Preparation of *bis*-Quaternary Ammonium Salts from Epichlorohydrin

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ABSTRACT: A novel *bis*-quaternary ammonium salt was prepared conveniently and almost quantitatively from *N,N*-dimethyldodecylamine, its hydrochloride, and epichlorohydrin. Reaction of *N,N*-dimethyldodecylamine with epichlorohydrin (in the presence of the amine hydrochloride) or various dichloro compounds was investigated by using ^1H nuclear magnetic resonance. The reaction route was studied by examining the reactivity of reagents with the amine and the effect of reaction temperature. The ease of the reaction with epichlorohydrin was found to be due to the assistance of amine hydrochloride in opening the epoxide ring and to neighboring-group participation by the hydroxyl group of the intermediate *mono*-ammonium salt in the quaternization step. Neighboring-group participation by the hydroxyl group in these quaternization reactions is also discussed.

JAOCS 73, 67–71 (1996).

KEY WORDS: *bis*-Quaternary alkylammonium salt, epichlorohydrin, neighboring-group participation, preparation, quaternization.

As industrial technology makes further progress, demands for high-performance surface-active compounds are increasing. To respond to these demands, novel surfactants have been successfully designed and developed. These may be classified into two types. One type is composed of two single-chain surfactants connected with a spacer (1–3) or as multichain amphipathic compounds with two hydrophilic groups (4), for which the inter- or intramolecular hydrophobic interaction is enhanced compared with conventional single-chain surfactants. This kind of surfactant shows good water solubility, excellent micelle-forming property, high ability to lower aqueous surface tension, and good lime soap-dispersing ability. The other type has a hydrophilic head group at both ends of a hydrophobic alkylene chain (α,ω–type surfactants) (5,6). These α,ω–type surfactants are characterized by higher critical micelle concentration (CMC), smaller-size aggregates, and a higher degree of ionization of micelles than those of conventional surfactants that have one hydrophilic head group per alkyl group.

In this paper, to synthesize a new type of surfactant, we report the reaction of long-chain alkyldimethylamine with epichlorohydrin in the presence of the amine hydrochloride to afford the *bis*-ammonium salt, in which two quaternary alkylammonium chlorides are formally connected with a spacer. Although epichlorohydrin has been used for the reaction with alkylamine, many kinds of products have been reported depending on the reaction conditions (7–12). Furthermore, two patents (13,14) claimed the product *bis*-ammonium salt from the reaction of alkylamine with epichlorohydrin in a hydrochloric acid/isopropanol/water system, but the reaction path was left ambiguous and may be different from that in this work.

In the present case, the reaction proceeds conveniently and almost quantitatively under mild conditions. Neighboring-group participation by the hydroxyl group contributing to the ease of this quaternization reaction is discussed. The reaction route was studied by ^1H NMR.

EXPERIMENTAL PROCEDURES

The reagents used were all purchased from commercial sources, and their purity was confirmed by gas–liquid chromatography. Infrared spectra were recorded on an FT-IR 1600 (Perkin-Elmer Limited, Beaconsfield Bucks, England) with samples as KBr disks. Mass spectra were run on a JMS-DX 303 (JEOL Ltd., Tokyo, Japan) spectrometer. ^1H Nuclear magnetic resonance (NMR) spectra were recorded at 600 MHz with an AM 600 (Bruker, Fallanden, Switzerland) spectrometer on samples in $CDCl_3$ and D_2O. The reaction was followed by thin-layer chromatography (silica gel plates) with a mixture of ethyl acetate/acetone/ammonium solution (29%)/water (3.0:3.5:0.5:0.5, vol/vol) as the eluent.

Reaction of N,N-dimethyldodecylamine with epichlorohydrin. A mixture of N,N-dimethyldodecylamine (1.71 g, 8.0 mmol), its hydrochloride (0.99 g, 4.0 mmol), epichlorohydrin (0.37 g, 4.0 mmol), and ethanol (5 mL) was stirred for 8 h at room temperature (run 3, Table 3) and then heated to reflux for 8 h (run 4). Immediately after all remaining solvent was evaporated under reduced pressure at room temperature, the yield of product was determined by ^1H NMR with naphthalene as an internal standard. *Mono-* (**Ia**) and *bis*-ammonium salts (**Ib**) were isolated respectively from runs 3 and 4 by recrystallization from acetone (**Ia**: 1.06 g, 77% yield; **Ib**: 2.22 g, 93% yield).

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Preparation of mono-*ammonium salt from 1,3-dichloro-2-propanol, 1,3-dichloropropane, 1,4-dichloro-2-butanol, and* bis-*2-chloroethyl ether.* A mixture of N,N-dimethyldodecylamine (0.86 g, 4.0 mmol) and dichloro compound (12.0 mmol) in ethanol (20 mL) was heated to reflux for 24 h. After evaporation of the solvent under reduced pressure, *mono*-ammonium salts were purified by recrystallization from acetone (**IIa**: 1.02 g, 74% yield; **IIIa**: 0.89 g, 68% yield; **Va**: 1.03 g, 72% yield). For the *mono*-ammonium salt from 1,4-dichloro-2-butanol, the amount of product was determined by ^1H NMR with naphthalene as an internal standard (91% NMR yield), and the purification was done by silica-gel column chromatography with a chloroform-methanol (6:1, vol/vol) eluent (**IVa**: 0.60 g, 42% yield).

Identification of the structure of mono-*ammonium salt from 1,4-dichloro-2-butanol.* The excess trimethylamine gas was condensed into the solution of *mono*-ammonium salt from 1,4-dichloro-2-butanol (0.15 g) in dichloromethane (2 mL) for 1 h, and the solution was stirred at room temperature for 24 h. The produced crystal was separated by filtration, and its NMR spectra were measured in D_2O.

Preparation of bis-*ammonium salt from 1,3-dichloro-2-propanol, 1,3-dichloropropane, 1,4-dichloro-2-butanol, and* bis-*2-chloroethyl ether.* A mixture of N,N-dimethyldodecylamine (4.26 g, 20.0 mmol) and dichloro compound (4.0 mmol) in 1-propanol (10 mL) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure; *bis*-ammonium salts were isolated by washing with acetone and then purified by recrystallization from acetone (**IIb**: 1.62 g, 73% yield; **IIIb**: 1.38 g, 64% yield; **IVb**: 1.56 g, 69% yield; **Vb**: 1.52 g, 67% yield).

Determination of the formation rate of mono- *and* bis-*ammonium salt from epichlorohydrin, 1,3-dichloro-2-propanol, 1,3-dichloropropane, 1,4-dichloro-2-butanol, and* bis-*2-chloroethyl ether.* A mixture of chloro compound (4.0 mmol) and *N,N*-dimethyldodecylamine (2.57 g, 12.0 mmol) in ethanol (5 mL) was heated to reflux. Small portions of reaction solution were taken at specific intervals of reaction time, and the solvent was evaporated. The amount of products was determined by ^1H NMR with the unreacted amine serving as an internal standard. For epichlorohydrin, instead of 12.0 mmol of N,N-dimethyldodecylamine, 8.0 mmol amine and 4.0 mmol amine hydrochloride were used.

RESULTS AND DISCUSSION

Mono- and *bis*-quaternary ammonium salts from epichlorohydrin and various dichloro compounds were synthesized, and the results are listed in Tables 1 and 2.

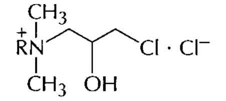
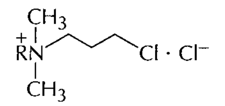
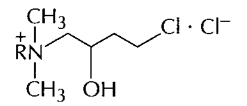
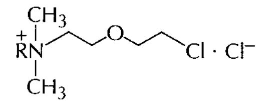
From the results of ^1H NMR and elemental analysis, the structures of *mono*-ammonium salts (**Ia and IIa**) and *bis*-ammonium salts (**Ib** and **IIb**) from epichlorohydrin and 1,3-dichloro-2-propanol are similar to each other.

To better understand the reaction of *N,N*-dimethyldodecylamine hydrochloride with epichlorohydrin, effects of the ratio of reagents and the reaction temperature were examined. The results are summarized in Table 3.

By stirring the equivalent mixture of *N,N*-dimethyldodecylamine hydrochloride and epichlorohydrin in ethanol for 20 h at room temperature, *mono*-ammonium salt **Ia** was obtained in a yield of 31% (run 1). By adding N,N-dimethyldodecylamine in the amount of one-tenth of the hydrochloride to this system, the yield of *mono*-ammonium salt **Ia** increased to 50% within 8 h. The addition of *N,N*-dimethyldodecylamine at twice the amount of its hydrochloride increased the yield to 93% within the same reaction period (runs 2 and 3), but no *bis*-ammonium salt **Ib** was detected in the reaction mixture by ^1H NMR.

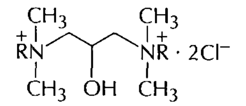
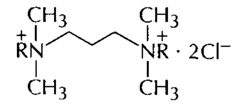
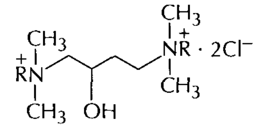
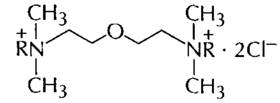
Further reaction, however, proceeded when the reaction was carried out at an elevated temperature. Thus, when the mixture of *N,N*-dimethyldodecylamine, its hydrochloride, and

TABLE 1
Characterization of *mono*-Ammonium Salts

	Compound ($R = C_{12}H_{25}$)	m.p. (°C)	^1H NMR (δ, $CDCl_3$)	Anal. found (calcd.)%[a]
Ia		46–49	0.88 (*t*, 3H), 1.20–1.45 (*m*, 18H), 1.78 (*m*, 2H), 3.41 (*d*, 6H), 3.49–3.68 (*m*, 4H), 3.78 (*m*, 2H), 4.60 (*m*, 1H)	H, 10.89 (10.84) C, 59.25 (59.05) N, 4.06 (4.05) Cl, 20.20 (20.50)
IIIa		52–55	0.88 (*t*, 3H), 1.20–1.45 (*m*, 18H), 2.32 (*m*, 2H), 3.43 (*s*, 6H), 3.48 (*m*, 2H), 3.74 (*t*, 2H), 3.85 (*t*, 2H)	H, 11.11 (10.98) C, 57.52 (57.78) N, 3.98 (3.96) Cl, 19.79 (20.06)
IVa		waxy	0.88 (*t*, 3H), 1.20–1.45 (*m*, 18H), 1.72 (*m*, 1H), 1.81 (*m*, 1H), 1.89 (*m*, 1H), 2.23 (*m*, 1H), 3.25 (*d*, 1H), 3.41 (*d*, 6H), 3.52 (*m*, 2H), 3.77 (*m*, 1H), 3.85 (*m*, 1H), 3.96 (*q*, 1H), 4.49 (*m*, 1H)	H, 11.22 (11.04) C, 56.81 (56.92) N, 3.70 (3.69) Cl, 18.72 (18.67)
Va		59–62	0.88 (*t*, 3H), 1.20–1.45 (*m*, 18H), 1.78 (*m*, 1H), 3.44 (*s*, 6H), 3.59 (*m*, 2H), 3.69 (*m*, 2H), 3.81 (*m*, 2H), 4.01 (*m*, 2H), 4.07 (*m*, 2H)	H, 10.68 (11.03) C, 61.02 (60.66) N, 4.01 (3.93) Cl, 19.61 (19.89)

[a] Because obtained products are highly hygroscopic, calculated values are based on the assumption that the compound contains bonding water.

TABLE 2
Characterization of *bis*-Ammonium Salts

	Compound ($R = C_{12}H_{25}$)	m.p. (°C)	^{1}H NMR (δ, $CDCl_3$)	Anal. found (calcd.)%[a]
Ib		86–87	0.88 (*t*, 6H), 1.20–1.45 (*m*, 36H), 1.78 (*m*, 2H), 1.87 (*m*, 2H), 3.39 (*s*, 6H), 3.42 (*s*, 6H), 3.52 (*t*, 4H), 3.67 (*t*, 2H), 4.32 (*d*, 2H), 5.19 (*m*, 1H)	H, 12.34 (12.29) C, 64.16 (64.28) N, 4.84 (4.84) Cl, 12.08 (12.24)
IIIb		192–194 (decomp.)	0.88 (*t*, 6H), 1.20–1.45 (*m*, 36H), 1.78 (*m*, 4H), 2.29 (*m*, 2H), 3.35 (*d*, 12H), 3.49 (*t*, 4H), 3.89 (*t*, 4H)	H, 12.62 (12.65) C, 66.45 (66.75) N, 4.89 (5.02) Cl, 12.58 (12.71)
IVb		233–237 (decomp.)	0.88 (*t*, 6H), 1.20–1.45 (*m*, 36H), 1.66–1.92 (*m*, 4H), 2.18 (*m*, 1H), 2.52 (*m*, 1H), 3.28 (*s*, 6H), 3.33 (*d*, 6H), 3.36–3.60 (*m*, 5H), 3.79 (*m*, 1H), 4.01 (*m*, 1H), 4.30 (*d*, 1H), 4.56 (*m*, 1H)	H, 12.39 (12.33) C, 64.65 (64.59) N, 4.70 (4.71) Cl, 12.00 (11.92)
Vb		205–208 (decomp.)	0.88 (*t*, 6H), 1.20–1.45 (*m*, 36H), 1.71 (*m*, 4H), 3.44 (*s*, 12H), 3.58 (*t*, 4H), 3.03 (*s*, 4H), 4.32 (*s*, 4H)	H, 12.22 (12.34) C, 64.94 (64.98) N, 4.69 (4.74) Cl, 12.12 (11.99)

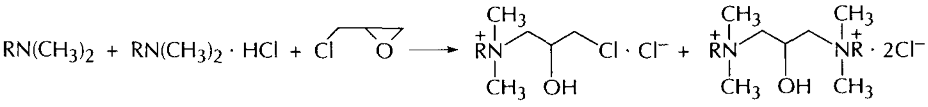
[a] Because obtained products are highly hygroscopic, calculated values are based on the assumption that the compound contains bonding water.

epichlorohydrin in the molar ratio of 2:1:1 was stirred for 8 h at room temperature (at this step, only **Ia** formed almost quantitatively) and then heated to reflux for another 8 h, only *bis*-ammonium salt **Ib** was obtained, and no **Ia** remained (run 4). From these results it appears that the intermediate of this reaction is the *mono*-ammonium salt **Ia** and not glycidylammonium chloride. When the reaction temperature was raised to the refluxing temperature of 1-propanol, the reaction time was greatly shortened, while still keeping the reaction clean (run 8). When the amount of amine was decreased, the reaction time needed to be longer (runs 6–8).

To make the reaction route clearer, rates of the reaction of N,N-dimethyldodecylamine with epichlorohydrin, 1,3-dichloro-2-propanol, and 1,3-dichloropropane were examined by ^{1}H NMR (Fig. 1).

After fast generation from epichlorohydrin, *mono*-ammonium salt **Ia** also disappeared rapidly to afford *bis*-ammonium salt **Ib**. For 1,3-dichloro-2-propanol, the formation rate of *mono*-ammonium salt **IIa** (note that **Ia** and **IIa** are believed to be the same compound) is much smaller than that of **Ia**. For this reason, the formation of *bis*-ammonium salt **IIb** (the same compound as **Ib**) was slower than that of **Ib**. The formation of both *mono*- and *bis*-ammonium salts from 1,3-dichloropropane (**IIIa** and **IIIb**, respectively) was extremely slow in comparison with that from epichlorohydrin and 1,3-dichloro-2-propanol.

TABLE 3
Effects of Ratio of Reagents Used and Temperature on Reaction of N,N-Dimethyldodecylamine, Its Hydrochloride, and Epichlorohydrin



1 2 3 **Ia** **Ib**

$R = C_{12}H_{25}$

	Conditions						Yield (%)[a]	
	Molar ratio				Time			
Run	1	2	3	Temp.	(h)	Solvent	**Ia**	**Ib**
1	—	1.0	1.0	rt[b]	20	Ethanol	31	0
2	0.1	1.0	1.0	rt	8	Ethanol	50	0
3	2.0	1.0	1.0	rt	8	Ethanol	93	0
4	2.0	1.0	1.0	rt Then reflux	8 8	Ethanol	0	>95
5	1.0	1.0	1.0	Reflux	8	Ethanol	20	78
6	1.0	1.0	1.0	Reflux	8	1-Propanol	7	92
7	1.2	1.0	1.0	Reflux	5	1-Propanol	6	94
8	2.0	1.0	1.0	Reflux	3	1-Propanol	0	>95

[a] Calculated from ^{1}H NMR.
[b] rt = Room temperature.

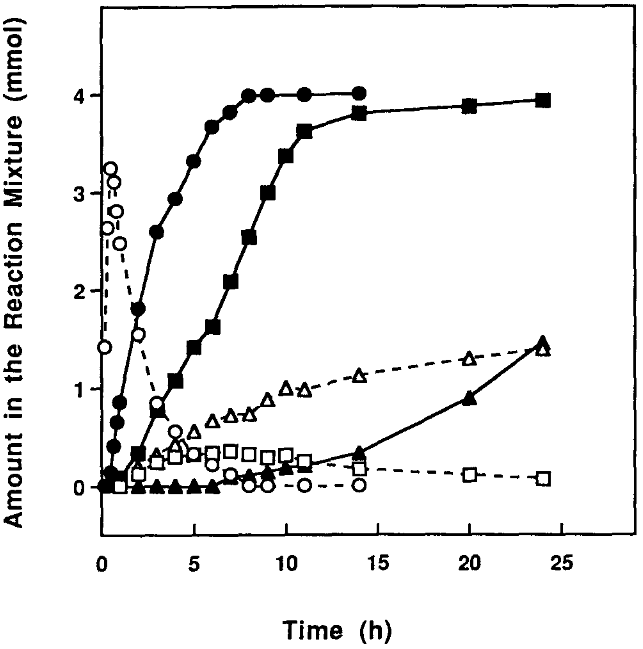


FIG. 1. Comparison of the formation rates of the ammonium salts from N,N-dimethyldodecylamine with epichlorohydrin and dichlorides. Reaction conditions: N,N-dimethyldodecylamine (8 mmol), its hydrochloride (4 mmol), and epichlorohydrin (4 mmol) were heated to reflux in ethanol (5 mL); N,N-dimethyldodecylamine (12 mmol) and dichloro compound (4 mmol) were heated to reflux in ethanol (5 mL). Amounts in the reaction mixture were calculated by ^{1}H NMR. Abbreviations: **I**, ammonium salt from epichlorohydrin; **II**, ammonium salt from 1,3-dichloro-2-propanol; **III**, ammonium salt from 1,3-dichloropropane; **a**, *mono*-ammonium salt; **b**, *bis*-ammonium salt.

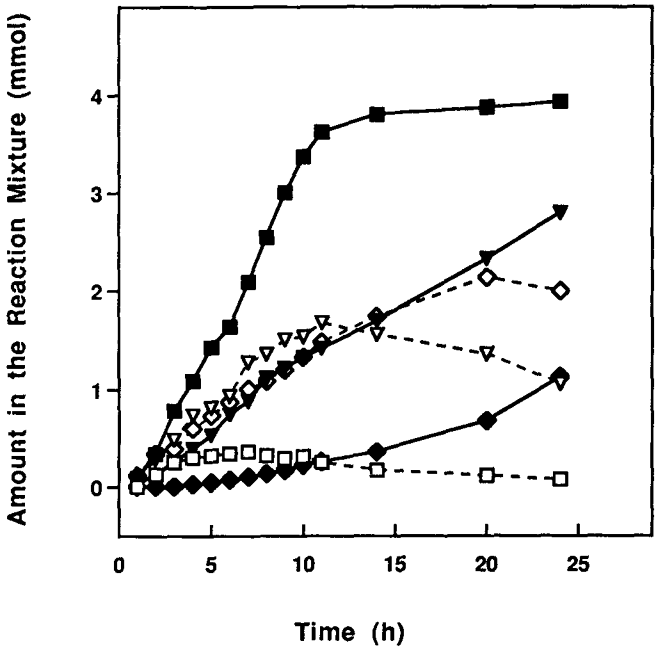
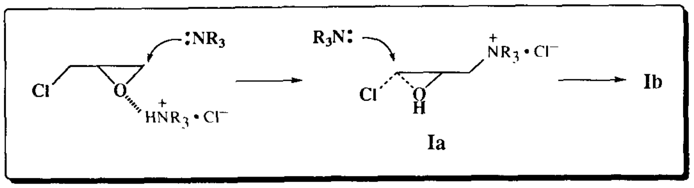


FIG. 2. Comparison of the formation rates of the ammonium salts from N,N-dimethyldodecylamine with dichlorides. Reaction conditions: N,N-dimethyldodecylamine (12 mmol) and dichloro compound (4 mmol) were heated to reflux in ethanol (5 mL). Amounts in the reaction mixture were calculated by ^{1}H NMR. Abbreviations: **II**, ammonium salt from 1,3-dichloro-2-propanol; **IV**, ammonium salt from 1,4-dichloro-2-butanol; **V**, ammonium salt from *bis*-2-chloroethyl ether; **a**, *mono*-ammonium salt; **b**, *bis*-ammonium salt.

From these results, the reaction of N,N-dimethyldodecylamine, its hydrochloride, and epichlorohydrin are considered to proceed as shown in Scheme 1.

At first, by assistance of the amine hydrochloride, the amine nitrogen attacks the epoxide carbon with ease to afford *mono*-ammonium salt **Ia** rapidly. Then another molecule of the amine attacks the chlorine-substituted carbon of **Ia** to displace the chloride, affording *bis*-ammonium salt **Ib**. It is reasonable to consider that neighboring-group participation by the hydroxyl group works in this step because the formation of **IIb** from **IIa** was much faster than that of **IIIb** from **IIIa**, which has no hydroxyl group on the β-carbon.

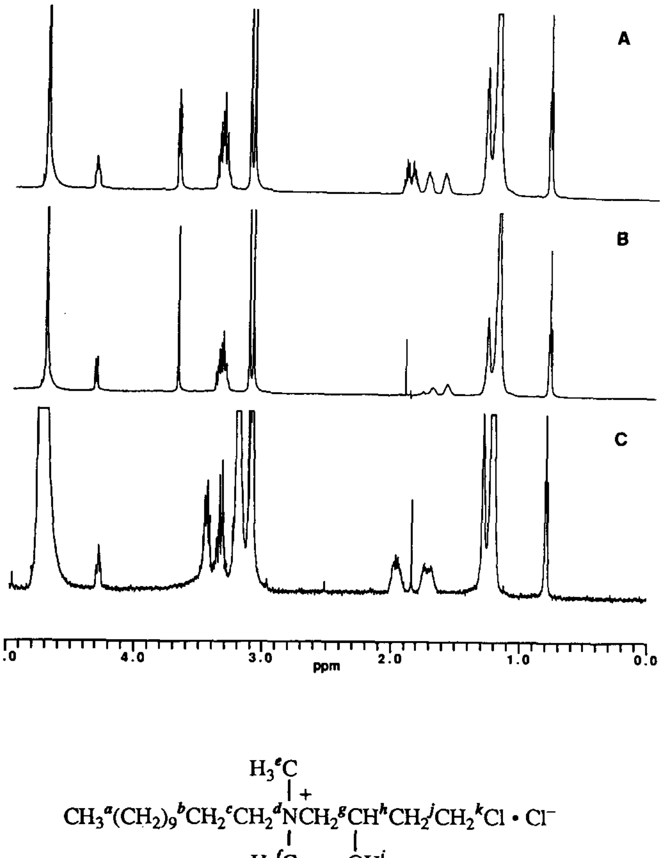
This neighboring-group participation is also estimated to work in the formation reaction of **IIa**. This estimation was confirmed by the reaction of the amine with 1,4-dichloro-2-butanol. As shown in Figure 2, the combined amount of *mono*-ammonium salt **IVa** and *bis*-ammonium salt **IVb** (corresponds to the total amount of generated **IVa**) after the same reaction period is almost the same as that of *mono*-ammonium salt **IIa** and *bis*-ammonium salt **IIb** (also corresponds to the total amount of generated **IIa**), but the formation rate of *bis*-ammonium salt **IVb** is slower than that of **IIb**, indicating that the reactivities of the two kinds of chloride in 1,4-dichloro-2-butanol are different from each other.



SCHEME 1

The difference in reactivities of these chlorides was apparent from the NMR study (Fig. 3) on the intermediate *mono*-ammonium salt, which was prepared in the presence of an excess amount of 1,4-dichloro-2-butanol (see Experimental Procedures section).

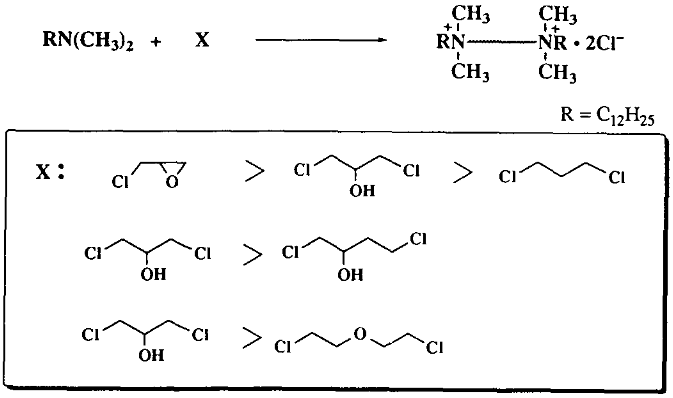
Because the signal of the protons (*k* in Fig. 3) geminal to the chlorine atom and those (*d* and *g*) geminal to the ammonio group both appear in the range of 3.8–3.2 ppm, they need to be distinguished from each other (Fig. 3A). First, the ^{1}H–^{1}H homodecoupled spectrum (Fig. 3B) was measured upon irradiating the protons of 2.0–1.8 ppm (*j*), which are the β positional protons from the hydroxyl group. It indicates that the signal of 3.73 ppm corresponds to the γ positional protons (*g* or *k*) from the hydroxyl group because the signal of 4.36 ppm (*h*) and that of 3.73 ppm have decoupled to a doublet and singlet, respectively. Next, the intermediate *mono*-ammonium salt was treated with trimethylamine, expecting the shift of the signal of the protons geminal to the chlorine atom, and the NMR spectra of the starting chloride (**IVa**; Fig. 3A) and the resulting *bis*-ammonium salt were compared. Figure 3C indicates that the signal of 3.73 ppm is due to the protons γ posi-



$$CH_3^a(CH_2)_9{}^bCH_2{}^cCH_2{}^d\overset{H_3{}^eC}{\overset{|}{\underset{\underset{H_3{}^fC}{|}}{N^+}}}CH_2{}^gCH^h\underset{\underset{OH^i}{|}}{}CH_2{}^jCH_2{}^kCl \cdot Cl^-$$

FIG. 3. NMR spectra (in D_2O): A) *mono*-ammonium salt **IVa** from 1,4-dichloro-2-butanol; B) upon irradiating the protons of 2.0–1.8 ppm of A); and C) *bis*-ammonium salt prepared from **IVa** and trimethylamine.

tional to the hydroxyl group and geminal to the chlorine atom at the same time, because the signal of 3.73 ppm of the starting chloride disappeared on changing to the trimethylammonium derivative. So, the structure of the intermediate *mono*-ammonium salt **IVa** from 1,4-dichloro-2-butanol is as shown under the NMR spectra in Figure 3, demonstrating the extreme contribution of the hydroxyl group located at a specific distance, that is, the neighboring-group participation of the hydroxyl group. Small neighboring-group participation effects can also be seen in the formation reaction of **IVb** from **IVa** by the comparison with **IIIb** from **IIIa** (Fig. 1) and **Vb** from **Va** (Fig. 2). Neighboring-group participation by the hydroxyl group is related to chainlength (15). For *bis*-2-chloroethyl ether, both the formation rates of *mono*- (**Va**) and *bis*-ammonium salts (**Vb**) are small. Although the distance between oxygen and the substitution reaction center is equal to that of 1,3-dichloro-2-propanol, the weaker nucleophilicity and the steric hindrance around the oxygen of the ether may bring about the difference in the results. The relative reactivities of reagents are summarized in Scheme 2.



SCHEME 2

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[Received August 30, 1994; accepted September 27, 1995]