar to that obtained with [NaOH] = 0.01 and the highest catalytic effect is approximately at the same [**1**].

Table 2. Cyclizations of PhBr7 and PhI7 in Aqueous Solution of 2, with [NaOH] = 0.01[a]

10^3 × [**2**], M	PhBr7	PhI7	k_I / k_{Br}
0	2.33	1.40	0.60
0.10	2.33	2.10	0.90
0.15	2.58	2.42	0.94
0.20	3.30	4.80	1.45
0.30	3.58	5.58	1.56
0.50	4.03	6.26	1.55
1.00	4.46	6.95	1.56
1.50	4.45	6.87	1.54
2.00	4.52	7.50	1.66
5.00	4.91	7.55	1.54
10.0	4.91	7.62	1.55
15.0	4.93	7.20	1.46
20.0	4.82	7.28	1.51

[a] Values of $10^4 \times k_{obs}$, s^{-1}, at 25.0°C, with 10^{-4} M substrate.

Rate constants are higher than with [NaOH] = 0.01 and rate constant decrease with increasing [**1**] is less marked. Increasing [NaOH] increases the percentage of deprotonated form **1a** that makes phenoxide ions more nucleophilic. Ratio k_I / k_{Br} at high [**1**] does not vary with [NaOH], showing that changing the extent of deprotonation of **1** affects the nucleophile but not the leaving halides.

In Table 2 we report k_{obs} for the cyclization of PhBr7 and PhI7 in **2** with [NaOH] = 0.01. Surprisingly, the rate constants do not go through a maximum but increase monotonically with increasing [**2**], and become constant at high [**2**]. **2** seems not to undergo deprotonation and attempts to measure apparent pK_a of **2** by ^1H and ^{13}C NMR have been unsuccessful so far.[18] This can be explained if monovalent hydroxide ion is not able to replace bivalent sulfate ion or, if deprotonation is present, it does not influence nucleophilicity of the phenoxide.

Rate constants in **2** are higher than both in **1** and in $(CTA)_2SO_4$,[10a] while ratio k_I / k_{Br} is approximately the same. This effect can be explained if the phenoxide ion is not stabilised by hydrogen bonding by hydroxyethyl group of the surfactant. That could be due to conformation of **2**, that forces the hydroxyethyl group and the phenoxide to be far away, and/or to the sulfate ion that, interacting with the hydroxyethyl group, makes **2** unable to form hydrogen bonding with the nucleophile.

Only the synthesis of surfactant **2** and its use in hair conditioning are reported[19] so we must use $(CTA)_2SO_4$ as a reference for the behaviour of SO_4^{2-} as a counterion. $(CTA)_2SO_4$ has a low cmc (2×10^{-4} M) and a low fractional charge ($\alpha = 0.07$).[20] Nevertheless, $(CTA)_2SO_4$ micelles show little tendency to grow, even in $[Na_2SO_4] = 1$. These observations indicate that SO_4^{2-} interacts strongly with cationic head groups but electrostatically whereas Br^-, and nitrate ions,[2a] bind specificity. Br^- does not interact with the CH_2CH_2OH group but with the quaternary ammonium ion. The Br^- binding has been found to bind **1** even in strong base when only the **1a** form is present and the surfactant is zwitterionic.[21] On the contrary, SO_4^{2-} has non-specific interaction with the surfactant. It may compete with OH^- and interact with the CH_2CH_2OH group. Whatever is the anion involved, OH^- or SO_4^{2-}, and the degree of hydrogen transfer from the surfactant to the anion, the phenoxide is scarcely influenced. Consequently, once the substrate is fully micellar bound, the rate constants become independent of [**2**].

To examine differences in the aggregate structure of **1** and **2**, we carried out a NMR study. ^1H and ^{13}C NMR spectra of **1** and **2** ($[D] = 0.05$ in D_2O) do not show any differences in the line width that depend on the nature of the counterion, indicating that the micelles of **1** and **2** do not differ in dimension and shape. ^{13}C chemical shifts are very similar and $^3J_{HH}$ coupling constants are the same for the two surfactants, showing that also the average conformation of **1** and **2** do not differ.

For atoms with spin quantum number $I > ½$ (i.e., $^{14}N = 1$), the main relaxation mechanism in solution generally involves interaction of the nuclear quadrupole moment with fluctuating electric field gradients at the nucleus. Under extreme narrowing conditions, the longitudinal (T_1) and the transverse (T_2) relaxation times are equal and the line width ($\Delta v_{½}$) of the observed signal is directly proportional to the relaxation rate and inversely to T_2. $\Delta v_{½}$ is given by Equation 3[22]

$$\Delta v_{½} = K\, q\, 2\tau_c \qquad (3)$$

where K is a constant for a given nucleus, q is the mean-square electric field gradient at the nucleus and τ_c is the correlation time, characteristic of the random molecular motions that produce the fluctuating field gradient. For ^{14}N, the cationic centre of **1** and **2**, parameters q and τ_c depend on the bonding properties of the ion, including solvation and mobility, and interactions with the counterions. The separation of these quantities is difficult, but comparison of data for different systems is informative. $\Delta v_{½}$ is the average between the line width of the monomer in solution and the surfactant in the aggregate. Measures were carried out at a concentration much higher than cmc, and the contribution of the free monomer was neglected.

The measured line widths for ^{14}N are 35 and 20 Hz for **1** and **2**, respectively. This difference reflects, in our opinion, a lower mobility and a tighter packing of surfactant **1** in the region of the cationic centre. This effect can be due to cation-anion interactions that are stronger for Br^- than for SO_4^{2-}. Br^- is a specific ion and is located close to the cationic centre while SO_4^{2-}, that is a coulombic ion, is strongly hydrated. We think that these data support the idea of SO_4^{2-} interacting more strongly with the hydroxyl group of **2** than with N^+, while in the case of **1** the main interaction of Br^- is with N^+.

EXPERIMENTAL

Materials. Preparation and purification of 2-(3-bromopropyloxy)phenol, 2-(3-iodopropyloxy)phenol, and N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium bromide (**1**) have been described.[10a,11a,14a]

N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium sulfate (2). N-hexadecyl-N-(2-hydroxyethyl)-N,N-dimethylammonium sulfate was obtained by the corresponding bromide **1** with Ag_2SO_4 in MeOH and crystallized (Et_2O - EtOAc). It contained no Ag^+ or Br^-. ^1H NMR δ ($CDCl_3$) 4.200 (1H, sb, OH), 4.045 (2H, sb, OCH_2), 3.698 (2H, sb, NCH_2), 3.340 (2H, 1-CH_2), 3.293 (6H, s, CH_3), 1.666 (2H, sb, 2-CH_2) 1.258 (26H, mb, 3 - 15-CH_2), 0.881 (3H, t, 16-CH_3). ^{13}C NMR δ ($CDCl_3$) 65.53, 64.69, 56.08, 51.80, 31.96, 29.81, 29.72, 29.70, 29.52, 29.42, 26.50, 22.85, 22.71, 14.14.

Kinetics. Reactions were followed in deionized, distilled, CO_2-free water as described.[10a]

NMR. ^1H, ^{13}C, ^{14}N NMR measures have been carried out on Bruker AC300P instrument operating at 6.96 Tesla.

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