

# A Convenient Synthesis of Quaternary Ammonium Gemini Surfactants from Long-Chain Alkyldimethylamines and Epichlorohydrin

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**Abstract:** Aqueous micellar systems proved to be an excellent reaction medium for the selective synthesis of *bis*-quaternary ammonium salts **5a–c** from epichlorohydrin **2** and long-chain alkyldimethylamines **1a–c**, in the presence of the corresponding amine chlorohydrates **3a–c** as functional surfactants. Unlike alcohol or alcohol–water mixtures as reaction medium, *mono*-quaternary ammonium salts **4a–c** were formed, if any, in very small amounts under micellar conditions, allowing a more direct and rapid access to these quaternary ammonium gemini surfactants.

**Key words:** gemini surfactants, *bis*-quaternary ammonium compounds, epichlorohydrin, quaternization, micellar system

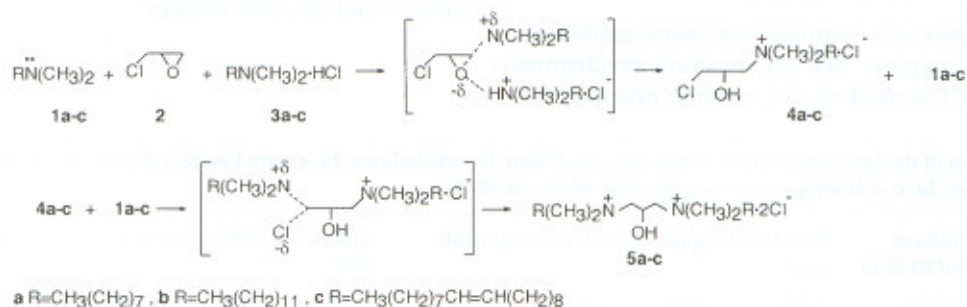
*Bis*-quaternary ammonium salts are the most common cationic gemini surfactants.<sup>1</sup> They possess at least two hydrophobic chains and two cationic groups connected with a spacer group, typically a polyethylene or polyoxyethylene group. They have better surface-active and micelle-forming properties than corresponding conventional surfactants of equivalent chain length.<sup>2</sup> These remarkable properties give them excellent properties as cationic surfactants, good extractive abilities as phase transfer catalysts, and good antimicrobial activity.<sup>3</sup>

Quaternization reactions of long-chain tri-alkylamines have been very extensively studied, largely with dihalogenated substrates to provide the spacer group.<sup>4</sup> Another attractive variant involves the reaction between tertiary amines and an alkylene oxide substrate, such as an epichlorohydrin, because alkylene oxides have shown to be more reactive than dihalogenated substrates.<sup>5</sup> The reaction of a long-chain tri-alkylamine **1a–c** and epichlorohydrin **2** is a

two-step process involving nucleophilic substitution with the amine hydrochloride **3a–c** assistance to open the epoxide ring affording the intermediate *mono*-ammonium salt **4a–c**, followed by amine attack on the chlorine-substituted carbon of **4a–c** yielding *bis*-ammonium salt **5a–c** (Scheme 1). So far described syntheses of **5a–c** from **1a–c** and **2** proceed through **4a–c** in the presence of protic polar solvents, such as alcohols,<sup>5</sup> or alcohol–water mixtures<sup>6</sup> able to solubilize all reactants, especially the long-chain tri-alkylamine.

The fast selective synthesis of **5a–c** and the use of inexpensive solvents are especially attractive for production purposes. In this connection, we report herein that the substitution reaction in aqueous micellar medium enables more facile and cheaper access to *bis*-quaternary ammonium salts from long-chain alkyldimethylamines and epichlorohydrin. The key feature of this process can be found in the ability of micellar media to influence rates of substitution reactions.<sup>7</sup> Yields and selectivity for hydroalcoholic and aqueous micellar systems are compared in order to have a better assessment of the advantages of this method.

Following a previous report,<sup>5</sup> the preparation of the *bis*-quaternary ammonium salts from **1a–c** and **2** in the presence of the corresponding amine hydrochlorides **3a–c** and ethanol as reaction medium, was corroborated to be unfeasible at 50 °C because the conversion of **4a–c** into **5a–c** does not take place in appreciable extension at low temperature (entries 1, 5 and 9 in Table 1). However, the quaternization reaction provided the *bis*-quaternary



Scheme 1

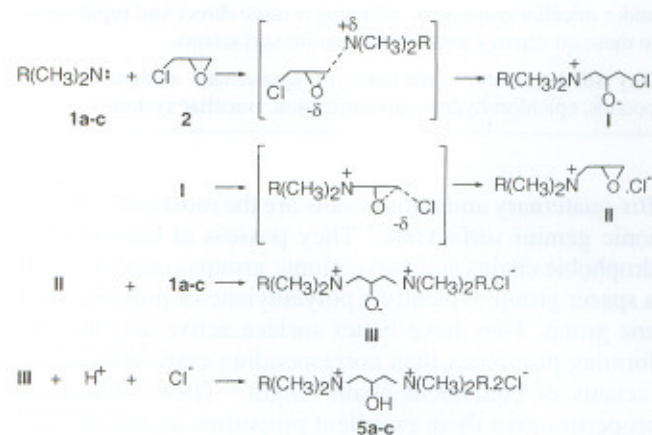
ammonium salts **5a–c** in 84%, 92% and 76% yields, respectively, after conversion of the *mono*-quaternary ammonium salts **4a–c**, at 80 °C (entries 1, 5 and 9 in Table 2).<sup>8</sup> All reactions have been followed by combined HPLC and colorimetric methods.<sup>9</sup>

In another set of experiments, the use of ethanol–water mixtures was examined to find better reaction conditions.<sup>10</sup> The convenient effect of adding water to ethanol is remarkable (entries 2, 3; 6, 7; 10, 11 in Tables 1 and 2). A significant enhancement of the rate of production of the *mono*-quaternary ammonium salts **4a–c** was observed at 50 °C, but the yields of **5a–c** did not improve enough because only a small increase took place by increasing the water in the binary mixture (entries 2, 3; 6, 7; 10, 11 in Table 1). Nevertheless, the rates of production of **5a–c** were significantly improved. In fact, in the ethanol–water (50:50) mixture the yield of **5a** rises up to 91% in only 2.5 h, at 80 °C (entries 2, 3 in Table 2). Under these reaction conditions, the results were also much better for compounds **5b** and **5c** (entries 6, 7; 10, 11 in Table 2).

Encouraged by these results, we tried to increase the rate of production of **5a–c** still further, conducting the quaternization reaction directly in aqueous solution by taking advantage of the ability of **3a–c** to solubilize both **1a–c** and **2** in water.<sup>11</sup> Upon varying the amine–epichlorohydrin–amine hydrochloride molar ratio within a wide range, micellization occurred abruptly over a small concentration range, which was different for each system. The amount of amine hydrochloride needed to be lower as the alkyl chain length increased. Even though the solution appeared homogeneous, the formation of cationic micelles was detected by measuring the viscosity and conductivity of the reaction mixture. It was found that the rate of quaternization reaction was enhanced as expected, but there was another remarkable finding. To our surprise, the *bis*-quaternary ammonium salts **5a–c** were formed in high yields and good to excellent selectivity from the beginning of the reaction, even at 50 °C (entries 4, 8 and 12 in Tables 1 and 2). It should be noted that the desired products **5a–c** could not be obtained in aqueous ethanol medium at this temperature (entries 1–3, 5–7 and 9–11 in Table 1), in agreement with the fact that micelles do not form in solvents containing ethanol.<sup>12</sup>

The lack of an appreciable formation of *mono*-quaternary ammonium salts suggests that the reaction mechanism shown in Scheme 1 is unlikely for cationic micellar sys-

tems. Another argument to support this suggestion arises from the low availability of amine hydrochlorides **3a–c** to assist the epoxide opening since they are forming micelles. A plausible mechanism of formation of **5a–c** from **1a–c** and **2** in cationic micelles is depicted in Scheme 2. The reaction appears to proceed via a ring-opening step leading to the zwitterion **I**, which by further arrangement involving C–Cl bond breaking affords the epoxide **II** as intermediate. Then, another molecule of **1a–c** attacks the epoxide carbon with ease to give the intermediate **III**.<sup>13</sup> Finally, **5a–c** can be formed by proton attacking the alkoxide group of **III**. Protons and chloride anions are provided by a fast and partial dissociation of **3a–c** in water. The reaction between **II** and **3a–c** to give **5a–c** is unlikely since it is probably diffusion-controlled. Micellar recognition studies are currently under investigation in our laboratory.



**a** R=CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>, **b** R=CH<sub>3</sub>(CH<sub>2</sub>)<sub>11</sub>, **c** R=CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>CH=CH(CH<sub>2</sub>)<sub>8</sub>

Scheme 2

In summary, the *bis*-quaternary ammonium salt was directly obtained in good yield (greater than 86%) and excellent selectivity (greater than 97%), under micellar and mild conditions. This synthetic approach is believed to be cost-effective and facile on an industrial scale, offering an alternative method for the synthesis of quaternary ammonium gemini surfactants from long-chain alkyldimethylamines and epichlorohydrin.

**Table 1** Comparison of the Quaternization Reaction of Long-Chain Tri-alkylamines **1a–c** with Epichlorohydrin **2** and the Corresponding Amine Hydrochlorides **3a–c** in Homogeneous and Micellar Media, at 50 °C

Entry	Amine	Solvent EtOH:H <sub>2</sub> O (% v/v)	Yield of Bis-quaternary Ammonium Salt (%) <sup>a</sup>				Selectivity of Bis-quaternary Ammonium Salt Reaction (%) <sup>b</sup>				Reaction Medium
			2.0 h	4.0 h	6.0 h	8.0 h	2.0 h	4.0 h	6.0 h	8.0 h	
1	<b>1a</b>	100:0	<1	<1	1	2	2	1	2	2	homog. <sup>c</sup>
2		80:20	1	2	3	7	3	2	4	7	homog. <sup>c</sup>
3		50:50	2	2	5	9	1.6	2	5	9	homog. <sup>c</sup>

**Table 1** Comparison of the Quaternization Reaction of Long-Chain Tri-alkylamines **1a–c** with Epichlorohydrin **2** and the Corresponding Amine Hydrochlorides **3a–c** in Homogeneous and Micellar Media, at 50 °C (continued)

Entry	Amine	Solvent EtOH:H <sub>2</sub> O (% v/v)	Yield of Bis-quaternary Ammonium Salt (%) <sup>a</sup>				Selectivity of Bis-quaternary Ammonium Salt (%) <sup>b</sup>				Reaction Medium
			2.0 h	4.0 h	6.0 h	8.0 h	2.0 h	4.0 h	6.0 h	8.0 h	
4		0:100	25	63	90	88	90	94	99	97	micellar <sup>d</sup>
5	<b>1b</b>	100:0	<1	<1	1	2	2	2	2	3	homog. <sup>c</sup>
6		80:20	2	2	3	4	6	3	3	4	homog. <sup>c</sup>
7		50:50	1	2	4	5	3	3	4	4	homog. <sup>c</sup>
8		0:100	22	40	53	87	92	91	97	97	micellar <sup>f</sup>
9	<b>1c</b>	100:0	1	1	1	<1	1	1	1	1	homog. <sup>g</sup>
10		80:20	1	<1	<1	<1	4	2	<1	<1	homog. <sup>g</sup>
11		50:50	1	<1	<1	<1	2	1	<1	1	homog. <sup>g</sup>
12		0:100	30	56	81	86	98	99	100	100	micellar <sup>h</sup>

<sup>a</sup> Quantitatively determined by combined techniques.<sup>9</sup><sup>b</sup> Selectivity is defined as the percentage of the consumed epichlorohydrin that forms the *bis*-quaternary ammonium salt.<sup>c</sup> **1a:2:3a** (2:1:1).<sup>d</sup> **1a:2:3a** (2:1:3.1).<sup>e</sup> **1b:2:3b** (2:1:1).<sup>f</sup> **1b:2:3b** (2:1:1.5).<sup>g</sup> **1c:2:3c** (2:1:1).<sup>h</sup> **1b:2:3b** (2:1:1.3).**Table 2** Comparison of the Quaternization Reaction of Long-Chain Tri-alkylamines **1a–c** with Epichlorohydrin **2** and the Corresponding Amine Hydrochlorides **3a–c** in Homogeneous and Micellar Media, at 80 °C

Entry	Amine	Solvent EtOH:H <sub>2</sub> O (% v/v)	Yield of Bis-quaternary Ammonium Salt (%) <sup>a</sup>				Selectivity of Bis-quaternary Ammonium Salt (%) <sup>b</sup>				Reaction Medium
			2.0 h	4.0 h	6.0 h	8.0 h	2.0 h	4.0 h	6.0 h	8.0 h	
1	<b>1a</b>	100:0	10	31	54	84	13	38	64	93	homog. <sup>c</sup>
2		80:20	16	47	76	87	15	50	78	90	homog. <sup>c</sup>
3		50:50	76	91	92	92	64	96	96	96	homog. <sup>c</sup>
4		0:100	89	90	89	90	99	99	98	99	micellar <sup>d</sup>
5	<b>1b</b>	100:0	19	61	82	92	21	63	83	95	homog. <sup>c</sup>
6		80:20	34	71	91	91	36	78	93	93	homog. <sup>c</sup>
7		50:50	51	84	89	91	58	89	93	97	homog. <sup>c</sup>
8		0:100	76	86	89	90	95	95	94	97	micellar <sup>f</sup>
9	<b>1c</b>	100:0	6	18	41	76	16	22	44	83	homog. <sup>g</sup>
10		80:20	12	42	74	89	17	43	83	96	homog. <sup>g</sup>
11		50:50	32	74	85	89	29	73	92	96	homog. <sup>g</sup>
12		0:100	64	85	85	87	95	99	97	99	micellar <sup>h</sup>

<sup>a</sup> Quantitatively determined by combined techniques.<sup>9</sup><sup>b</sup> Selectivity is defined as the percentage of the consumed epichlorohydrin that forms the *bis*-quaternary ammonium salt.<sup>c</sup> **1a:2:3a** (2:1:1).<sup>d</sup> **1a:2:3a** (2:1:3.1).<sup>e</sup> **1b:2:3b** (2:1:1).<sup>f</sup> **1b:2:3b** (2:1:1.5).<sup>g</sup> **1c:2:3c** (2:1:1).<sup>h</sup> **1b:2:3b** (2:1:1.3).

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- (8) Compounds **4a-c** and **5a-c** have been isolated in a pure analytical form and their spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were consistent with the structure. Spectral data for **4b** and **5b** are in full agreement with those previously reported in ref.<sup>5</sup> Isolated yields were slightly lower (6–8%) than those obtained by the combined technique based on the combined HPLC and colorimetric methods described in ref.<sup>9</sup>
- (9) (a) Simultaneous determination of *mono*- and *bis*-quaternary salts **4a-c** and **5a-c** from crudes of reaction by ion-exchange HPLC was not successful due to the unacceptable reproducibility. We overcame these difficulties by combining reversed-phase ion-pair HPLC using sodium *p*-toluen-sulfonate as UV-absorbing ion-pair reagent, and UV quantification of quaternary ammonium-bromophenol blue complexes extracted with chloroform from a mixture of a suitable aliquot of the reaction mixture in alkaline solution (10% sodium carbonate) and bromophenol blue (0.001 N). After comparison with standard mixtures, the experimental error was found to be about 2–3%. (b) The HPLC method was based on that of: Dowle, C. J.; Campbell, W. C. *Analyst* **1989**, *114*, 883. (c) The colorimetric determination method was based on that of: van Steveninck, J.; Maas, M. In *Cationic Surfactants, Surfactant Science Series*, Vol. 4; Jungermann, E., Ed.; Marcel Dekker, Inc.: New York, **1970**, Chap. 13.
- (10) 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**, 0.78g, 4 mmol) in ethanol–water (80:20, 5 mL) mixture was heated until complete dissolution at 50 °C. The epichlorohydrin (**2**, 0.37g, 4 mmol) was then added under vigorous agitation. After being stirred for 8–10 hours, 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. It afforded the *mono*-quaternary ammonium salt **4a** (0.96 g, 84% isolated yield, 90% analytical yield). The *bis*-quaternary ammonium salt **5a** (1.53 g, 87% isolated yield, 92% analytical yield), was obtained by performing the reaction with the same amount of reagents and solvent, at 80 °C.
- (11) A typical procedure was as follows. A stirred solution of *N,N*-dimethyloctylamine hydrochloride (**3a**, 2.36 g, 12.4 mmol) in water (5 mL) was heated until complete dissolution at 50 °C. A mixture of *N,N*-dimethyloctylamine (**1a**, 1.26 g, 8 mmol) and epichlorohydrin (**2**, 0.37 g, 4 mmol) was then added at once under vigorous agitation, with spontaneous micellization. The solution was stirred for 6–8 hours. After evaporation of the solvent under vacuum at room temperature, the residue was washed with acetone and the quaternary ammonium salts were isolated by recrystallization from acetone. It afforded the *bis*-quaternary ammonium salt **5a** (1.48 g, 84% isolated yield, 88% analytical yield), instead of the *mono*-quaternary ammonium salt **4a**, as described in ref.<sup>9</sup> There was no problem to separate the surfactants **5a-c** from the excess of **3a-c** because these amine hydrochlorides are soluble in cold acetone, while the *bis*-quaternary ammonium salts are insoluble ones.
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