Long Chain Carboxylic Acids Containing Ether Linkage: V. N-Methyl Substituted Glycine-Type Amphoterics Containing Alkoxy Radical

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ABSTRACT

The substituted glycine-type amphoteric surfactants containing long chain alkoxy and methylated amino groups, such as N-(2-alkoxyethyl)methylaminoacetic acids and (N-[2-alkoxyethyl]- N-[carboxymethyl]dimethylammonium) chlorides, or N-(N-[2-alkoxyethyl]-2-aminoethyl) aminoacetic acids were synthesized, and their growth inhibitory activities against g positive, g negative bacilli, and some fungi were studied. The effect of substitution of methyl groups upon the amino group of the long chain alkoxyaminoacetic acids on their antimicrobial activities was examined, and the increasing effect, due to methyl substitution, was confirmed. The introduction of an aminoethyl radical between the alkoxyethyl and amino radicals of the substituted glycines also increased their antimicrobial activities. Dimethyl-substituted betain-type amphoterics showed less antimicrobial activities than the corresponding glycine-type amphoterics. Moreover, aqueous solution of these substituted glycine-type amphoteric compounds showed better surface activities at pH 4.0, 10.0 than at neutral pH.

INTRODUCTION

Previously, the authors reported the synthesis and the antimicrobial and surface-active properties of the amphoterics containing ether group: N-(2-alkoxyethyl)-3-aminopropionic acid hydrochloride, $ROC_2H_4NHC_2H_4COOH \cdot HCl$, and O-(2-alkylaminoethyl)-3-oxypropionic acid hydrochloride, $RNHC_2H_4OC_2H_4COOH \cdot HCl$ (1). It was mentioned that these compounds had good antimicrobial properties and surface activities over a wide pH range. In this article, we discuss the synthesis of substituted glycine-type amphoterics containing N-methyl groups or an aminoethyl radical between the alkoxy and amino radicals. The surface-active and antimicrobial properties of these compounds also were studied to examine the influence of the N-methyl or intervening aminoethyl groups on those properties.

EXPERIMENTAL PROCEDURES AND RESULTS

The synthesis of these amphoteric surfactants is illustrated in Figure 1.

Material

2-Alkoxyethanol (I), 2-alkoxyethylamine (III), 2-(2-alkoxyethyl)-aminoethylamine (IX) were prepared from the corresponding alcohols by the method described in a previous article (1).

N-(2-Alkoxyethyl)Aminoacetic Acid Hydrochloride (V)

The preparation was mainly according to Smith's method (2) for the synthesis of ethylenediamine tetraacetic acid and the patent method of I.G. Farbenindustrie A.G. for preparing dodecylamino acetic acid (3). The preparation of N-(2-dodecyloxyethyl)aminoacetic acid hydrochloride (Va) is described here as an example. In a four-necked flask fitted with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel, 9.2 g 2-dodecyloxyethylamine and 13.3 g 38% sodium bisulfite aqueous solution were placed, and 3.3 g 37% formalin solution slowly were introduced at 50-60 C with stirring. An aqueous solution (32.7 g) of 7.5% sodium cyanide was added to the above mixture. After the addition of sodium cyanide solution, the mixture was stirred at 70-80 C for 1 hr. Then, the product was saponified with 12 g 35% sodium hydroxide solution for 3 hr at 100 C. After acidifying the reaction with hydrochloric acid, the crude N-(2-dodecyloxyethyl)-aminoacetic acid hydrochloride was dissolved in acetone to remove sodium chloride or insoluble matter. After distilling the solvent from the filtered solution, the residue was recrystallized from 2 points ethanol:1 point acetone until constant melting point (mp) was obtained. (Va) was a colorless plate and its mp was 123-125 C. Analytical data are presented in Table I with those of N-(2-undecyloxyethyl)- and N-(2-tridecyloxyethyl) amino-acetic acid hydrochlorides.

N-Methyl-(2-Alkoxy)Ethylamine (VI)

The preparation was based largely upon Clemo's synthesis of 4-hydroxy-3-methoxy-β-phenyl-N-methylisopropylamine (4). The preparation of N-methyl-(2-dodecyloxy)ethylamine (VIa) is described here as an example. Methylamine hydrochloride (67.5 g). 57.2 g potassium hydroxide dissolved in 10 ml water and 65 ml methanol, 24.9 g 2-dodecyoxyethylchloride, and 65 ml methanol were heated at 120-140 C for 20 hr in an autoclave fitted with a stirrer. Methanol was distilled from the reactant, and the residue was extracted with ether. The ether extract was washed with saturated NaCl solution to remove the excess of potassium hydroxide and dried overnight over sodium sulfate. After the evaporation of ether from the extract, the

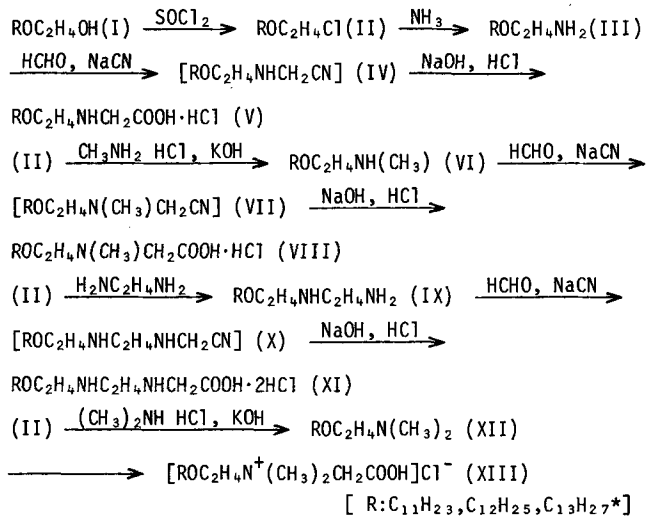

FIG. 1. The preparation of amphoterics * = Amphoterics (V) and (XI) which had $C_{13}H_{27}$ radicals prepared.

TABLE I

Characteristics of Amphoterics (V), (VIII)
[$ROC_2H_4N(R')CH_2COOH \cdot HCl$]

	Alkyl groups		Melting point C	Carbon, % (calculated)	Hydrogen, % (calculated)	Chlorine, % (calculated)	Nitrogen, % (calculated)
[V]	$C_{11}H_{23}$	H	107-109	57.86 (58.14)	10.26 (10.40)	11.53 (11.44)	4.50 (4.52)
	$C_{12}H_{25}$	H	123-125	59.44 (59.33)	10.52 (10.58)	11.17 (10.95)	4.35 (4.32)
	$C_{13}H_{27}$	H	111-113	60.86 (60.42)	10.70 (10.74)	11.13 (10.49)	4.23 (4.15)
[VIII]	$C_{11}H_{23}$	CH_3	81-82	59.47 (59.33)	10.56 (10.58)	10.94 (10.95)	4.00 (4.32)
	$C_{12}H_{25}$	CH_3	83-85	60.06 (60.42)	10.58 (10.74)	10.88 (10.49)	3.98 (4.14)

TABLE II

Characteristics of N-methylated Amines (VI), (XII)
[ROC_2H_4-X]

	Alkyl group	Amine group	Boiling point C/mmHg	n_D^t	Carbon, % (calculated)	Hydrogen, % (calculated)	Nitrogen, % (calculated)
[VI]	$C_{11}H_{23}$	$-N(CH_3)H$	115-119/2.0	1.4353^{25}	73.61 (73.30)	13.42 (13.62)	4.28 (6.11)
	$C_{12}H_{25}$		128-132/1.0	1.4392^{25}	74.66 (74.01)	13.90 (13.66)	5.75 (5.75)
[XII]	$C_{11}H_{23}$	$-N(CH_3)_2$	115-122/1.0	1.4379^{20}	74.59 (74.01)	13.49 (13.66)	5.83 (5.75)
	$C_{12}H_{25}$		125-129/2.0	1.4380^{25}	74.34 (74.64)	13.40 (13.70)	5.11 (5.44)

TABLE III

Characteristics of Amphoterics (XI), (XIII)
(XI) [$ROC_2H_4NHC_2H_4NHCH_2COOH \cdot 2HCl$]
(XIV) [$ROC_2H_4N^+(CH_3)_2CH_2COOH$]$Cl^-$

	Alkyl group	Melting point C	Carbon, % (calculated)	Hydrogen, % (calculated)	Chlorine, % (calculated)	Nitrogen, % (calculated)
[XI]	$C_{11}H_{23}$	128-131	52.74 (52.44)	10.03 (9.84)	17.93 (18.21)	7.38 (7.19)
	$C_{12}H_{25}$	155-157	53.84 (53.59)	10.02 (9.99)	18.12 (17.58)	7.10 (6.94)
	$C_{13}H_{27}$	152-153	55.00 (54.67)	9.98 (10.14)	16.68 (16.98)	6.67 (6.71)
[XIII]	$C_{11}H_{23}$	103-104	59.97 (60.42)	10.36 (10.74)	10.20 (10.49)	4.48 (4.14)
	$C_{12}H_{25}$	107-108	61.58 (61.43)	10.61 (10.88)	10.10 (10.07)	4.19 (3.98)

TABLE IV

Minimum Inhibition Concentration of Amphoterics against Microorganisms (μg/ml)

	[V]			[VIII]		[XI]		[XIII]	
Names of tested microorganisms	$C_{11}H_{23}$	$C_{12}H_{25}$	$C_{13}H_{27}$	$C_{11}H_{23}$	$C_{12}H_{25}$	$C_{12}H_{25}$	$C_{13}H_{27}$	$C_{11}H_{23}$	$C_{12}H_{25}$
Staphylococcus aureus 209 P	100<	100	25	100	25	12.5	12.5	100<	50[a]
S. aureus Terashima	100<	100	25	100	25	25	12.5	100<	50[a]
S. epidermidis 10131	100<	100	12.5	100	25	25	12.5	100<	50[a]
S. epidermidis Kawamura	100<	100	25	100<	50	25	12.5	100<	50[a]
Streptococcus faecalis	100<	100	12.5	50	12.5	6.25	12.5	100	50[a]
Bacillus subtilis PCI-219	100<	50	12.5	50	12.5	6.25	12.5	50	50[a]
Escherichia coli NIHJ	100<	100<	100<	100<	100<	100<	100<	100<	100<[a]
Salmonella typhimurium	100<	100<	100<	100<	100<	100<	100<	100<	100<[a]
Klebsiella pneumoniae	100	100<	12.5	50	25	25	12.5	50	25[a]
Pseudomonas aeruginosa A_3	100<	100<	100<	100<	100<	100<	100<	100<	100<[a]
Proteus vulgaris	100<	100<	100<	50	25	100<	100<	100	50[a]
Aspergillus fumigatus IAM-2612	100<	100<	100<	100<	50	100<	100<	100<	100[b]
Asp. niger ATCC-9642	100	100<	100<	100<	50	100<	100<	100<	100[b]
Asp. terreus	100<	100<	100<	100<	100	100<	100<	100<	100[b]
Penicillium chrysogenum 49-132	100	100<	100<	100<	50	100<	100<	100<	50[b]
Trichophyton asteroides	100	12.5	100<	100	50	100	100	100<	50[b]

[a]Heart infusion agar pH 7.2 at 37 C, 24 hr.

[b]Sabouraud agar pH 6.5 at 27 C, 5 days.

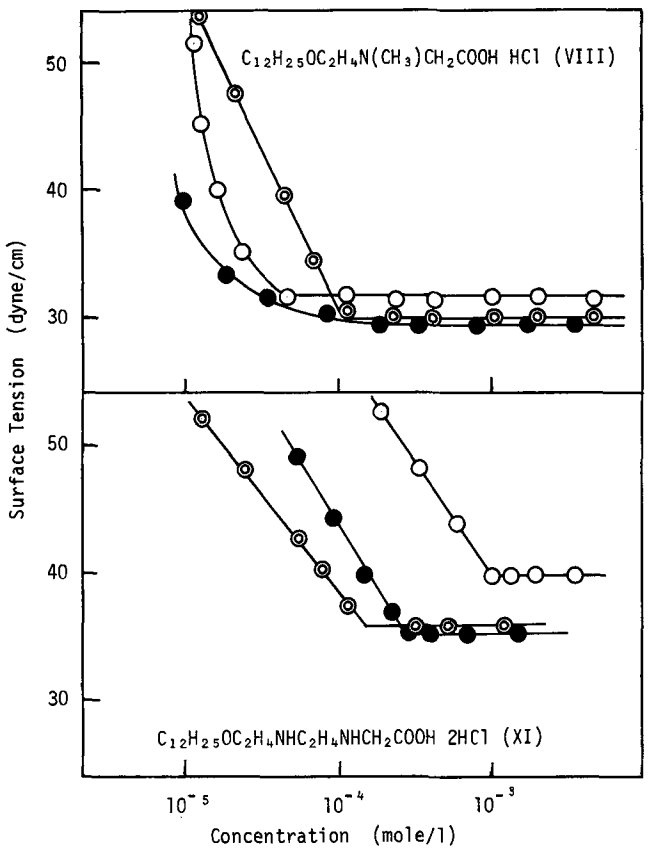

FIG. 2. Surface tension-concentration curves of amphoterics (VIIIa), (XIa). —o—o—o— = water, —●—●—●— = pH 4, and —⊙—⊙—⊙— = pH 10.

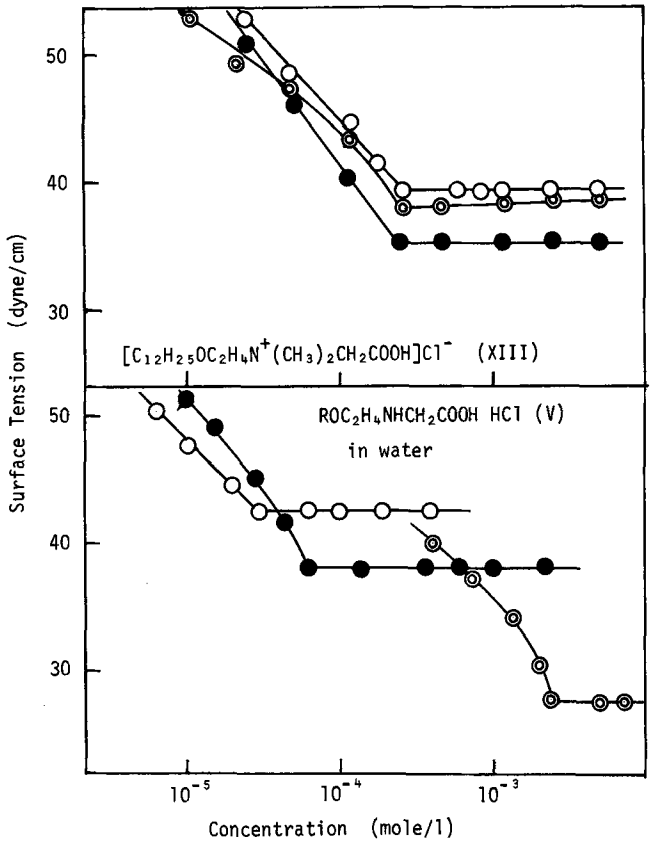

FIG. 3. Surface tension-concentration curves of amphoterics. In upper half of figure, (XIIIa), —o—o—o— = water, —●—●—●— = pH 4, —⊙—⊙—⊙— = pH 10; in lower half of figure, (V), —o—o—o— = $C_{11}H_{23}$, —●—●—●— = $C_{12}H_{25}$, and —⊙—⊙—⊙— = $C_{13}H_{27}$.

residue was distilled in vacuo. N-Methyl-(2-dodecyloxy)ethylamine (VIa) was a colorless liquid and its boiling point (bp) was 128-132 C/1.0 mmHg. Analytical data are presented in Table II with those of N-methyl-(2-undecyloxy)ethylamine. The latter was crude, but it was used in the further synthesis.

N-(2-Alkoxyethyl)Methylaminoacetic Acid Hydrochloride (VIII)

N-(2-Alkoxyethyl)methylaminoacetic acid hydrochloride (VIII) was prepared by the cyanomethylation of (VI), followed by hydrolysis of the nitrile (VII). The procedure of cyanomethylation and hydrolysis was the same as in the preparation of (V). The products were colorless plates, and their analytical data are presented in Table I.

N-(N-[2-Alkoxyethyl]-2-Aminoethyl)Aminoacetic Acid Hydrochloride (XI)

N-(N-[2-Alkoxyethyl]-2-aminoethyl)aminoacetic acid hydrochloride (XI) was prepared from 2-(2-alkoxyethyl) aminoethylamine (IX) via corresponding nitrile (X) in a similar way as the preparation of (V). The products were colorless plates and their analytical data are presented in Table III.

N-(2-Alkoxyethyl)Dimethylamine (XII)

N-(2-Alkoxyethyl)dimethylamine (XII) was prepared from (II) and a large excess of dimethylamine hydrochloride in a similar method as the preparation of (VI). The products were colorless liquids and their analytical data are presented in Table I.

(N-[2-Alkyloxyethyl]-N-[Carboxymethyl] Dimethylammonium)-Chloride (XIII)

As an example, the preparation of (N-[2-dodecyloxyethyl]-N-[carboxy methyl] diemthylammonium)chloride (XIIIa) is described here. It was prepared by using Linfield's method for the synthesis of N-octadecyl-N,N-dimethyl-α-betain (5). A mixture of 16.6 g N-(2-dodecyloxyethyl) dimethylamine (XII), 7.9 g ethylchloroacetate, and 24.5 g methanol was placed to a conical flask fitted with a stirrer and a reflux condenser and heated with stirring at the reflux temperature (70 C) for 6 hr. After the reaction was completed, the content was cooled to room temperature and 2.6 g powdered NaOH was added. The reaction mixture was refluxed for an additional 3 hr and allowed to settle overnight to deposit the salt. After the filtration of the salt, methanol was evaporated, and the residue was dried in vacuo. The residue was digested with acetone to remove the insoluble salt, and concentrated hydrochloric acid was added to the filtrate, then refluxed for 3 hr. The product was recrystallized from acetone until constant mp was obtained. The product was a colorless plate and melted at 107-108 C. Analytical data are shown in Table III with those of (N-[2-undecyloxyethyl]-N-[carboxymethyl]dimethylammonium)chloride (XIIIb).

Antibacterial and Antifungal Study

Antifungal and antibacterial evaluation against some g positive cocci and g negative bacilli was carried out by serial agar dilution method. The results are summarized in Table IV.

Study of Surface Tension

These amphoterics prepared above are easily soluble in water. Samples were dissolved in water or Clark-Lub's buffer solutions (pH 4.0 and 10.0) to learn the influence of the different pH environment. Surface tensions of their solutions at different concentrations were measured by Wilhelmy tensiometer, and the surface tension-concentration curves of solutions of N-(2-dodecyloxyethyl)-methyl-

aminoacetic acid hydrochloride (VIIIa), N-[N-[2-dodecyloxyethyl]-2-aminoethyl)aminoacetic acid hydrochloride (XIa), and (N-[2-dodecyloxyethyl]-N-[carboxymethyl] dimethylammonium)chloride (XIIIa) are plotted in Figures 2 and 3 as examples.

DISCUSSION

MP

As shown in Table I, the mp of the hydrochloric acid salts of 2-alkoxyethylaminoacetic acid decreased in order C_{12}, C_{13}, C_{11} in the same series. This order is the same as obtained for the hydrochloric acid salts of N-(2-alkoxyethyl)-3-aminopropionic acid reported previously (1). Comparing the aminoacetic acid series with the aminopropionic acid ones, the former had higher mp, but at the diamino substituted acids of the acetic acid series showed lower mp than those of the propionic acid series. Addition of an aminoethyl group also increased the mp of the compounds, as in the case of the substituted propionic acid series. The introduction of a methyl group at N of the long chain alkoxy substituted glycines lowered their mp, but betain-type amphoterics (XIII) showed higher mp than the N-methyl substituted amphoterics (VIII). The difference of mp in these N-methyl substituted amphoterics group was smaller than that of mp in the present nonsubstituted amphoterics.

Antimicrobial Activities

From Table IV, it was found that all amphoterics were more effective against g positive cocci than g negative bacilli and fungi, and the introduction of methyl group increased the antimicrobial activities against each microbe. Betain-type amphoterics, having N-disubstituted methyl groups showed the least antimicrobial activities out of the three types of methyl-substituted amphoterics. As for the alkoxy radicals as hydrophobic groups, there was not a definite difference in antimicrobial activities between dodecyloxy and tridecyloxy radicals, but undecyloxy radical showed less antimicrobial activity. The introduction of an aminoethyl radical between the alkoxyethyl and amino radicals of the substituted glycines increased their antimicrobial activities.

Surface Activities

From the surface tension-concentration curves of solutions of these amphoteric compounds (Figs. 2 and 3), breaking points were obtained at ca. 10^{-3}-10^{-4} mole/liter and they deviated to the lower concentration as the chain length was increased from undecyloxy to tridecyloxy. It was found the surface tensions lowering effect of these amphoterics was more remarkable in the buffer solution than in water. It can be assumed that this result is due to the presence of potassium biphthalate, sodium hydroxide, and potassium chloride constituting the buffer solution. There was a little difference between the surface tensions of the two solutions at pH 4.0 and 10.0. The introduction of a methyl radical to the N atom of alkoxyaminoacetic acid did not show a systematic influence upon surface activities. Betain-type amphoterics were least surface active of the three. The presence of an ethylamino group between alkoxyethyl and ethyl groups in the alkoxyethylaminoacetic acid lowering their surface activities. It also was found that antimicrobial activities did not directly relate to surface-active properties.

ACKNOWLEDGMENTS

This work was supported in part by a grant for Scientific Research from the Ministry of Education. Elemental analysis was performed by S. Nakada and biological evaluations by H. Okuda.

REFERENCES

1. Abe, Y., S. Osanai, and S. Matsumura, JAOCS 49:357 (1972).
2. Smith, R., J.L. Bullock, F.C. Bersworth, and A.E. Martell, J. Org. Chem. 14:355 (1949).
3. I.G. Farbenindustrie, A.G., British Pat. 460,372 (1937).
4. Clemo, G.R., and J.H. Turnbull, J. Chem. Soc. 67:533 (1945).
5. Linfield, W.M., P.G. Abend, and G.A. Davis, JAOCS 40:114 (1963).

[Received January 7, 1974]