

Micellar-Improved Synthesis of Bis-quaternary Ammonium Salts by the Epichlorohydrin Route

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ABSTRACT: A convenient procedure for the synthesis of bis-quaternary ammonium salts from long-chain alkyldimethylamines and epichlorohydrin is studied. An improved preparation of bis-quaternary ammonium salts from *N,N*-dimethyloctylamine, *N,N*-dimethyldodecylamine or *N,N*-dimethyloleylamine, their amine hydrochlorides, and epichlorohydrin can be achieved by carrying out the reaction in an aqueous micellar medium. The amine hydrochlorides are used as functional surfactants to produce the self-micellization and solubilization of reactants. The formation of micelles is a necessary condition for a successful quaternization. Comparison of the quaternization performance in ethanol, ethanol/water mixtures, and aqueous micellar medium leads to the conclusion that this micellar-improved synthesis enables easier and cheaper access to bis-quaternary ammonium salts by avoiding the formation of the mono-quaternary ammonium salts as intermediates, and by using water as solvent under mild reaction conditions. Mechanistic aspects of the quaternization reaction in micellized medium are also suggested.

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KEY WORDS: Aqueous micellar medium, bis-quaternary ammonium salt, epichlorohydrin, functional surfactant, quaternization reaction.

Bis-quaternary ammonium salts have found broad utility ranging from industrial to personal-care applications (1–6). Since they have unique aggregation abilities and better surface-active properties than single-chain surfactants of equivalent chain length (7,8), their micelle-forming properties and surfactant effects are difficult, if not impossible, to reproduce by using classical cationic surfactants (9–11). The preparation of bis-quaternary ammonium compounds today is based on three different synthetic routes: (i) reaction of long-chain tertiary amines with dihalogenated substrates, such as organic dibromides or dichlorides; (ii) reaction of *N,N,N',N'*-tetramethylpolyethylenediamines with alkyl halides; and (iii) reaction of long-chain tertiary amines with a haloalkylene oxide substrate, commonly epichlorohydrin. The dihalogenated route is preferred when the or-

ganic dihalides are commercially available, whereas the alkyl halide route is chosen to prepare bis-quaternary ammonium salts with a diethylene spacer (12). The haloalkylene oxide route is also attractive because haloalkylene oxides are more reactive than dihalogenated substrates (13,14). All of these procedures involve the use of alcohols, such as ethanol, propanol, and isopropanol, or alcohol/water mixtures, as reaction medium.

Today, fast and selective quaternization reactions using inexpensive solvents are especially attractive for commercial-scale production. In this connection, our primary impulse to improve the preparation of bis-quaternary ammonium salts by the epichlorohydrin route arose from the unique features of the micellar systems for alteration of rates and/or paths of reaction (15–18). Our earliest results were in agreement with this expectation (19). Aqueous micellar systems were an excellent reaction medium for the selective synthesis of bis-quaternary ammonium salts **5a–c** from long-chain alkyldimethylamines **1a–c** and epichlorohydrin **2**, using the amine hydrochlorides **3a–c** as functional surfactants for the successful micellar incorporation of reagents (see Scheme 1).

We report here the results of a more complete study on the micellar-improved synthesis of bis-quaternary ammonium salts **5a–c**. This synthesis was conducted beyond the region where micelles enlarge rapidly and incipient network formation or gelation takes place during the process. A comparative study was also made to achieve a full understanding of the advantages that the micellar medium exhibits in alcoholic and hydroalcoholic media, such as ethanol and ethanol/water mixtures. Among these, we found the almost complete lack of formation of the mono-quaternary ammonium salts **4a–c** during the course of the reaction using water as solvent, at any temperature. Finally, some key factors in the achievement of high selectivity for bis-quaternary ammonium salts in a micellar medium are discussed.

EXPERIMENTAL PROCEDURES

Materials. Epichlorohydrin (99%, Merck, Darmstadt, Germany), *N,N*-dimethyloctylamine (95%, Aldrich, Milwaukee, WI), *N,N*-dimethyldodecylamine (97%, Aldrich), and oleylamine (98%, Aldrich) were purchased from commercial

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Abbreviations: b.p., boiling point; HPLC, high-performance liquid chromatography; m.p., melting point; NMR, nuclear magnetic resonance; UV, ultraviolet.

sources. These chemicals were used without further purification. *N,N*-Dimethyloleylamine (>95%) was obtained from oleylamine and purified by Kugelrohr distillation under vacuum, as described below. High-purity *N,N*-dimethyloctylamine hydrochloride, *N,N*-dimethyl dodecylamine hydrochloride, and oleylamine hydrochloride were obtained from the corresponding amines and dried under vacuum prior to use.

Analytical methods. The purity of the amines was confirmed by GC analysis using a Shimadzu GC-17AATF chromatograph equipped with an SPB-5 capillary column (Supelco, Bellefonte, PA; 30 m \times 0.25 mm, 0.25 μ m film thickness) and a flame-ionization detector. The isolated mono-quaternary ammonium salts **4a–c** and bis-quaternary ammonium salts **5a–c** were characterized by nuclear magnetic resonance (NMR). ^1H and ^{13}C NMR spectra were determined on a Bruker FT-200 spectrometer, using CDCl_3 as solvent. Melting points (m.p.) were determined on a Buchi 510 micro M.P. apparatus and were not corrected. The high-performance liquid chromatography (HPLC) analyses were performed on a Shimadzu HPLC-A10 chromatograph equipped with a diode-array detector. The ultraviolet (UV) analyses were performed on a Shimadzu UV-2401 PC spectrophotometer.

Reactions were followed by withdrawing samples of the reaction mixture (0.125 mL each time) during the course of the reaction until the increase in the yield of products was negligible. After dilution and cooling, the samples were immediately analyzed for the determination of mono- and bis-quaternary salts, as follows.

Quaternary ammonium salts and their mixtures, in the presence of the corresponding amines and hydrochlorides, were identified by HPLC using a strong cation exchange column (Allsphere SCX, Alltech, Deerfield, IL; 250 \times 4.6 mm i.d., 5 μ m) under the following conditions: eluent, acetonitrile/water (20:10) containing 0.01 M sodium benzoate to act as counter ion; flow rate, 0.8 mL/min; detection, UV at 254 nm; temperature, 30°C. Although the separation of cationic compounds was possible, this method proved to be unreliable for quantitative purposes because of the unacceptable reproducibility arising from an unstable column conditioning. We overcame this difficulty as follows.

The mono- and bis-quaternary ammonium salt concentrations were estimated by combining the molar balances of the total content of quaternary ammonium salts,

$$\left(\begin{array}{c} \text{molar} \\ \text{concentration of} \\ \text{both quaternary} \\ \text{ammonium salts} \end{array} \right) = \left(\begin{array}{c} \text{molar} \\ \text{concentration of} \\ \text{mono-quaternary} \\ \text{ammonium salt} \end{array} \right) + \left(\begin{array}{c} \text{molar} \\ \text{concentration of} \\ \text{bis-quaternary} \\ \text{ammonium salt} \end{array} \right) \quad [1]$$

and the total ammonium ion as a function of both quaternary ammonium salts,

$$\left(\begin{array}{c} \text{molar} \\ \text{concentration} \\ \text{of total} \\ \text{ammonium ion} \end{array} \right) = \left(\begin{array}{c} \text{molar} \\ \text{concentration of} \\ \text{mono-quaternary} \\ \text{ammonium salt} \end{array} \right) + 2 \times \left(\begin{array}{c} \text{molar} \\ \text{concentration of} \\ \text{bis-quaternary} \\ \text{ammonium salt} \end{array} \right) \quad [2]$$

The molar concentrations of the total quaternary ammo-

nium salts and total ammonium ion were experimentally determined by reversed-phase ion-pair HPLC and UV colorimetric quantification, respectively, as described below. Equations 1 and 2 were solved simultaneously to obtain the molar concentration of each quaternary ammonium salt. After comparison with standard mixtures, the overall experimental error was found to be about 3–5%.

The quantitative determination of the total molar concentration of both quaternary ammonium salts in samples from the reaction mixture was successfully achieved by the reversed-phase ion-pair HPLC, using a base-deactivated silica column (Hipersyl BDS C-18, Sigma-Aldrich, St. Louis, MO; 250 \times 4.6 mm). After changing the mobile phase composition and varying the pairing-ion concentration, the following conditions gave the best resolution between analogous amine hydrochlorides, mono- and bis-quaternary ammonium salts. Eluent, acetonitrile/water/acetic acid (80:18:2 for salts from *N,N*-dimethyloctylamine and *N,N*-dimethyldodecylamine; and 80:15:5 for salts from *N,N*-dimethyloleylamine) containing *p*-toluenesulfonate (0.005 M sodium *p*-toluenesulfonate) as pairing-anion; flow rate, 1 mL/min for 5 min, followed by a linear increase to 3 mL/min in 3 min, held 3 mL/min for 2 min, and finally, a linear decrease from 3 to 1 mL/min in 3 min; detection, UV, 256 nm; temperature, 30°C.

The molar concentration of the total ammonium ion in the samples from the reaction mixture was determined by UV quantification of the 2:1 and 1:1 quaternary ammonium–bromophenol blue complexes (for **4a–c** and **5a–c**, respectively) that were prepared and extracted as follows (20). An aliquot (0.1 mL) of the reaction mixture was poured into 10 mL of distilled water. Bromophenol blue (4 mL of 0.001 N sodium hydroxide, freshly prepared) was added to the solution after establishing sufficiently alkaline conditions (1 mL of 10% sodium carbonate) to ensure that there were no complexes from nonquaternary amines and amine hydrochlorides. Quaternary ammonium–bromophenol blue complexes were extracted into chloroform (1.5 mL) with vigorous stirring for 5 min. The concentration of complexes was quantified by UV absorption at 600 nm.

Preparation of *N,N*-dimethyloleylamine 1c. In following a reported procedure (7,21), formic acid (87.3 g, 1.9 mol) was added dropwise to a stirred solution of oleylamine (40.6 g, 0.15 mol) and methanol (120 mL) kept cool with an ice water bath. After adding a formaldehyde solution (106.7 g of 37 wt%, 3.6 mol), the solution was heated to reflux for 12 h. The low-boiling point compounds were then removed at 50°C and a sodium hydroxide solution (25 wt%) was added until the solution became weakly alkaline (pH 9). After refluxing the solution for 3 h, the crude product was extracted with ethyl ether. Finally, the solvent was removed *in vacuo* and the *N,N*-dimethyloleylamine **1c** was directly isolated by Kugelrohr distillation (180°C/0.95 torr) with an 81.3% yield (36.0 g).

Preparation of amine hydrochlorides 3a–c. According to a reported procedure (22), a solution of the tertiary amine **1a–c** (10 mL) in dry toluene (15 mL) was saturated with dry hy-

drogen chloride generated by addition of sulfuric acid (95–97%) to hydrochloric acid (37%). The resulting insoluble hydrochloride **3a–c** was filtered and washed with toluene. All hydrochlorides were dried at room temperature under reduced pressure prior to use.

Preparation of alkyltrimethylammonium salts 4a–c and 5a–c in hydroalcoholic medium. A typical procedure was as follows. A stirred solution of *N,N*-dimethyloctylamine **1a** (1.26 g, 8 mmol) and *N,N*-dimethyloctylamine hydrochloride **3a** (0.78 g, 4 mmol) in 5 mL of ethanol/water (80:20, vol/vol) was heated until dissolution was complete at the desired temperature (50 or 80°C). The epichlorohydrin **2** (0.37 g, 4 mmol) was then added with vigorous agitation. After being stirred for 8–10 h, the reaction mixture was immediately cooled and the solvent was removed under vacuum at room temperature. The residue was washed with acetone, and the quaternary ammonium salts were isolated by recrystallization from acetone. Quaternization afforded the bis-quaternary ammonium salt **5a** (1.53 g, 87% isolated yield, 92% analytical yield) at 80°C whereas at 50°C, only the mono-quaternary ammonium salt **4a** (0.96 g, 84% isolated yield, 90% analytical yield) formed. **4a**: m.p. 41–42°C; ¹H NMR (200 MHz), CDCl₃ δ 0.845 (*m*, 2H), 0.874 (*t*, 3H), 1.292–1.373 (*m*, 8H), 1.954 (*m*, 2H), 3.196 (*t*, 2H), 3.333 (*s*, 6H), 3.650–3.710 (*d*, 2H), 3.280–3.480 (*d*, 2H), 4.339 (*m*, 1H) ppm. **5a**: m.p. 79–81°C; ¹H NMR (200 MHz), CDCl₃ δ 0.850 (*m*, 4H), 0.870 (*t*, 6H), 1.310–1.430 (*m*, 16H), 1.964 (*m*, 4H), 3.145 (*t*, 4H), 3.290 (*s*, 12H), 3.279–3.479 (*m*, 4H), 4.790 (*m*, 1H) ppm. The alkyltrimethylammonium salts **4b/5b** and **4c/5c** were prepared by the same procedure starting from *N,N*-dimethyldodecylamine **1b** and *N,N*-dimethyloleyleamine **1c**, respectively. **4b**: m.p. 46–49°C; ¹H NMR (200 MHz), CDCl₃ δ 0.860 (*t*, 3H), 0.890 (*m*, 2H), 1.300–1.350 (*m*, 16H), 1.990 (*m*, 2H), 3.200 (*t*, 2H), 3.600 (*s*, 6H), 3.600–3.800 (*m*, 4H), 4.300 (*m*, 1H) ppm. **5b**: m.p. 86–87°C; ¹H NMR (200 MHz), CDCl₃ δ 0.863 (*t*, 6H), 0.892 (*m*, 4H), 1.230–1.320 (*m*, 32H), 1.760 (*m*, 4H), 2.870 (*s*, 12H), 3.370 (*t*, 4H), 3.400–4.160 (*m*, 4H), 5.100 (*m*, 1H) ppm. **4c**: waxy; ¹H NMR (200 MHz), CDCl₃ δ 0.870 (*m*, 2H), 0.920 (*t*, 3H), 1.300 (*m*, 12H), 1.251–1.367 (*m*, 8H), 1.971 (*m*, 2H), 1.980 (*m*, 4H), 3.190 (*t*, 2H), 3.320 (*s*, 6H), 3.300–3.650 (*m*, 4H), 4.350 (*m*, 1H), 5.250 (*m*, 2H) ppm. **5c**: waxy; ¹H NMR (200 MHz), CDCl₃ δ 0.880 (*m*, 4H), 0.940 (*t*, 6H), 1.270 (*m*, 24H), 1.260–1.380 (*m*, 16H), 1.980 (*m*, 4H), 1.990 (*m*, 8H), 3.150 (*t*, 4H), 3.290 (*s*, 12H), 3.280–3.480 (*m*, 4H), 4.790 (*m*, 1H), 5.150 (*m*, 4H) ppm.

Preparation of bis-octyltrimethylammonium salt 5a in aqueous micellar medium. A typical procedure was as follows. After the complete dissolution of *N,N*-dimethyloctylamine hydrochloride **3a** (2.36 g, 12.4 mmol) in water (5 mL) at the desired temperature (50 or 80°C), a mixture of *N,N*-dimethyloctylamine **1a** (1.26 g, 8 mmol) and epichlorohydrin **2** (0.37 g, 4 mmol) was added at once under vigorous agitation, with self-micellization. The reaction was completed when the yield of the bis-quaternary ammonium salt **5a** did not increase further with increasing reaction times (6–8 h). After evaporation of the water under vacuum at room tempera-

ture, the residue was washed with acetone, and the quaternary ammonium salts were isolated by recrystallization from acetone. This process afforded the bis-quaternary ammonium salt **5a** as highly hygroscopic white crystals (1.85 g, 86% isolated yield). To our surprise, unlike alcohol or alcohol/water mixtures as reaction media, the mono-quaternary ammonium salt **4a** was not formed as an intermediate during the whole course of the quaternization at 80°C. And even more unexpectedly, the same happened at the lower temperature (50°C).

Preparation of bis-dodecyltrimethylammonium salt 5b in aqueous micellar medium. Compound **5b** was prepared from *N,N*-dimethyldodecylamine **1b** (0.85 g, 4 mmol), epichlorohydrin **2** (0.37 g, 4 mmol), and *N,N*-dimethyldodecylamine hydrochloride **3b** (1.5 g, 6 mmol) following the same procedure as described for **5a**. Recrystallization from acetone gave pure bis-quaternary ammonium salt **5b** as hygroscopic white crystals (1.93 g, 87% isolated yield). Again, the almost complete lack of formation of the mono-quaternary ammonium salt **4b** (less than 5% analytical yield) during the course of the reaction was the distinctive feature of the quaternization in an aqueous micellar medium.

Preparation of bis-oleyltrimethylammonium salt 5c in aqueous micellar medium. Compound **5c** was prepared from *N,N*-dimethyloleyleamine **1c** (0.48 g, 1.6 mmol), epichlorohydrin **2** (0.16 g, 1.6 mmol), and *N,N*-dimethyloleyleamine hydrochloride **3c** (0.7 g, 2.1 mmol) according to the preceding procedure described for **5a**. Recrystallization from acetone gave pure bis-quaternary ammonium salt **5c** as a pale yellow waxy product (0.95 g, 83% isolated yield). Again, the mono-quaternary ammonium salt **4c** was formed in very small amounts (less than 5% analytical yield) in micellized medium.

RESULTS AND DISCUSSION

Our search for a selective method that exhibits advantages arising from the use of water as solvent under mild reaction conditions was guided by earlier works on bis-quaternary ammonium salts from epichlorohydrin (4,13). To develop and compare the new method with conventional ones, we initially examined the use of ethanol and ethanol/water mixtures as a reaction medium. The study was focused on the quaternization reaction of *N,N*-dimethyloctylamine **1a**, *N,N*-dimethyldodecylamine **1b**, and *N,N*-dimethyl oleylamine **1c** with epichlorohydrin **2** in the presence of its amine hydrochlorides **3a–c**. The quaternization rates and selectivity to bis-alkyltrimethylammonium salts **5a–c** were strongly dependent on the reaction medium.

Figure 1 shows the data from quaternization reactions for a dimethylalkylamine/hydrochloride/epichlorohydrin (2:1:1) molar ratio in ethanol and ethanol/water (80:20; 50:50, vol/vol) mixtures as reaction media at 50 and 80°C. As reported by Kim *et al.* (13), the preparation of bis-quaternary ammonium salts **5a–c** using ethanol as solvent is not feasible at 50°C but is possible at 80°C. In addition, this distinctive feature does not change even if ethanol/water (80:20; 50:50,

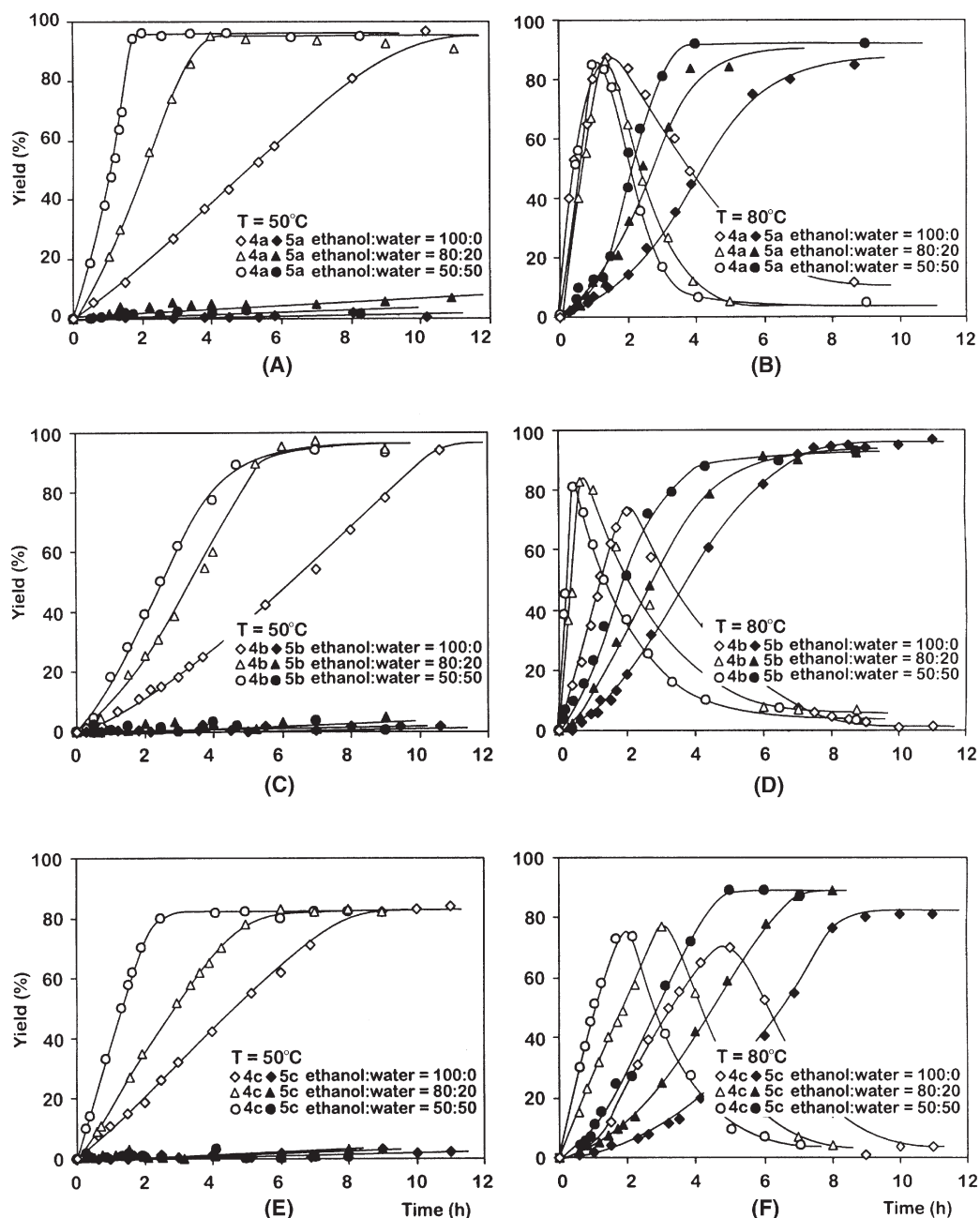


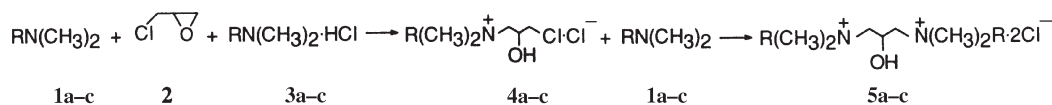
FIG. 1. Yields of mono-quaternary ammonium salts **4a–c** and bis-quaternary ammonium salts **5a–c** as a function of reaction time for quaternization reactions in ethanol and ethanol/water mixtures at 50 and 80°C, with **1a–c/3a–c/2** (2:1:1) molar ratios. (A,B) **1a**: *N,N*-dimethyloctylamine. (C,D) **1b**: *N,N*-dimethyldodecylamine. (E,F) **1c**: *N,N*-dimethyloleamine.

vol/vol) mixtures are used as homogeneous reaction media. These results support a two-step mechanism with the involvement of **4a–c** as direct intermediates (see Scheme 1) and make evident an activation energy for bis-quaternization that is much higher than for mono-quaternization.

In focusing attention on experiments with ethanol (b.p. 78.4°C) as solvent, it is apparent that the preferential formation of mono-quaternary salts **4a–c** is advantageous to produce them, especially at 50°C, but it is inconvenient to prepare bis-quaternary ammonium salts **5a–c**.

At best, good conversions of **4a–c** to **5a–c** can be achieved

only after reaction for 6–10 h at 80°C. The addition of water to ethanol afforded better reaction conditions since an enhancement of the rate of quaternization reactions was possible without increasing the temperature. Although yields of **4a–c** and **5a–c** were nearly 85–90% regardless of the amount of water in the reaction medium, a significant reduction of the reaction times was obtained by increasing the amount of water from 0 to 50% vol/vol in the ethanol/water mixture. At 50°C, the reaction times to reach maximal yields of **4a** were up to five times shorter than those for pure ethanol. At 80°C, the reaction time to achieve the maximal yield of



where, a: R = C₈H₁₇ b: R = C₁₂H₂₅ c: R = CH₃(CH₂)₇CH = CH(CH₂)₈

SCHEME 1

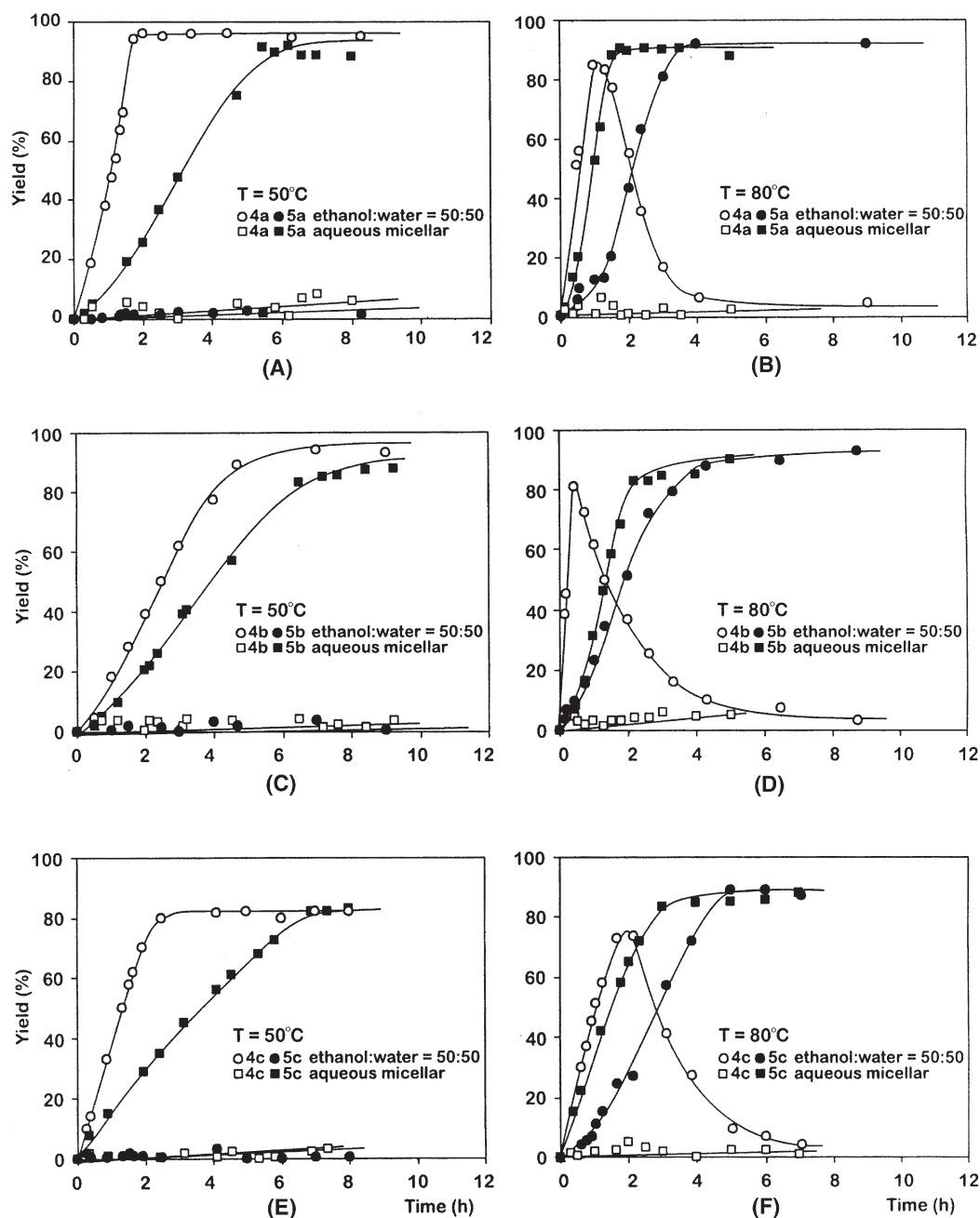


FIG. 2. Comparison of yields of mono-quaternary ammonium salts **4a-c** and bis-quaternary ammonium salts **5a-c** for quaternization in aqueous ethanol/water mixture and aqueous micellar medium at 50 and 80°C. **1a-c/3a-c/2** (2:1:1) molar ratio for ethanol/water (50:50, vol/vol) mixture. **1a/3a/2** (2:3.1:1), **1b/3b/2** (1:1.5:1), and **1c/3c/2** (1:1.3:1) molar ratios for aqueous micellar medium. (A,B) **1a**: N,N-dimethyloctylamine. (C,D) **1b**: N,N-dimethyldodecylamine. (E,F) **1c**: N,N-dimethyloleamine.

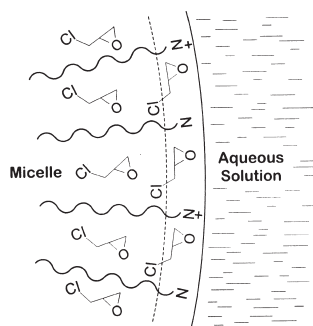


FIG. 3. Schematic representation of amine hydrochloride micellization with long-chain alkyldimethylamine and epichlorohydrin solubilization.

bis-quaternary ammonium salt **5a** was reduced by half, from 8 to 4 h. Even though this improvement is certainly useful for the production of both quaternary ammonium salts, we tried to improve the quaternization reaction further by conducting it directly in water. To this purpose, we took advantage of the ability of the amine chlorohydrates **3a–c** to solubilize both long-chain alkyldimethylamines **1a–c** and epichlorohydrin **2**.

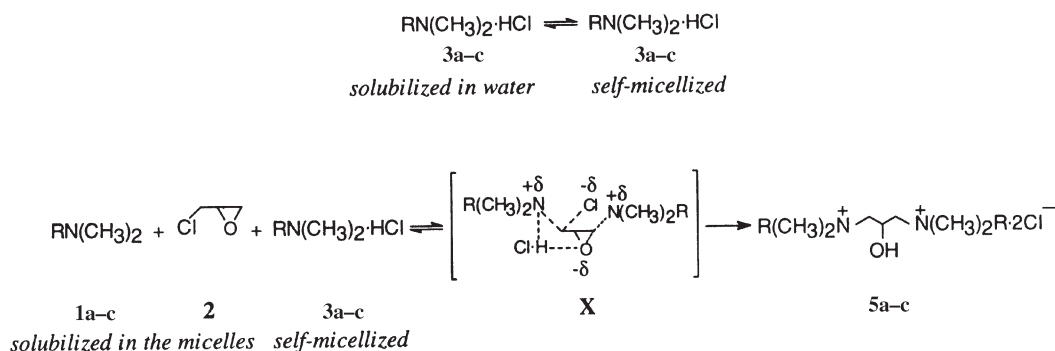
To better understand the novel use of **3a–c** as functional surfactants, i.e., reactants as well as surfactants for the successful micellar incorporation of both **1a–c** and **2**, a new series of trials was carried out in pure water. Upon varying the **1a–c/3a–c/2** molar ratio over a wide range, we determined that self-micellization took place because of the amine hydrochlorides. Even though the reaction medium appeared to be homogeneous, the formation of cationic micelles was detected by measuring the viscosity and conductivity of the reaction medium at the beginning and during the quaternization reactions. Once the aqueous micellar medium is formed with the initial aid of the amine hydrochlorides **3a–c**, the quaternization process takes place with increasing micellization because the product salts play the role of more effective surfactants than **3a–c**.

We found that the self-micellization phenomenon occurred over a narrow range of **1a–c/3a–c/2** molar ratios,

which were different for each amine system. For example, typical molar ratios for *N,N*-dimethyloctylamine, *N,N*-dimethyldodecylamine, and *N,N*-dimethyloleamine systems were 2:3.1:1, 1:1.5:1, and 1:1.3:3, respectively. As expected, the amount of amine hydrochloride needed to be lower as the alkyl chain length increased. If the initial molar ratios of reactants are slightly different from these optimal values, either the micellization does not take place or else micelles enlarge rapidly and an incipient gelation takes place during the process. By avoiding conditions where the quaternization reactions are extremely slow, if they occur at all, the preparation of **5a–c** in micellized medium exhibits appreciable advantages, as discussed below.

Results for the micellar-improved preparation of **5a–c** are shown in Figure 2. These differ from what happens in the experiments with an ethanol/water (50:50, vol/vol) mixture. It can be seen that quaternization rates are enhanced in the micellar medium as would be expected, but the most remarkable—and unexpected—finding is the almost complete lack of formation of mono-quaternary ammonium salts **4a–c** as a reaction intermediate. In contrast to alcoholic and hydroalcoholic quaternization, the bis-quaternary ammonium salts **5a–c** could feasibly be selectively obtained even at 50°C. Moreover, in comparison with the best hydroalcoholic condition given by ethanol/water (50:50, vol/vol) mixtures at 80°C, the reaction times to achieve the maximal yield of **5a–c** (90%) are reduced by half, from 4 to 2 h.

The experimental evidence suggests that quaternization in aqueous micellar medium proceeds by a reaction path different from that proposed for homogeneous reaction in ethanol (11) or aqueous ethanol medium. Since micelles disrupt in solvents containing ethanol but do not disrupt in water, the observed changes in quaternization rates and selectivity can be attributed to micellar effects, and the formation of micelles was a necessary condition to achieve the desired end. One possibility is that the quaternization in aqueous medium occurs at the micelle–water interface rather than the hydrocarbonlike core of the micelles. This could be attributed to the following factors: (i) Cationic micelles oriented to the aqueous phase are formed by shaping an



where, a: R = C₈H₁₇ b: R = C₁₂H₂₅ c: R = CH₃(CH₂)₇CH = CH(CH₂)₈

SCHEME 2

assembly among the amine hydrochlorides and alkyl-dimethylamine long-chain hydrophobic groups as shown in Figure 3; (ii) alkyl-dimethylamines **1a-c** and amine hydrochlorides **3a-c** micellized in this way with epichlorohydrin **2** solubilized in the core of micelles could not contact active groups of **1a-c** and **3a-c**; therefore, in contrast with homogeneous reaction media, the quaternization reaction only takes place within a region very close to the micelle-water interface; (iii) the micelle structure creates an orderly and compact arrangement of reactants, which is favorable for a **1a-c** and **3a-c** concerted attack on **2**, affording the direct and selective formation of bis-quaternary ammonium salts **5a-c**, without the formation of mono-quaternary ammonium salts **4a-c**. A plausible mechanism is depicted in Scheme 2.

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