STUDIES ON PREPARATION AND PROPERTIES OF NOVEL AMPHIPHILIC COMPOUNDS DERIVED FROM POLYOLS INCLUDING SUGARS

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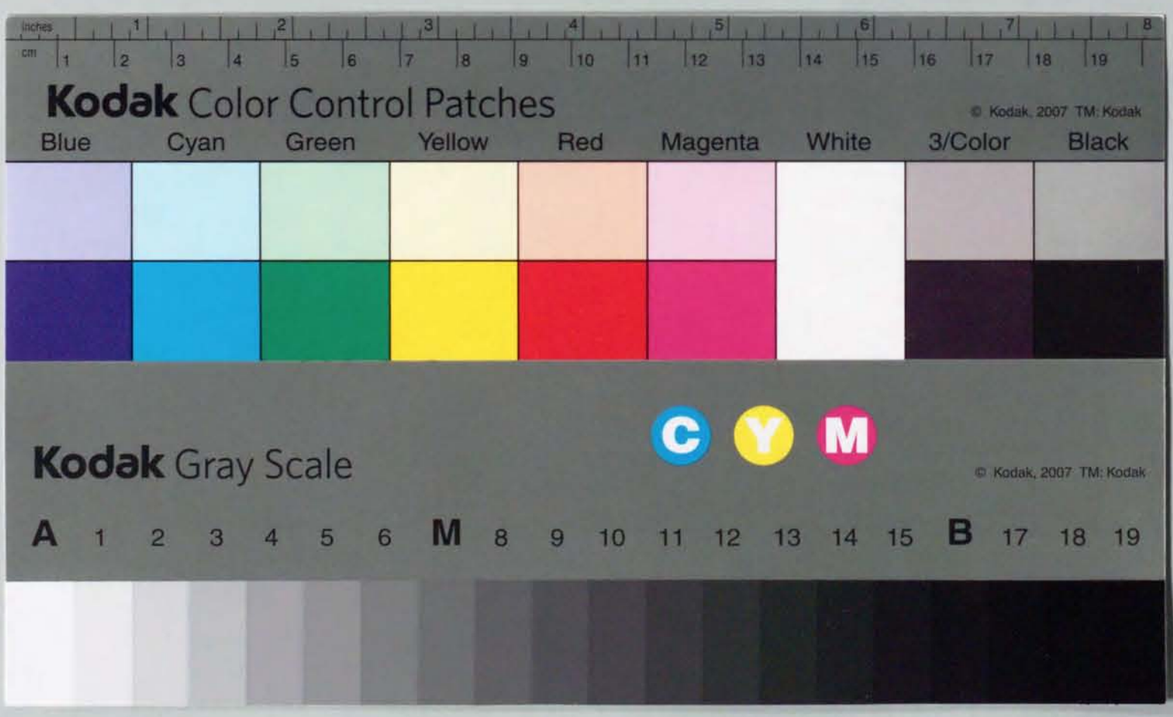

STUDIES ON PREPARATION AND PROPERTIES OF NOVEL AMPHIPHILIC COMPOUNDS DERIVED FROM POLYOLS INCLUDING SUGARS

（糖をはじめとするポリオール類からの新規両親媒性化合物の合成と性質に関する研究）

1998

TOSHIYUKI KIDA

Preface

The work of this thesis has been carried out under the guidance of Professor Isao Ikeda at the Department of Molecular Chemistry, Faculty of Engineering, Osaka University.

The objectives of this thesis are to prepare new amphiphilic compounds derived from polyols including sugars and to clarify their properties and functions. The author hopes that the results obtained in this work will contribute to further development of sugar and surfactant chemistry.

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Contents

General Introduction

Sugars play multiple roles in all forms of life. First, they serve as the stocks and sources of energy. Starch in plants and glycogen in animals are polysaccharides that can be rapidly mobilized to yield glucose, a prime source for energy generation. Secondly, polysaccharides are structural elements in the cell walls of bacteria and plants, and in the exoskeletons of arthropods. In fact, cellulose, the main constituent of plant cell walls, is the most abundant organic compound in the biosphere. Thirdly, ribose and deoxyribose form part of the structural framework of DNA and RNA. The conformational flexibility of these sugar rings is important in the storage and expression of genetic information.

Recently, it has been revealed that sugars on the cell surfaces play important roles in intercellular recognition and adhesion. Elucidation of the mechanism of these interaction and their application to new recognition devices have become active research areas.

Furthermore, from the industrial point of view, much attention has been paid to sugars–in most cases polysaccharides–as highly biodegradable and renewable materials. Indeed, they have been widely utilized in food, cosmetics, and drugs.

Polyols other than sugars, such as pentaerythritol [tetrakis(hydroxymethyl)methane] and trimethylolethane [1,1,1-tris(hydroxymethyl)ethane], are also industrially important compounds as sources for lubricating oils and coating materials. Recently, some new functional compounds such as dendrimers[1] and tripodal ligands[2] have been developed by using the multifunctionality and three-dimensional framework of the polyols.

Under these backgrounds, the objects of the present studies are to prepare new amphiphilic compounds derived from the polyols including sugars and to clarify their properties and functions.

Chapter 1 describes the preparation, surface-active properties, and acid-decomposition properties of novel surfactants derived from glucono-1,5-lactone and *N*-acetyl-D-glucosamine. The preparation of novel amphiphilic compounds derived from L-ascorbic acid (Vitamin C) is also

described.

In chapter 2, surfactants bearing sugar-amide head groups were prepared. In addition to their surface-active properties, enantioselective hydrolysis of an amino acid ester in the presence of their micelles was investigated.

Chapter 3 deals with the facile synthesis of polyglycidyl ethers from polyols and epichlorohydrin, and the preparation and the unique interfacial properties of a novel triple-chain surfactant bearing three anionic head groups, which was derived from 1,1,1-tris(glycidyloxymethyl)ethane obtained by the above synthetic method.

In chapter 4, selective transport of saccharides through a bulk liquid membrane using reversed micelle carriers which were formed by a variety of amphiphilic compounds including gluconamide-type surfactants was investigated. Additionally, the mechanism of selective transport by this system was discussed.

Chapter 5 describes the preparation of novel amphiphilic cycloinulohexaoses, their surface-active properties, and their complexing abilities toward alkali metal or alkaline earth metal cations in water.

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Toshiyuki Kida, Yasuhiko Inoue, Wanbin Zhang, Yohji Nakatsuji, and Isao Ikeda, *Bull. Chem. Soc. Jpn.*, **71**, 1201(1998).

10 Enantioselective Hydrolysis of an α-Amino Acid Ester in Sugar-Derived Surfactant Micelles
Toshiyuki Kida, Kazuhiko Isogawa, Wanbin Zhang, Yohji Nakatsuji, and Isao Ikeda, *Tetrahedron Lett.*, **39**, 4339(1998).

Chapter 1. Preparation and Properties of Novel Amphiphilic Compounds Derived from Sugars and Related Compounds

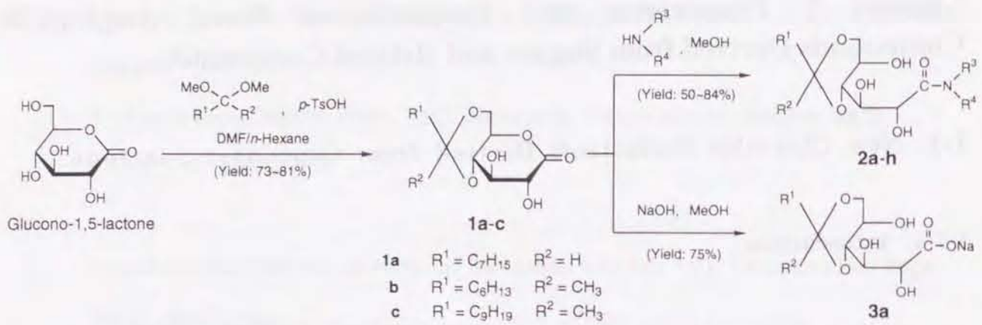
1-1. New Cleavable Surfactants Derived from Glucono-1,5-lactone

1-1-1. Introduction

Sugar-derived amphipathic compounds such as sucrose fatty acid esters[1,2] and alkyl glycosides[3-8] have been widely utilized in food, cosmetics, drugs, and the biochemical field. Recently, they have attracted attention again because of some of their advantages over other amphiphiles as follows: They are prepared from naturally occurring resources and have excellent surface-active properties. Furthermore, they are safe for human use and assumed to be ecologically useful.

The author has tried to develop a new sugar-derived amphiphile which has a new function in addition to the above-mentioned properties and is easily available. Recently the author found that new amphipathic carboxylates could be easily prepared by acetalization of glucono-1,5-lactone, which is an oxidation product of glucose, with a long-chain alkyl aldehyde or ketone, followed by hydrolysis under alkaline conditions.[9] These compounds are stable and show surface-active properties under neutral or alkaline conditions; whereas, under acidic conditions they decompose into non-surface active species because their hydrophobic and hydrophilic groups are linked through an acid-sensitive acetal bond. Thus they can be utilized as a new cleavable surfactant.[10-17]

In this section, the author synthesized new amido nonionic surfactants possessing acid-decomposition properties by acetalization of glucono-1,5-lactone with a long-chain carbonyl compound, followed by amidation with an appropriate amine. These surfactants are expected to be safer for human use than the corresponding carboxylates and are potentially useful in the biochemical field. During recent years, many amido nonionic amphiphiles derived from sugars have been reported,[18-24] however, no compounds among them have acid-decomposable properties. Here the author reports a synthetic method for the amido nonionic cleavable surfactants, their surface-active properties, and their acid-decomposition properties. The desired compounds **2a-h** and sodium 4,6-*O*-octylidenegluconate **3a** as a reference compound were synthesized according to Scheme 1-1.



	R¹	R²	R³	R⁴		R¹	R²	R³	R⁴
2a	C_7H_{15}	H	CH_2CH_2OH	H	**2f**	C_6H_{13}	CH_3		
2b	C_7H_{15}	H	CH_2CH_2OH	CH_2CH_2OH	**2g**	C_9H_{19}	CH_3	CH_2CH_2OH	H
2c	C_7H_{15}	H			**2h**	C_9H_{19}	CH_3		
2d	C_6H_{13}	CH_3	CH_2CH_2OH	H	**3a**	C_7H_{15}	H		
2e	C_6H_{13}	CH_3	CH_2CH_2OH	CH_2CH_2OH					

Scheme 1-1

1-1-2. Experimental Section

Materials. All reagents were commercially available and were used without further purification except dimethylformamide (DMF), which was dried over molecular sieves 4A before use.

Analytical Methods. The infrared (IR) spectra were recorded on an Hitachi 260-10 spectrometer (Hitachi Co., Tokyo, Japan). ^{1}H nuclear magnetic resonance (NMR) spectra was measured with a JEOL JNM-GSX400 (400 MHz, JEOL Ltd., Tokyo, Japan) spectrometer using tetramethylsilane (TMS) as an internal standard. Fast atom bombardment (FAB)-mass spectra were recorded on a JEOL JMS-DX303 HF spectrometer. The gas-liquid chromatography (GLC) was performed using a Shimadzu GC-8APF (Shimadzu Ltd., Kyoto, Japan) equipped with 20% tricresyl phosphate (TCP) on a Uniport R 60/80 packed glass column (1 m length).

Synthesis of 2,2-dimethoxyoctane: This compound was synthesized according to the previously reported method.[25] A mixture of 2-octanone (6.41 g, 50 mmol), methyl orthoformate (26.53 g, 250 mmol) and methanol (3.2 g, 100 mmol) in the presence of p-toluenesulfonic acid monohydrate (0.48 g, 2.5 mmol) was refluxed for 24 h. After neutralization with Na_2CO_3 (0.53 g, 5

mmol), the methanol and the unreacted methyl orthoformate were removed in vacuo. The residue was extracted with H_2O (80 mL) and Et_2O (2 x 80 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated. The resulting oil was purified by Kugelrohr distillation under reduced pressure to give the pure product (bp 50 ℃/0.9 Torr, 90% yield). IR (neat): 2920, 1460, 1370, 1050 cm^{-1}.

Synthesis of 4,6-O-alkylideneglucono-1,5-lactone (1a-c): In this section, these compounds were prepared by the following two methods using azeotropic compounds.

Method A: A mixture of octanal, 2-octanone or 2-undecanone (20 mmol), glucono-1,5-lactone (4.28 g, 24 mmol), *p*-toluenesulfonic acid monohydrate (0.76 g, 4 mmol), DMF (30 mL) and benzene (50 mL) was placed in a round-bottom flask equipped with a Dean-Stark trap. The mixture was refluxed for 6-8 h; about 0.4 mL of H_2O was collected in a Dean-Stark trap. After the solution was filtered through a short column filled with alumina (neutral) to remove *p*-toluenesulfonic acid, the solvent was evaporated in vacuo. The residue was extracted with brine (100 mL) and Et_2O (3 x 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by recrystallization from benzene/*n*-hexane for **1a** and **1b** or from *n*-hexane for **1c**. All isolated compounds **1a-c** were found to consist of a mixture of two diastereomers (ratio 1:1) which have different configurations at the acetal carbon atom on the 1,3-dioxane ring by ^{1}H-NMR spectroscopy. These isomers were used in the subsequent reactions without further separation.

Method B: Instead of aldehyde (or ketone) and DMF/benzene in Method A, its dimethyl acetal derivative as a reagent and DMF/*n*-hexane as a solvent, respectively, were used in this method. In this case, about 1mL of methanol was collected in a Dean-Stark trap after completion of the reaction (total reaction time: 6-10 h). The work-up procedures were carried out in the same manner as described in Method A.

The yields and analytical data of compounds **1a-c** are summarized in Table 1-1.

Synthesis of 4,6-*O*-alkylidenegluconamide derivatives (2a-h): These compounds were synthesized by the reaction of 4,6-*O*-alkylideneglucono-1,5-lactone with monoethanolamine, diethanolamine or morpholine. The mixture of 4,6-*O*-alkylideneglucono-1,5-lactone (2 mmol) and amine (3 mmol) was stirred in methanol (5 mL) under reflux conditions for 2 h (in the case of **2b** and **2e** for 20 h in ethanol). After evaporation of the solvent and the unreacted amine under reduced

pressure, the residue was extracted with brine (20 mL) and Et_2O or ethyl acetate (3 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by recrystallization from ethyl acetate/n-hexane (**2a**, **2d**, and **2g**), or *n*-hexane (**2h**). In the case of **2b**, **2c**, **2e**, and **2f**, purification was carried out by preparative high-performance liquid chromatography (HPLC) (column: Inertsil PREP-ODS 10 mm, 20 x 250 mm, GASUKURO KOGYO INC., Tokyo, Japan) using methanol as an eluent. These isolated products **2a-h** were characterized by IR and ^{1}H-NMR spectroscopy and elemental analyses. Yields and analytical data are summarized in Table 1-2.

Synthesis of sodium 4,6-*O*-octylideneglucononate (**3a**): 4,6-*O*-Octylideneglucono-1,5-lactone (2.88 g, 10 mmol) was added into a sodium hydroxide (0.48 g, 12 mmol)/methanol (40 mL) solution. The mixture was refluxed for 3 h. After evaporation of the methanol under reduced pressure, the residue was purified by recrystallization from ethanol/water (9:1) to give pure **3a** (2.40 g, 73 % yield). decom. p.: 213-215 ℃; IR (neat): 3220, 2940, 1600, 1120 cm^{-1}; FAB-mass [m/e, relative intensity]: 351[$(M+Na)^+$, 41], 329[$(M+1)^+$, 37], 115[100]; ^{1}H-NMR [in D_2O, sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard]: d 0.85(t, 3H), 1.27-1.38(m, 10H), 1.62-1.71(m, 2H), 3.81-4.06(m, 4H), 4.10(d, J = 4.4 Hz, 1H), 4.20-4.24(m, 1H), 4.96(t, J = 4.9 Hz, 0.5H) and 5.06(t, J = 4.9 Hz, 0.5H).

Surface-active properties: The cloud point (T_{cp}) and Krafft point (T_{Kp}) were determined by the naked eye with a 1 wt% (or 0.1 wt%) aqueous solution. The surface tensions of the surfactant solutions were measured at 20 ℃ with a Wilhelmy tensiometer (Shimadzu ST-1; Shimadzu Ltd., Kyoto, Japan; glass plate). The critical micelle concentration (CMC) was determined from the break point of each surface tension vs. concentration (on log scale) curve. Surface-active properties of compounds **2a-h** were measured under neutral conditions (~ pH 6), while those for compound **3a** were measured at pH 11 (prepared with NaOH aq.).

Decomposition properties: Acid-decomposition properties of the surfactants were evaluated by determining the quantity of liberated octanal (from **2a** and **3a**) or 2-octanone (from **2d**) with GLC under acidic conditions (pH 1 or 3, prepared with HCl aq.). Typical procedures for compound **2a** are as follows: Compound **2a** (34.9 mg, 0.1 mmol) was dissolved in hydrochloric acid (5 mL, pH 1). *n*-Hexane (5 mL) and *p*-xylene (10.6 mg, 0.1 mmol, as an internal standard) were added into this solution. The mixture was shaken at 20 ℃ and some of the solution was sampled from

the hexane layer after a certain period. The quantity of liberated octanal into the hexane layer was determined by the GLC-calibration curve analysis.

Table 1-1. Yields and Analytical Data of Compounds **1a**, **1b** and **1c**[a,b,c]

Compound	Yield (%) Method A	Method B	^{1}H-NMR (acetone-d_6) δ, J (Hz)	Anal. Found (Calcd.)
1a	72	81	0.88 (t, 3H), 1.29-1.40 (m, 10H), 1.57-1.67 (m, 2H), (dd, J = 6.3 and 7.3, 0.5H), 3.91-3.99 (m, 1H), 4.14-4.17 3.86 (m, 1.5H), 4.35 (m, 0.5H), 4.40-4.45 (m, 1.5H), 4.59 (dd, J = 3.4 and 4.4, 0.5H), 4.74 (dd, J = 3.4 and 4.4, 0.5H), 4.85 (-OH, 0.5H), 4.86 (t, J = 4.4, 0.5H), 4.96 (-OH, 0.5H),5.01 (t, J = 3, 0.5H), 5.42 (-OH, 1H)	C: 58.62 (58.32) H: 8.47 (8.39)
1b	55	73	0.88 (t, 3H), 1.27-1.44 (m, 11H), 1.59-1.68 (m, 2H), 3.90 (dd, J = 5.9 and 8.8, 0.5H, H-6a), 3.93 (dd, J=6.6 and 8.8, 0.5H, H-6a), 4.09-4.15 (m, 2H, H-6e and H-2), 4.35-4.39 (m, 1H, H-3), 4.43 (dd, J = 6.6 and 12.5, 0.5H, H-5), 4.48 (dd, J = 5.9 and 12.5, 0.5H, H-5), 4.63 (dd, J = 4.4 and 6.6, 0.5H, H-4), 4.66 (dd, J = 4.4 and 5.9, 0.5H, H-4), 4.85 (-OH), 5.42 (-OH)	C: 58.06 (58.32) H: 8.43 (8.39)
1c	55	—[d]	0.88 (t, 3H), 1.27-1.44 (m, 17H), 1.59-1.68 (m, 2H), 3.90 (dd, J = 5.9 and 8.3, 0.5H, H-6a), 3.93 (dd, J = 6.4 and 8.3, 0.5H, H-6a), 4.09-4.15 (m, 2H, H-6e and H-2), 4.34-4.38 (m, 1H, H-3), 4.43 (dd, J = 6.3 and 12.2, 0.5H, H-5), 4.48 (dd, J = 6.4 and 12.2, 0.5H, H-5), 4.63 (dd, J = 3.9 and 6.4, 0.5H, H-4), 4.66 (dd, J = 4.4, 5.9, 0.5H, H-4), 4.87 (-OH, d, J = 2.0, 0.5H), 4.88 (-OH, d, J = 2.0, 0.5H), 5.44 (-OH, d, J = 4.4, 0.5H), 5.45 (-OH, d, J = 4.4, 0.5H)	C: 61.70 (61.80) H: 9.26 (9.15)

[a]Melting point; **1a**: 93-95 ℃; **1b**: 71-74 ℃; **1c**: 88-90 ℃.
[b]IR spectra; **1a**: 3600-3200, 2950-2850, 1750, 1100 cm^{-1} ; **1b**: 3550-3300, 3000-2850, 1800-1730, 1140 cm^{-1} ; **1c**: 3500-3450, 3000-2850, 1780-1750, 1080 cm^{-1}.
[c]FAB mass spectra; m/z(rel. intens.) : **1a**: 289[$(M+1)^+$, 77], 161[50], 69[100]; **1b**: 289[$(M+1)^+$, 100], 129[97], 93[76]; **1c**: 331[$(M+1)^+$, 13], 185[73], 93[100].
[d]Not carried out.

Table 1-2. Yields and Analytical Data of Compounds **2a-h**[a, b, c]

Compound	Yield (%)	^{1}H-NMR[d] δ, *J* (Hz)	Anal. Found (Calcd.)[e]
2 a	60	0.88 (t, 3H), 1.29-1.38 (m, 10H), 1.53-1.56 (m, 2H), 3.35 (t, *J* = 6, 2H), 3.61 (m, 2H), 3.37 (m, 0.5H), 3.85 (m, 1.5H), 3.98 (m, 2H), 4.08 (m, 1H), 4.21 (dd, *J* = 4.4, 5.9, 1H), 4.83 (t, *J* = 4.9, 0.5H), 4.93 (t, *J* = 4.9, 0.5H)	C: 54.66(55.00) H: 8.98 (8.94) N: 3.99 (4.01)
2 b	50	0.88 (t, 3H), 1.29-1.38 (m, 10H), 1.53-1.58 (m, 2H), 3.36-3.43 (m, 1H), 3.60-3.65 (m, 1H), 3.72-3.87 (m, 8H), 3.96-4.10 (m, 3H and 3OH), 4.31-4.39 (2OH), 4.74-4.77 (m, 1H), 4.83 (t, *J* = 4.9, 0.5H), 4.93 (t, *J* = 4.9, 0.5H)	C: 53.99(53.72) H: 9.12 (9.02) N: 3.34 (3.48)
2c	73	0.88 (t, 3H), 1.30-1.39 (m, 10H), 1.54-1.62 (m, 2H), 3.61-3.64 (m, 8H), 3.77-3.84 (m, 1H), 3.86-3.88 (m, 2H), 3.99-4.11 (m, 2H), 4.66 (t, 1H), 4.83(t, *J* = 4.9, 0.5H), 4.94(t, *J* = 4.9, 0.5H)	C: 57.36(57.58) H: 8.91 (8.86) N: 3.56 (3.73)
2 d	78	0.88 (t, 3H), 1.24-1.36 (m, 11H), 1.55-1.62 (m, 2H), 3.32-3.40 (m, 2H), 3.62 (t, *J* = 5.4, 2H), 3.76-3.82 (m, 1H), 3.89-3.99 (m, 2H), 4.03-4.07 (m, 1H), 4.10-4.19 (m, 1H), 4.22 (t, *J* = 4.4, 1H)	C: 54.73(55.00) H: 8.92(8.94) N: 4.05(4.01)
2 e	55	0.88 (t, 3H), 1.29-1.37 (m, 11H), 1.58-1.63 (m, 2H), 3.37-3.41 (m, 1H), 3.59-3.77 (m, 8H), 3.88-4.15 (m, 4H and 2OH), 4.30-4.38 (2OH), 4.72-4.76 (m 1H)	C: 55.34(54.95) H: 9.14(8.96) N: 3.17(3.56)
2 f	73	0.88 (t, 3H), 1.25-1.36 (m, 11H), 1.55-1.63 (m, 2H), 3.60-3.70 (m, 9H), 3.87 (t, *J* = 3, 1H), 3.89-3.95 (m, 1H), 4.03-4.07 (m, 1H), 4.08-4.16 (m, 1H), 4.65 (t, *J* = 4, 1H)	C: 57.44(57.58) H: 8.99(8.86) N: 3.49(3.73)
2 g	84	0.88 (t, 3H), 1.24-1.38 (m, 17H), 1.55-1.62 (m, 2H), 3.33-3.38 (m, 2H), 3.60-3.64 (m, 2H), 3.76-3.83 (m, 1H), 3.89-3.99 (m, 2H and OH), 4.02-4.07 (m, 1H), 4.09-4.19 (m, 1H and OH), 4.20-4.24 (m, 1H), 4.80 (OH), 7.48 (NH)	C: 58.14(58.29) H: 9.52(9.53) N: 3.46(3.58)
2 h	70	0.88 (t, 3H), 1.26-1.30 (m, 14H), 1.33 (s, 3H), 1.56-1.62 (m, 2H), 3.10-3.30 (-OH, br), 3.55-3.72 (m, 9H), 3.89 (m, 1H), 3.97 (dd, *J* = 6 and 8, 1H), 4.06 (m, 1H), 4.12 (m, 1H), 4.15-4.25 (-OH, br), 4.61 (d, *J* = 2.4, 1H)	C: 60.30(60.41) H: 9.45(9.41) N: 3.37(3.35)

[a]Melting point; **2a**: 101-104 ℃; **2b**: viscous liquid; **2c**: waxy; **2d**: 60-63 ℃; **2e**: viscous liquid; **2f**: viscous liquid; **2g**: 62-65 ℃; **2h**: 86-89 ℃

[b]IR spectra; **2a**, **2d**, **2g**: 3450-3300, 2950, 2880, 1680-1620, 1100-1060 cm^{-1}; **2b**, **2e**: 3500-3200, 2950, 2880, 1640-1600, 1120, 1040 cm^{-1}; **2c**, **2f**, **2h**: 3500-3300, 2950, 2850, 1680-1600, 1130 cm^{-1}.

[c]FAB mass spectra; m/z (rel. intens.); **2a**: 350[(M+1)$^+$, 100], 220[58], 93[56], 62[95]; **2b**: 394[(M+1)$^+$, 100], 266[47], 106[94]; **2c**: 376[(M+1)$^+$, 100], 248[58], 114[61], 88[70]; **2d**: 350[(M+1)$^+$, 95], 222[100], 62[45]; **2e**: 394[(M+1)$^+$, 86], 266[100], 106[82]; **2f**: 376[(M+1)$^+$, 60], 248[100], 114[63], 88[57]; **2g**: 392[(M+1)$^+$, 83], 222[100], 93[48], 62[57]; **2h**: 418[(M+1)$^+$, 53], 248[62], 185[100], 93[100].

[d]Acetone-d_6 for **2a-g** and $CDCl_3$ for **2h** as a solvent.

[e]A calculated value for **2b** is based on the assumption that this contains 0.5 mole of water.

1-1-3. Results and Discussion

Synthesis of surfactants **2a-h** and **3a** was carried out according to the routes in Scheme 1-1. The intermediates, 4,6-*O*-alkylideneglucono-1,5-lactones **1a-c**, were prepared by two different methods (A and B). Both results of yields are summarized in Table 1-1. In method A, glucono-1,5-lactone reacted with a long-chain alkyl aldehyde or ketone in the presence of an acid catalyst. Water generated during the acetalization was removed from the reaction system as a benzene azeotrope. In method B, instead of the carbonyl compounds, the corresponding dimethyl acetal derivatives were used. In this case, the acetalization proceeded at a lower temperature than that in method A, and the resulting products, 4,6-*O*-alkylideneglucono-1,5-lactones, were obtained in higher yields compared with the yields in method A. The lower reaction temperature might suppress the thermal decomposition of glucono-1,5-lactone, and so it leads to the higher yields of the desired compounds. The reactions of 4,6-*O*-alkylideneglucono-1,5-lactone **1** with amines gave the corresponding 4,6-*O*-alkylidenegluconamide derivatives **2**. The products were purified by recrystallization or preparative HPLC. The yields and analytical data of compounds **2a-h** are shown in Table 1-2. Additionally, hydrolysis of 4,6-*O*-octylideneglucono-1,5-lactone under alkaline conditions into sodium 4,6-*O*-octylidenegluconate **3a** was also carried out.

The plots of surface tension vs. concentration for compounds **2a-g** and **3a** are shown in Figure 2. The cloud point (T_{cp}) for nonionic compounds **2** or Krafft point (T_{Kp}) for **3a**, the critical micelle concentration (CMC), and the ability to lower surface tension (γCMC) of these surfactants are summarized in Table 3. Those values for compound **2h** could not be measured because of its low solubility in water.

The cloud points of nonionic compounds **2a-g** were more than 82 ℃ at 1 wt% concentration, and those results clearly show that they have good water solubilities. The Krafft point for **3a** was less than 0 ℃ at 0.1 wt% concentration (pH 11). The ketone-derived compounds **2d-f** showed higher CMC values than the aldehyde-derived compounds **2a-c** containing the same number of carbon atoms in the alkylidene part. This is consistent with the general tendency that the CMC value of a surfactant bearing a branched hydrophobic chain is higher than that of a surfactant having the corresponding straight-chain.[26] The micelle forming ability of the ketone-derived compound increased with an

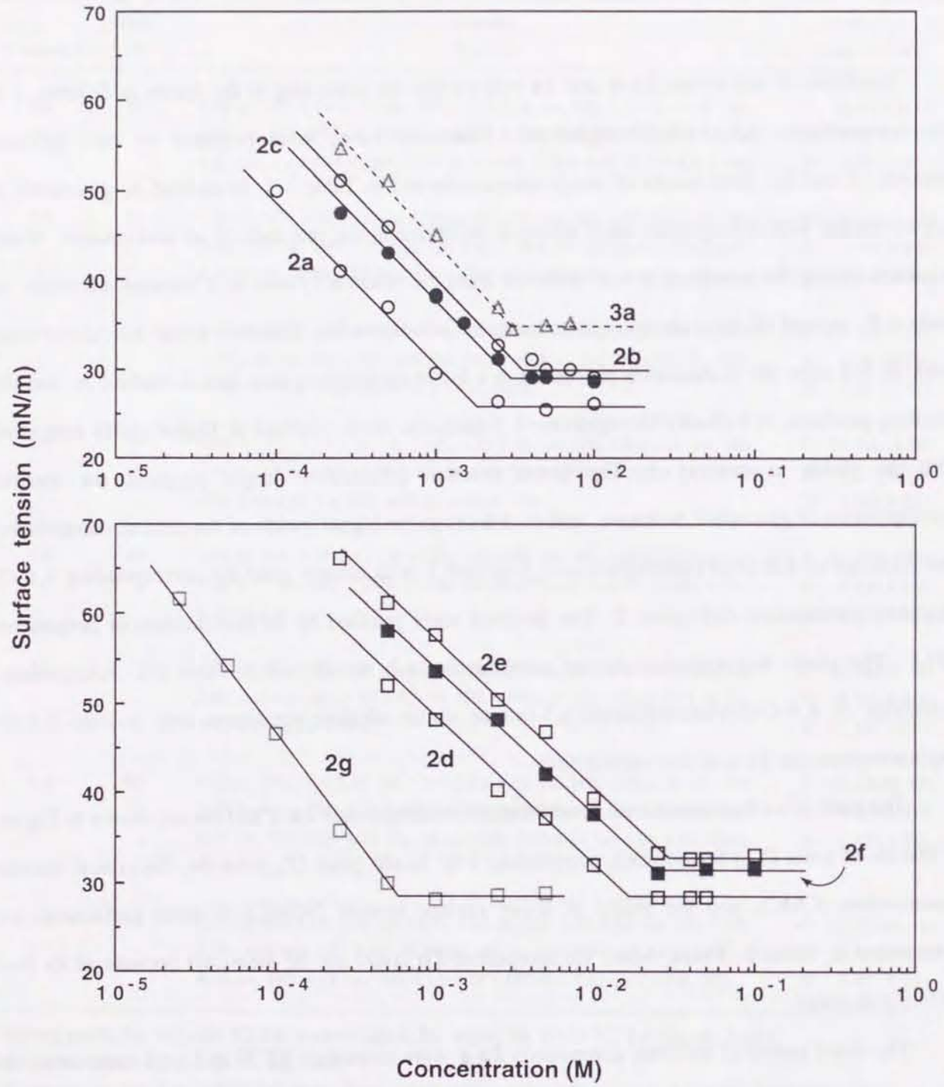


Figure 1-1. Surface tension vs. concentration plots of compounds **2a-f** [in aqueous solution (~ pH 6)] and **3a** (in pH 11 solution) at 20 °C.

Table 1-3. Surface-Active Properties of Compounds **2a-g**[a] and **3a**[b]

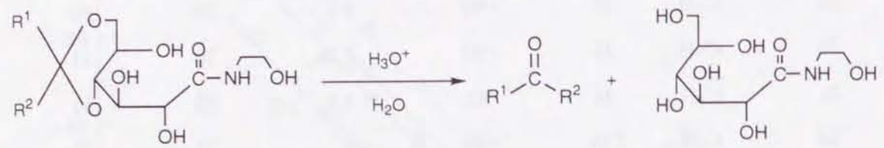
Compound	R^1	R^2	T_{cp}[c] (or T_{Kp}[d]) (°C)	CMC (mM)	γ_{CMC} (mN/m)	10^2 A (nm^2)
2a	C_7H_{15}	H	>90	1.8	26	50
2b	C_7H_{15}	H	>90	3.2	30	51
2c	C_7H_{15}	H	82	3.0	29	51
2d	C_6H_{13}	CH_3	>90	16	29	56
2e	C_6H_{13}	CH_3	>90	29	33	55
2f	C_6H_{13}	CH_3	>90	23	31	56
2g	C_9H_{19}	CH_3	>90	0.57	28	38
2h[e]	C_9H_{19}	CH_3	–	–	–	–
3a	C_7H_{15}	H	< 0[d]	3.0	35	94

[a]At 20 °C, pH 6. [b]At 20 °C, pH 11. [c]Measured at 1 wt% concentration.
[d]For **3a**, the Krafft point (T_{Kp}) was measured at 0.1 wt% concentration. **3a** was only slightly soluble in alkaline solution at 1wt% concentration.
[e]**2h** was only slightly soluble in water at any temperature even at 0.1 wt% concentration.

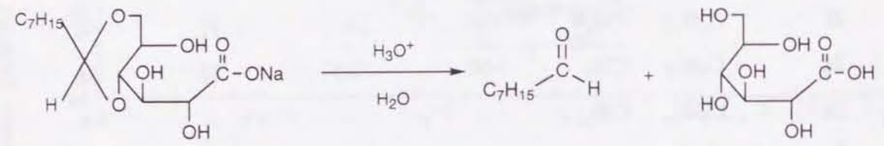
increase in the alkyl chain length (**2d** and **2g**). Concerning the nonionic compounds possessing the same hydrophobic chain (for example, **2a**, **2b** and **2c**), both the micelle forming property and the ability to lower surface tension increased in the order of diethanolamide < morpholide < monoethanolamide. The γCMC values of nonionic compounds **2a**, **2b**, **2c** were smaller than that of carboxylate compound **3a** which has a structure similar to that of **2a-c** except for the terminal hydrophilic moiety. It is interesting that these compounds **2a-f** showed greater ability to lower surface tension in spite of their relatively short hydrophobic chain compared to the conventional nonionic surfactants such as alcohol ethoxylates.[27] It is noted that the area per molecule at the liquid-gas interface (A)[28] of a series of compounds **2** decreased with an increase in the number of carbon atoms in the R^1 group. On the other hand, the difference in the kind of terminal amide moiety had little effect on the area per molecule at the surface of these types of compounds.

Under acidic conditions, compounds **2** and **3** would be expected to decompose into non-surface active species, that is, gluconamide derivatives (or gluconic acid) and carbonyl compounds

because their hydrophobic and hydrophilic groups are linked through an acid-sensitive acetal bond. Therefore, these compounds can be used as cleavable surfactants which have attracted the attention of many researchers.[10-17] Scheme 1-2 shows the expected hydrolytic cleavage route for compounds **2a**, **2d** and **3a**.



2a, 2d **2a** : $R^1 = C_7H_{15}$, $R^2 = H$ **2d** : $R^1 = C_6H_{13}$, $R^2 = CH_3$



3a

Scheme 1-2

The acid-decomposition properties of those sugar-derived compounds were evaluated by determining the quantity of aldehyde or ketone generated during their hydrolysis using the GLC technique. Figure 1-2 shows the decomposition profiles of compounds **2a** and **2d** at pH 1. All surfactants were used at concentrations above their CMC. The reactions followed pseudo-first-order kinetics up to

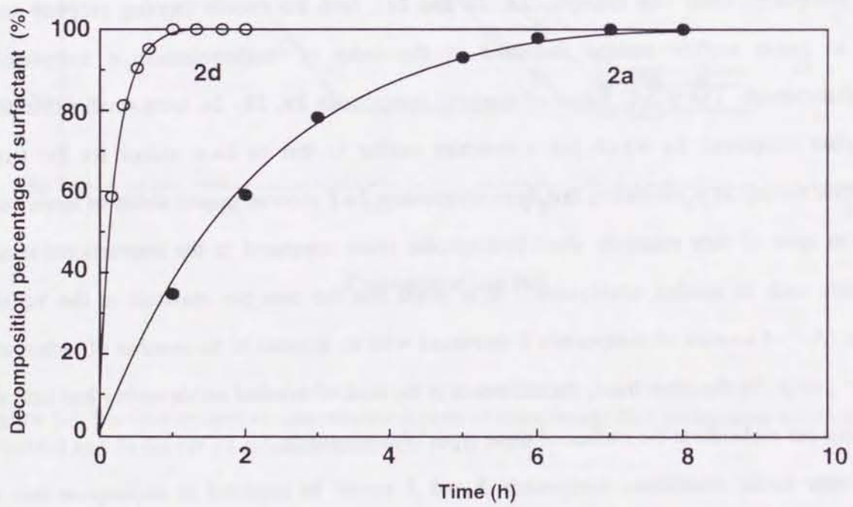
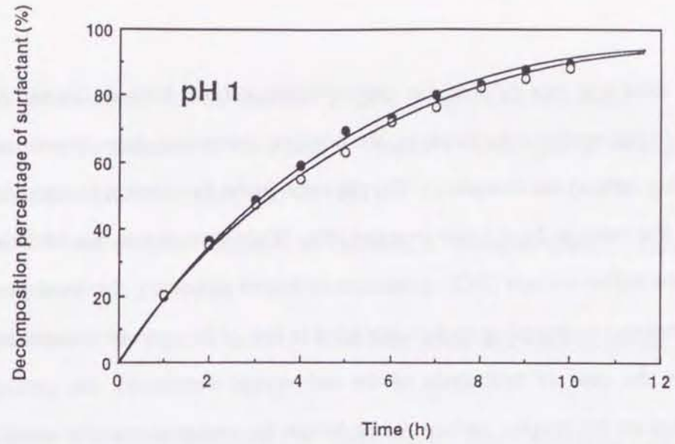


Figure1-2. Decomposition percentage of surfactant vs. time plots for compounds **2a** and **2d** at pH 1 (20 °C). Surfactant concentration : 20 mM.



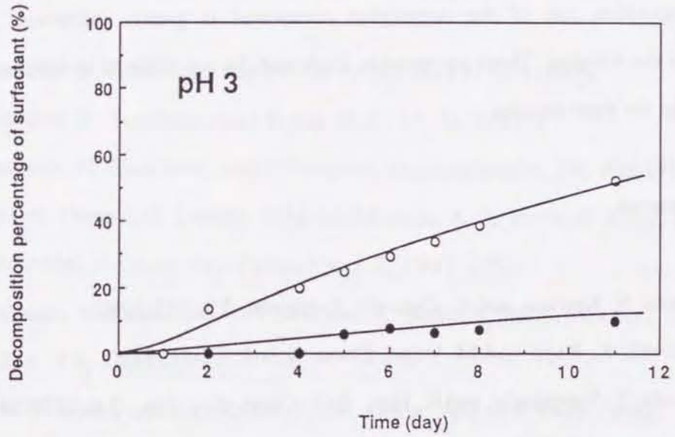


Figure 1-3. Decomposition percentage of surfactant vs. time plots of compounds **2a** and **3a** at pH 1 (upper) and pH 3 (lower), at 20 °C; ○, **2a**; ●, **3a**. Surfactant concentration, 5mM.

approximately 90 % decomposition. The observed rate constants for hydrolysis of compounds **2a** and **2d** were $k_{2a} = 1.3 \times 10^{-4}\ s^{-1}$ and $k_{2d} = 1.5 \times 10^{-3}\ s^{-1}$, respectively. This difference in decomposition rate is explained by considering the greater stability of the carbocation generated from compound **2d** in the hydrolysis than that of the carbocation from compound **2a**. At pH 3 the ketone-derived compound completely decomposed after 3 days, whereas the aldehyde derivative did not completely decompose even after 3 weeks. Furthermore, the decomposition property of compound **2a** was compared with that of the carboxylate **3a** bearing the same hydrophobic chain. Their decomposition profiles at pH 1 and pH 3 are illustrated in Figure 1-3.

At pH 1 there was little difference in decomposition profiles between **2a** and **3a**. On the other hand, at pH 3 (initial proton concentration), the nonionic compound decomposed more rapidly than the corresponding carboxylate compound. The pH value in the **3a** solution changed from 3 to ca. 4.3 after 1h, while that value in **2a** solution changed little. When the solution was maintained at pH 3 by using Clark-Lubs buffer solution (HCl - potassium hydrogen phthalate), the decomposition rate of the carboxylate compound increased up to the same level as that of the nonionic compound. These results indicate that, in the case of hydrolysis of the carboxylate compound, the protonation onto the carboxylate anion on the micellar surface occurs before the protonation at the acetal oxygen atoms, and the decomposition rate of the carboxylate compound is greatly influenced by the proton concentration in the solution. These compounds **2a-h** and **3a** are stable at ambient temperature in a desiccator at least for three months.

1-1-4. References

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1-2. Preparation and Properties of New Surfactants Containing D-Glucosamine as the Building Block

1-2-1. Introduction

The author has been studying various types of new amphiphiles bearing a carbohydrate structure as a hydrophilic part, which can be easily prepared and has additional functions as well as excellent surface-active properties. Recently, the author has synthesized two types of surfactants by acetalization of glucono-1,5-lactone with a long-chain alkyl aldehyde or ketone, followed by hydrolysis under alkaline conditions[1] or amidation with an appropriate amine.[2] These compounds can be used as acid-cleavable surfactants,[3-12] because they show good surface-active properties under neutral or alkaline conditions, however, they decompose into non-surface active species under acidic conditions and lose their surface-active properties.

D-Glucosamine is one of the most popular compounds in the saccharide family because its structure is found in chitin or it is a main component of peptideglycan which constructs the backbone of the cell wall of numerous bacteria. Therefore, surfactants derived from D-glucosamine are expected not only to be useful from an ecological point of view but also to be applicable to the biological and medical fields. Until now, several studies have been reported on the D-glucosamine-derived surfactants.[13-18] For example, Matsumura et al. reported a synthetic method for the surfactants bearing amine hydrochloride as a hydrophilic group from *N*-acetyl-D-glucosamine, their surface-active properties and antimicrobial activities.[18] In all these reports, hydrophobic groups have been introduced onto the D-glucosamine structure mainly by *N*-acylation or glucosidation.

In this section, the author has developed another methodology for the preparation of a new D-glucosamine-derived surfactant in which the introduction of a hydrophobic alkyl chain onto D-glucosamine as an alkylidene part is included. According to this methodology, the author has prepared three types of new surfactants, sodium methyl 4,6-*O*-alkylidene-2-(carboxylatomethylamino)-2-deoxy-D-glucopyranoside **4**, methyl 4,6-*O*-alkylidene-2-deoxy-2-(trimethylammonio)-D-glucopyranoside iodide **5** and sodium methyl 2-acetamide-4,6-*O*-alkylidene-3-*O*-[1-(carboxylato)ethyl]-2-deoxy-D-glucopyranoside **6**, using *N*-acetyl-D-glucosamine as a starting material. Here the author

reports the synthetic method for these surfactants, their surface-active properties, acid-decomposition properties and biodegradabilities.

1-2-2. Experimental Section

Materials. All reagents were commercially available and were used without further purification except methanol and tetrahydrofuran (THF) which were distilled before use.

Analytical Methods. The infrared (IR) spectra were recorded on an Hitachi 260-10 spectrometer (Hitachi Co., Tokyo, Japan). ^{1}H nuclear magnetic resonance (NMR) spectra were measured with a JEOL JNM-GSX400 (400 MHz, JEOL Ltd., Tokyo, Japan) spectrometer using tetramethylsilane (TMS) as an internal standard. Fast atom bombardment (FAB)-mass spectra were recorded on a JEOL JMS-DX303 HF spectrometer. Gas-liquid chromatography (GLC) was performed using a Shimadzu GC-8APF (Shimadzu Ltd., Kyoto, Japan) equipped with a fused silica capillary column (liquid phase: DB-1, film thickness: 0.25 mm, column dimensions: 5 m x 0.25 mm, J&W SCIENTIFIC, California, U.S.A.).

Synthesis of 1,1-dimethoxydecane: This compound was synthesized according to a previously reported method.[19] A mixture of decanal (15.6 g, 0.1 mol), methyl orthoformate (53.1 g, 0.5 mol) and anhydrous methanol (9.61 g, 0.3 mol) in the presence of *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol) was refluxed for 20 h. After neutralization with Na_2CO_3 (1.04 g, 10 mmol), the methanol and the unreacted methyl orthoformate were removed in vacuo. The residue was extracted with H_2O (300 mL) and CH_2Cl_2 (300mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The resulting oil was purified by Kugelrohr distillation under reduced pressure to give the desired product (bp 60 ℃/0.05 Torr, 74 % yield). IR(neat): 2930, 2850, 1120, 1060 cm^{-1}. 1,1-Dimethoxyoctane and 1,1-dimethoxydodecane were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan) and used without further purification.

Synthesis of methyl 2-acetamide-4,6-*O*-alkylidene-2-deoxy-D-glucopyranoside (2a-f): *N*-Acetyl-D-glucosamine (22.1g, 0.1 mol) was stirred in anhydrous methanol (300 mL) under reflux conditions for 24 h in the presence of *p*-toluenesulfonic acid monohydrate (1.90 g, 0.01 mol). After evaporation of the methanol under reduced pressure, dimethylformamide (DMF) (40 mL),

an appropriate aliphatic aldehyde dimethyl acetal (0.12 mol) and *n*-hexane (40 mL) were added into the residue. The mixture was refluxed for 24 h in a round-bottom flask equipped with a Dean-Stark trap; a theoretical amount of methanol (8 mL) was collected in the Dean-Stark trap. After neutralization with Na_2CO_3 (2.12 g, 0.02 mol), the solvent was evaporated in vacuo. The resulting liquid was extracted with H_2O (300 mL) and CH_2Cl_2 (300 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was washed with *n*-hexane and then acetone to yield a white solid as a mixture of the corresponding α and β-anomers. These isomers were separated by silica gel column chromatography with a methanol:chloroform (0.5:99.5, vol/vol) eluent. Under these reaction conditions, the α-anomer was preferentially formed. The yields and analytical data are summarized in Table 1-4.

Synthesis of methyl 4,6-*O*-alkylidene-2-amino-2-deoxy-D-glucopyranoside(3a-d): Deacetylation of methyl 2-acetamide-4,6-*O*-alkylidene-2-deoxy-D-glucopyranoside **2** (0.02 mol) was carried out by refluxing for 24 h in 4 N aq. KOH (75 mL)/ethanol (75 mL). After evaporation of the ethanol, the resulting light-yellow solid was extracted with H_2O (300 mL) and Et_2O (300 mL). The ether layer was dried (anhydrous $MgSO_4$) and concentrated. The crude product was purified with silica gel column chromatography with a methanol:chloroform (1:99, vol/vol) eluent to yield the corresponding compound **3**.

Synthesis of sodium methyl 4,6-*O*-alkylidene-2-(carboxylatomethylamino)-2-deoxy-D-glucopyranoside (4a-d): The mixture of methyl 4,6-*O*-alkylidene-2-amino-2-deoxy-D-glucopyranoside **3** (0.01 mol), bromoacetic acid (1.39 g, 0.01 mol) and Na_2CO_3 (5.30 g, 0.05 mol) was stirred in methanol (100 mL) under reflux conditions for 48 h. After evaporation of the solvent, chloroform was added to the residue and the precipitate was filtered off through a Celite 545 short column. The filtrate was concentrated and the crude product was purified by silica gel column chromatography with a methanol:chloroform (3:97) eluent.

Synthesis of methyl 2-deoxy-4,6-*O*-dodecylidene-2-(trimethylammonio)-α-D-glucopyranoside iodide (5c): The mixture of methyl 2-amino-2-deoxy-4,6-*O*-dodecylidene-α-D-glucopyranoside **3c** (3.60 g, 10 mmol), Na_2CO_3 (2.65 g, 25 mmol) and methyl iodide (150 mL, 2.5 mol) was refluxed for 72 h. After removal of the methyl iodide, methylene chloride was added to the resulting solids. The insoluble solids were filtered off through a Celite 545 short column and the

Table 1-4. Yields and Analytical Data of Compounds **2a-f** [a,b,c]

Compound	Yield (%)	Melting point (°C)	^{1}H-NMR[d] δ
2a	35	174-175	0.87(t, 3H), 1.27-1.39(m, 10H), 1.64-1.68(m, 2H), 2.05 (s, 3H), 3.35(dd, 1H), 3.37(s, 3H), 3.47-3.50(br, OH), 3.55 (dd, 1H), 3.59-3.63(m, 1H), 3.77-3.83(m, 1H), 4.11(dd, 1H), 4.13-4.17(dd, 1H), 4.58(t, 1H), 4.68(d, 1H), 6.09(d, NH)
2b	55	171-172	0.88(t, 3H), 1.26-1.39(m, 14H), 1.62-1.67(m, 2H), 2.05 (s, 3H), 3.35(dd, 1H), 3.37(s, 3H), 3.47-3.50(br, OH), 3.53 (dd, 1H), 3.59-3.64(m, 1H), 3.78-3.84(dd, 1H), 4.12(dd, 1H), 4.13-4.17(m, 1H), 4.58(t,1H), 4.68(d, 1H), 6.10(d, NH)
2c	54	162-163	0.88(t, 3H), 1.25-1.39(m, 18H), 1.62-1.68(m, 2H), 2.06 (s, 3H), 3.28-3.29(br, OH), 3.35(dd, 1H), 3.37(s, 3H), 3.53 (dd, 1H), 3.59-3.62(m, 1H), 3.80-3.83(m,1H), 4.11(dd, 1H), 4.12-4.16(m, 1H), 4.57(t,1H), 4.68(d, 1H), 5.99(d, NH)
2d	12	234-236	0.86(t, 3H), 1.24-1.32(m, 10H), 1.50-1.53(m, 2H), 1.81 (s, 3H), 3.15(m, 2H), 3.31(s, 3H), 3.43-3.47(m, 3H), 4.03 (m, 1H), 4.32(d, 1H), 4.55(t, 1H), 5.14(br, OH), 7.77(d, NH)
2e	9	119-222	0.86(t, 3H), 1.24-1.32(m, 14H), 1.50-1.53(m, 2H), 1.81 (s, 3H), 3.15(m, 2H), 3.30(s, 3H), 3.43-3.47(m, 3H), 4.03 (dd, 1H), 4.31(d, 1H), 4.55(t, 1H), 5.14(d, OH), 7.77(d, NH)
2f	18	222-223	0.88(t, 3H), 1.23-1.36(m, 18H), 1.55-1.68(m, 2H), 1.94 (s, 3H), 3.21-3.24(m, 4H), 3.42-3.59(m, 3H), 3.70(m, 1H), 4.10-4.12(m, 1H), 4.44(d, 1H), 4.53(t, 1H), 5.01(br, OH), 7.66(d, NH)

[a] IR spectra; **2a-c**: 3600-3000, 2900, 1620, 1540, 1100 cm^{-1}. **2d-f**: 3600-3000, 2900, 1650, 1570, 1100cm^{-1}.

[b] FAB mass spectra; m/z(rel. intens.): **2a**: 346[(M+1)$^+$, 100], 314[26], 154[31], 136[24], 126[22]. **2b**: 374[(M+1)$^+$, 100], 342[27], 126[22]. **2c**: 402[(M+1)$^+$, 100], 370[24], 154[58], 136[43], 126[23]. **2d**: 346[(M+1)$^+$, 100], 314[21], 154[63], 136[45]. **2e**: 374[(M+1)$^+$, 100], 342[17], 154[60], 136[42]. **2f**: 402[(M+1)$^+$, 100], 370[24], 154[58], 136[43], 126[23].

[c] Anal.; **2a**: Calcd for $C_{17}H_{31}NO_6$: C, 59.11; H, 9.05; N, 4.05. Found: C, 59.17; H, 9.15; N, 4.02. **2b**: Calcd for $C_{19}H_{35}NO_6$: C, 61.10; H, 9.45; N, 3.75. Found: C, 61.28; H, 9.55; N, 3.67; **2c**: Calcd for $C_{21}H_{39}NO_6$: C, 62.82; H, 9.79; N, 3.49. Found: C, 62.67; H, 9.85; N, 3.38. **2d**: Calcd for $C_{17}H_{31}NO_6 \cdot H_2O$: C, 56.19; H, 9.15; N, 3.85. Found: C, 56.01; H, 8.92; N, 3.93. **2e**: Calcd for $C_{19}H_{35}NO_6 \cdot 0.5H_2O$: C, 59.66; H, 9.49; N, 3.66. Found: C, 59.35; H, 9.52; N, 3.77. **2f**: Calcd for $C_{21}H_{39}NO_6$: C, 62.82; H, 9.79; N, 3.49. Found: C, 62.60; H, 9.78; N, 3.43.

[d] $CDCl_3$ for **2a-c** and DMSO-d_6 for **2d-f** as a solvent. s: singlet, d: doublet, t: triplet, m: multiplet and br: broad

Table 1-5. Yields and Analytical Data of Compounds **4a-d**, **5c** and **6a-c** [a,b,c]

Compound	Yield (%)	Melting point (°C)	^{1}H-NMR ($CDCl_3$) δ
4a	79	210[d]	0.87(t, 3H), 1.27-1.39(m, 10H), 1.62-1.65(m, 2H), 2.90-3.75 (br, 11H), 4.08(m, 1H), 4.57(t, 1H), 4.79(d, 1H)
4b	88	220[d]	0.88(t, 3H), 1.26-1.39(m,14H), 1.62-1.68(m, 2H), 3.30-3.92 (br, 7H), 4.07(m, 1H), 4.10(m, 1H), 4.32(br, 2H), 4.56(t, 1H), 4.72(d, 1H)
4c	89	225[d]	0.88(t, 3H), 1.26-1.39(m, 18H), 1.61-1.68(m, 2H), 2.90-3.77 (br, 11H), 4.10(m, 1H), 4.57(t, 1H), 4.72(d, 1H)
4d	83	300[d]	0.88(t, 3H), 1.26-1.39(m, 18H), 1.61-1.68(m, 2H), 3.20-3.55 (br, 7H), 3.71(m, 1H), 4.11(m, 1H), 4.29(br, 2H), 4.39(d, 1H) 4.55(t, 1H)
5c	100	166-168	0.88(t, 3H), 1.26-1.40(m, 18H), 1.63-1.66(m, 2H), 3.47(s, 3H), 3.59(dd, 1H), 3.62(dd, 1H), 3.64(s, 9H), 3.68(dd, 1H), 3.80(br, OH), 4.11(dd, 1H), 4.33(dd, 1H), 4.43-4.44(m, 1H), 4.61(t, 1H), 5.31(d, 1H)
6a	76	106-107	0.87(t, 3H), 1.20-1.41(m, 13H), 1.60-1.62(m, 2H), 1.98(s, 3H), 3.30(s, 3H), 3.46-3.70(m, 5H), 3.92-4.20(m, 2H), 4.52(t, 1H) 4.79(d, 1H)
6b	78	106-108	0.88(t, 3H), 1.20-1.42(m, 17H), 1.63-1.68(m, 2H), 2.05(s, 3H), 3.30-3.86(m, 8H), 4.08-4.30(m, 2H), 4.57(t, 1H), 4.66(d, 1H)
6c	82	110-112	0.88(t, 3H), 1.20-1.42(m, 21H), 1.52-1.62(m, 2H), 1.98(s, 3H), 3.30-3.77(m, 8H), 3.94-4.13(m, 2H), 4.52(t, 1H), 4.88(d, 1H)

[a]IR spectra; **4a-d**: 3600-3000, 2900, 1600, 1100 cm^{-1}. **6a-d**: 3300, 2900, 1700, 1650, 1540, 1100cm^{-1}.

[b]FAB mass spectra; m/z(rel. intens.): **4a**: 384[$(M+1)^+$, 30], 329[15], 176[70], 63[40]. **4b**: 434[(M+Na)+, 69], 412[(M+1)+, 13], 154[93]. **4c**: 440[$(M+1)^+$, 42], 370[24], 329[24], 176[83], 154[93], 136[71]. **4d**: 462[$(M+Na)^+$, 62], 440[$(M+1)^+$, 42], 176[83], 154[93]. **5c**: 402[$(M-I)^+$, 100]; **6a**: 462[$(M+Na)^+$, 100], 440[$(M+1)^+$, 10], 149[41]. **6b**: 490[$(M+Na)^+$, 100], 468[$(M+1)^+$, 10]. **6c**: 518[$(M+Na)^+$, 100], 496[$(M+1)^+$, 18].

[c]Anal.; **5c**: Calcd for $C_{22}H_{44}NO_5I$: C, 49.90; H, 8.38; N, 2.65; I, 23.97. Found: C, 49.65; H, 8.35; N, 2.61; I, 23.90. Compounds **4a-d** and **6a-c** were too hygroscopic to give their satisfactory results for elemental analysis.

[d]Decomposition temperature.

filtrate was concentrated. The crude product was purified by recrystallization from benzene to yield the desired compound as a white solid (5.30 g, 100 %).

Synthesis of sodium methyl 2-acetamide-4,6-*O*-alkylidene-3-*O*-[1-(carboxylato) ethyl]-2-deoxy-α-D-glucopyranoside (6a-c): Compounds **6a-c** were synthesized according to a previously reported method.[20] Methyl 2-acetamide-4,6-*O*-alkylidene-2-deoxy-α-D-glucopyranoside **2a-c** (0.01 mol) was added to a suspension of sodium hydride (2.40 g net, 0.1 mol)/dry THF (80 mL) and the mixture was stirred at 60 ℃ for 1h. Next, 2-chloropropionic acid (2.17 g, 0.02 mol) was dropped into this suspension, and the mixture was stirred at 60 ℃ for 24 h. After deactivation of the unreacted sodium hydride by addition of methanol, the solvent was evaporated in vacuo. The resulting solids were dispersed in methylene chloride and the precipitate was filtered off through a Celite 545 short column. The filtrate was concentrated and the crude product was purified by silica gel column chromatography with a methanol:chloroform (2:98, vol/vol) eluent.

The yields and analytical data of compounds **4**, **5** and **6** are shown in Table 1-5.

Surface-active properties: The Krafft point (T_{Kp}) was determined by the naked eye with a 1 wt% (or 0.1 wt%) aqueous solution. The surface tension of the surfactant solutions in the presence of swamping electrolyte (0.1 M NaCl for **4a-d** and **6a-c**, or 0.1 M NaI for **5c**) was measured at 20 ℃ with a Wilhelmy tensiometer (Shimadzu ST-1; Shimadzu Ltd., Kyoto, Japan; glass plate). The critical micelle concentration (CMC) was determined from the break point of each surface tension vs. concentration (on log scale) curve. The ability to lower surface tension (γCMC) is based on the surface tension at the CMC. The area per molecule at the liquid-gas interface (A) in nm^2 was calculated from equations 1 and 2[21]:

$$\Gamma = -1/2.303RT\ (\delta\gamma/\delta \log C)T \qquad [1]$$

$$A = 10^{21}/N\Gamma \qquad [2]$$

where R = 8.31 $Jmol^{-1}K^{-1}$, $(\delta\gamma/\delta \log C)$ is the slope of γ versus logC curve below CMC at constant temperture, and N = Avogadro's number. The foaming properties were measured by the semi-micro TK Method at 20 ℃.[22] The surface-active properties of compounds **4a-d** and **6a-c** were measured at

pH 11 (aq. NaOH), while those for compound **5c** were measured under neutral conditions (pH 6).

Decomposition properties: The acid-decomposition properties of the surfactants were evaluated by determining the quantity of liberated octanal (from **4a**), decanal (from **4b**) or dodecanal (from **4c**, **4d**, **5c** and **6c**) with GLC under acidic conditions (2 % aq. HCl). Typical procedures for compound **4c** are as follows: Compound **4c** (0.220 g, 0.5 mmol) was dissolved in 2 % hydrochloric acid (20 mL) containing NaCl (6.0 g), and then *n*-hexane (3.5 mL) and *n*-tetradecane (50 mg, 0.25 mmol, as an internal standard) were added to this solution. The mixture was shaken at 20 ℃ and some of the solution was sampled from the *n*-hexane layer after a certain period. The quantity of liberated dodecanal into the *n*-hexane layer was determined by GLC-calibration curve analysis.

Biodegradation test: A biodegradation test was carried out according to the provisions of Sub-Section 4 of Section 4 of the Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances (1973, Law No.117, Japan) with activated sludge from a municipal sewage treatment plant in Osaka City. The biochemical oxygen demand (BOD) after 1 or 2 weeks was determined by the quantity (mg) of oxygen comsumed. Biodegradability was calculated from the following formula:

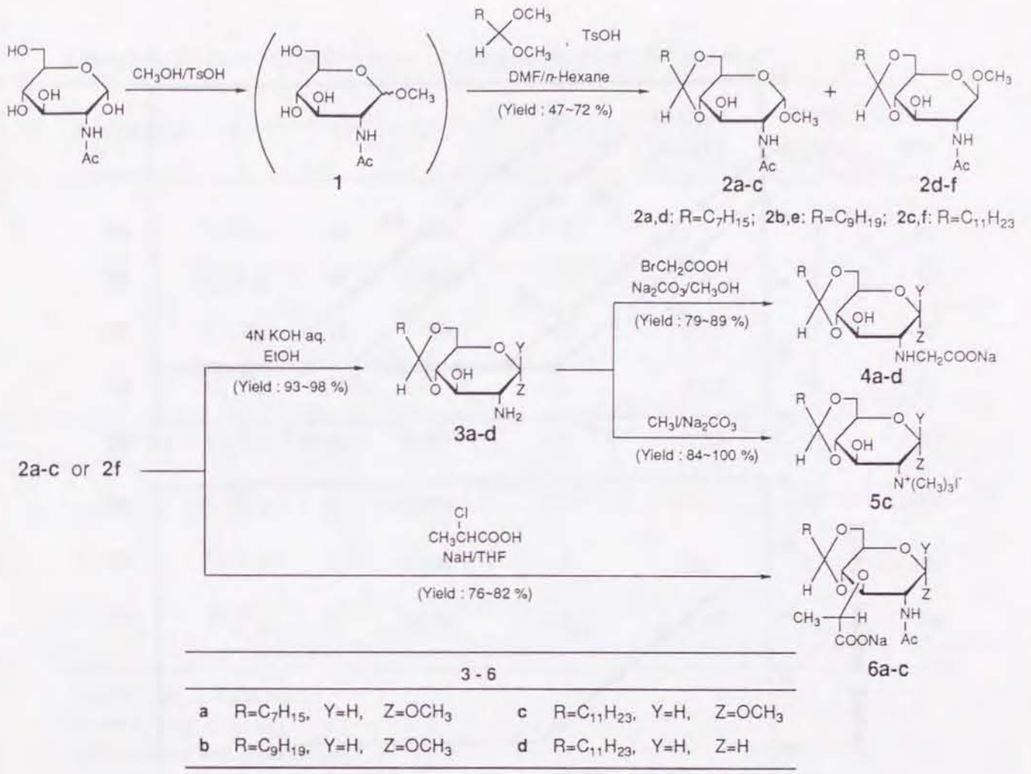
$$\text{Biodegradability (\%)} = \text{BOD/TOD} \times 100$$

where TOD (mg) refers the theoretical oxygen demand.

1-2-3. Results and Discussion

Surfactants **4**, **5** and **6** were synthesized according to the route in Scheme 1-3.

N-Acetyl-D-glucosamine bearing an anomeric OH group is unstable under alkaline conditions; therefore, the OH group was protected by methylation first. The resulting methyl glucoside was allowed to react with an appropriate aliphatic aldehyde dimethyl acetal *in situ* to yield a mixture of methyl 2-acetamide-4,6-*O*-alkylidene-2-deoxy-α-D-glucopyranoside and the corresponding β-anomer. Under the reaction conditions in this work, the α-anomer was preferentially formed. The mixture can be easily separated by silica gel column chromatography using methanol:chloroform (1:99) as an



Scheme 1-3

eluent. Compound **3**, which was obtained by deacetylation of compound **2** under alkaline conditions, reacted with bromoacetic acid to yield the surfactant **4**. On the other hand, the reaction of compound **3** with methyl iodide quantitatively produced the ammonium type of surfactant **5**. The reaction of compound **2** with 2-chloropropionic acid was carried out according to a previously reported method[20] to yield the surfactant **6**, which was designed as amphiphilic derivatives or analogues of muramic acid. Muramic acid is the main component of the bacterial cell wall. Its derivatives or analogues have attracted the attention of many researchers because of their significant biological activities.[23-28]

The plots of surface tension vs. concentration for compounds **4a-d**, **5c** and **6a-c** in the presence of swamping electrolyte are shown in Figure 1-4. The Kraft point (T_{Kp}), the critical micelle concentration (CMC), the ability to lower surface tension (γCMC), and the area per molecule at the liquid-gas interface (A) calculated by the Gibbs adsorption equation[21] of these surfactants are summarized in Table 1-6.

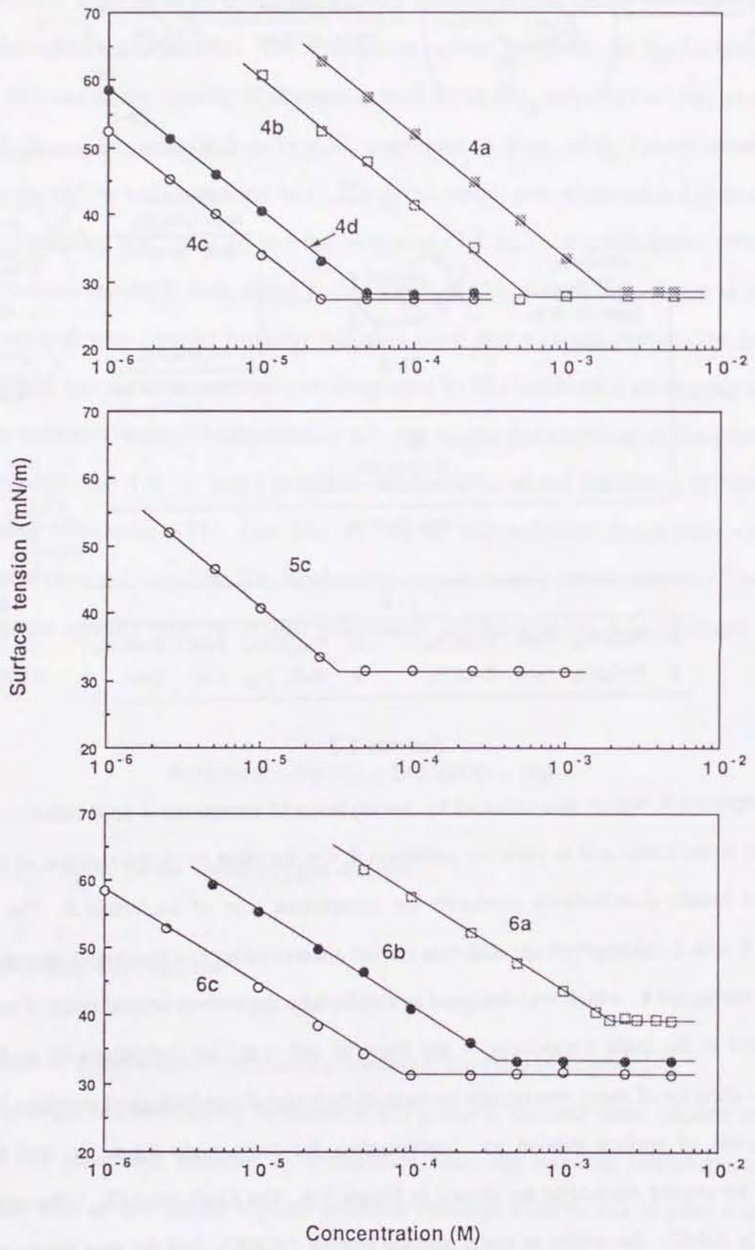


Figure 1-4. Surface tension vs. concentration plots of compounds **4a-d, 5c,** and **6a-c** at 20 °C. **4a-d, 6a-c:** At pH 11 in the presence of 0.1 M NaCl. **5c:** At pH 6 in the presence of 0.1 M NaI.

Table 1-6. Surface-Active Properties of Compounds **4a-d**[a], **5c**[b] and **6a-c**[a]

Compound	R	Y	Z	T_{Kp}[c] (°C)	10^4 CMC (mol/L)	γ_{CMC} (mN/m)	10^2 A (nm^2)
4a	C_7H_{15}	H	OMe	< 0[d]	19	29	51
4b	C_9H_{19}	H	OMe	< 0	5.8	28	50
4c	$C_{11}H_{23}$	H	OMe	< 0	0.22	27	50
4d	$C_{11}H_{23}$	OMe	H	< 0	0.45	28	51
5c	$C_{11}H_{23}$	H	OMe	< 0	0.32	32	50
6a	C_7H_{15}	H	OMe	< 0[d]	20	39	67
6b	C_9H_{19}	H	OMe	< 0	3.6	33	66
6c	$C_{11}H_{23}$	H	OMe	< 0	0.86	31	66

[a]At 20°C, pH 11, 0.1M NaCl.
[b]At 20°C, pH 6, 0.1M NaI.
[c]Measured at 1 wt% concentration.
[d]For **4a** and **6a**, the Krafft point (T_{Kp}) was measured at 0.1 wt% concentration, because both **4a** and **6a** were only slightly soluble in alkaline solution at 1 wt% concentration.

Although compounds **4a** and **6a** bearing a C7 alkyl chain as a "R" group (Scheme 1-3) were only slightly soluble in water at a 1 wt% concentration, compounds **4b-d** and **6b,c** bearing longer hydrophobic chains than **4a** and **6a** were freely soluble in water at a 1 wt% concentration at any temperature. This result may be explained by considering that the length of the alkyl chain of **4a** or **6a** is too short to form stable micelles in bulk water. Concerning compounds **4** and **6**, both the micelle forming property and the ability to lower surface tension increased with an increase in the length of their hydrophobic chain. Compound **4** showed a higher ability to lower surface tension than the corresponding compound **6** having the same alkyl group "R". There is a correlation between γCMC and "A" for **4** and **6**, indicating that the closer the packing of the molecules at the surface, the lower will be the value of γCMC. Comparison of compound **4c** with **4d** indicates that **4c**, possessing an α-OCH_3 group at the anomeric position, has a slightly higher micelle forming ability than **4d** possessing a β-OCH_3 group; however, little difference was observed in the γCMC and A values between these

compounds. These results are consistent with the tendency reported for CMC and γCMC values of alkyl α- and β-glucosides.[29] The ammonium type of compound **5c** showed higher CMC and γCMC values than the carboxylate type of compound **4c** bearing the same hydrophobic chain and the same configuration at the anomeric center.

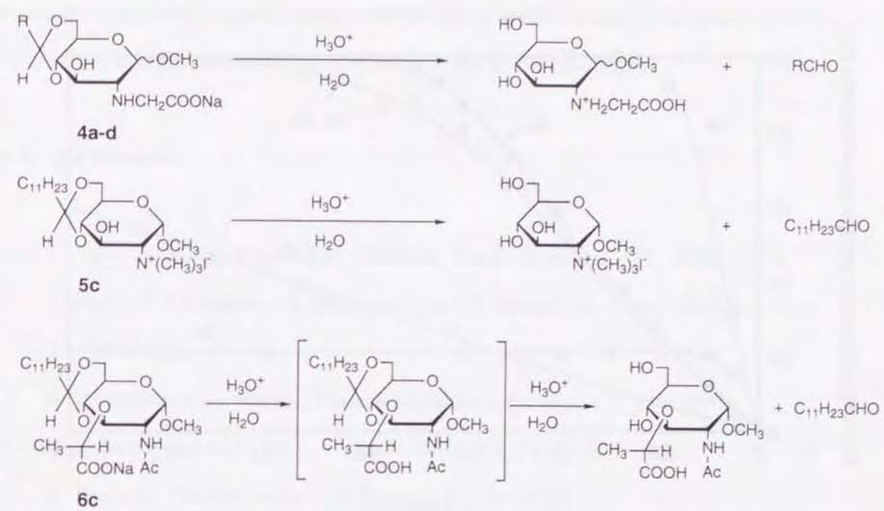
The foaming ability and foam stability of compounds **4**, **5** and **6** are summarized in Table 1-7. Compounds **4b**, **4c** and **4d** showed good foaming ability and excellent foam stability. Little difference was observed in foaming properties between the α-anomer **4c** and the β-anomer **4d**, in contrast to the data on the α- and β-anomer of alkyl glycosides.[29] Compounds **6** showed lower foam stability than compounds **4**, which is to be expected based on the increase in the area per molecule at the surface of **6** in comparison with **4**. The ammonium type of compound **5c** also showed lower foam stability.

Under acidic conditions, compounds **4**, **5** and **6** are expected to decompose into non-surface active species because their hydrophobic and hydrophilic groups are linked through an acid-sensitive

Table 1-7. Foaming Properties of Compounds **4a-d**, **5c** and **6a-c**[a]

Compound	R	Y	Z	Foam volume (mL) per min			
				0	3	5	10
4a[b]	C_7H_{15}	H	OMe	270	0	—	—
4b	C_9H_{19}	H	OMe	280	280	280	280
4c	$C_{11}H_{23}$	H	OMe	280	280	280	280
4d	$C_{11}H_{23}$	OMe	H	280	280	280	280
5c[c]	$C_{11}H_{23}$	H	OMe	280	80	30	0
6a[b]	C_7H_{15}	H	OMe	270	0	—	—
6b	C_9H_{19}	H	OMe	270	20	0	—
6c	$C_{11}H_{23}$	H	OMe	270	20	0	—

[a]At 20°C, pH 11, 1 wt%.
[b]Measured at 0.1 wt% concentration. Both **4a** and **6a** were only slightly soluble at 1 wt% concentration.
[c]At 20°C, pH 6, 1 wt%.



Scheme 1-4

acetal bond. Scheme 1-4 shows the expected hydrolytic cleavage routes for compounds **4**, **5c** and **6c**. The evaluation of the acid-decomposition properties of these compounds was carried out by determining the quantity of aldehyde generated during their hydrolyses using the GLC technique. Each surfactant concentration in the aqueous phase was adjusted to 25 mmol/L (above each CMC). The decomposition profiles of compounds **4a-d**, **5c** and **6c** in 2 % aqueous HCl are illustrated in Figure 1-5.

In a series of compounds **4**, the order of decreasing acid-decomposition rate is: **4a** >> **4b** > **4c** = **4d**, which is the same order of increasing CMC in this series. There was little difference in decomposition profiles between compound **4c** and **4d** which have the opposite configuration at the anomeric position. The ammonium type of compound **5c** decomposed more slowly than the corresponding carboxylate **4c**. Because of the electrostatic repulsion between protons in the bulk phase and the positively charged micellar surface, it may be hard for protons to attack the acetal groups through the Stern layers of the cationic micelles.[8] In the case of compound **6c**, because the water-insoluble carboxylic acid was predominantly formed under these experimental conditions, its decomposition percentage converged on only 20%.

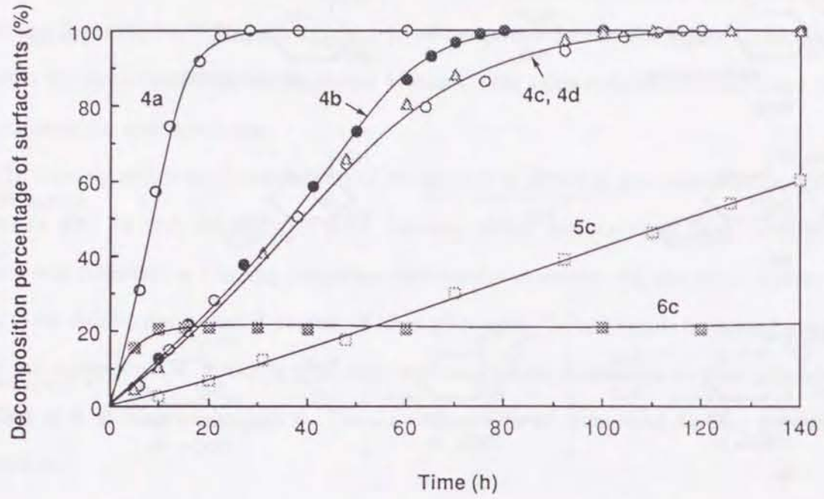


Figure 1-5. Decomposition percentage of surfactant vs. time plots of compounds **4a-d**, **5c**, and **6c** in 2% aq. HCl. Surfactant concentration: 25 mM.

The biodegradabilities (%) [BOD/TOD x 100] of compounds **4a**, **4c**, **4d**, **5c** and **6c** after 1 or 2 weeks are shown in Table 1-8 along with the data for sodium dodecanoate under the same conditions.

Table 1-8. Biodegradability of Surfactants **4a**, **4c**, **4d**, **5c**, and **6c**

Surfactant	BOD/TOD x 100 (%)	
	1 week	2 weeks
4a	9	24
4c	31	40
4d	20	27
5c	6	- 3
6c	36	52
$C_{11}H_{23}COONa$	34	43

BOD: biochemical oxygen demand
TOD: theoretical oxygen demand

The biodegradabilities of the carboxylate types of surfactants **4** and **6** were much higher than that of the ammonium type of surfactant **5** bearing the same hydrophobic alkyl chain. Concerning compounds **4**, the biodegradability was affected by both the length of the alkyl chain and the anomeric configuration. It is noteworthy that compound **6c** showed higher biodegradability than sodium dodecanoate under these experimental conditions. The negative biodegradation

value of the ammonium type of compound **5c** after 2 weeks is mainly attributed to the antimicrobial activity of this compound for microbes existing in the activated sludge.

1-2-4. References

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1-3. A Facile Synthesis of Lipophilic Acetal Derivatives of L-Ascorbic Acid (Vitamin C)

1-3-1. Introduction

Recently, L-ascorbic acid (vitamin C) has been used in widespread fields as food additives, pharmaceuticals and cosmetics. However, it is easily oxidized and unstable to both light and heat because of its specific structure, 2,3-endiol. Therefore, it is difficult to convert L-ascorbic acid into the lipophilic derivatives which show high solubility in organic solvents, and only a few reports have described the reaction of L-ascorbic acid with long-chain aliphatic compounds.[1-3] The higher fatty acid monoesters of L-ascorbic acid are representative lipophilic derivatives of L-ascorbic acid and they are known to have vitamin activities similar to L-ascorbic acid.[4,5] Especially, it is noteworthy that 6-*O*-palmitoyl-L-ascorbic acid exhibits higher antitumor activity than L-ascorbic acid.[6,7]

In this section the author reports a facile synthetic method for new lipophilic acetal derivatives of L-ascorbic acid, which are expected to be alternatives to the higher fatty acid monoesters of L-ascorbic acid and to be applicable to medical and biological fields. Concerning the acetal derivatives of ascorbic acid, 5,6-*O*-isopropylidene-L-ascorbic acid,[8] 5,6-*O*-benzylidene-L-ascorbic acid[9] and 5,6-*O*-cyclohexylidene-D-isoascorbic acid[10] have been synthesized before. However, the author found that those synthetic methods gave the desired long-chain alkyl or alkenyl acetal derivatives only in poor yields (<10%).

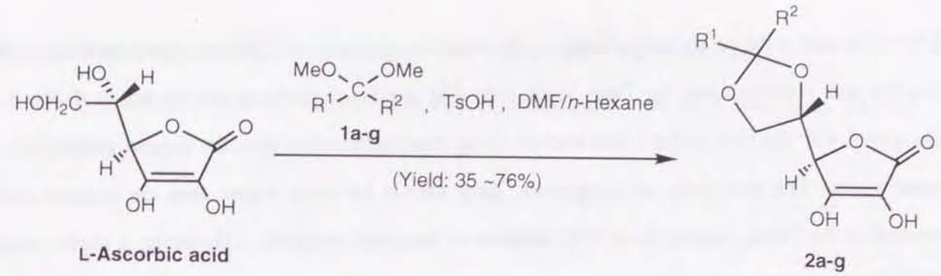
1-3-2. Experimental Section

All reagents were of reagent grade and were used without further purification except DMF, which was dried over molecular sieves 4A before use. IR spectra were recorded on a Hitachi infrared spectrometer 260-10. NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer with TMS as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 303 HF spectrometer. Elemental analyses were obtained using a Perkin-Elmer 240C analyzer. TLC was done on silica gel (Merck Silica $60F_{254}$ sheets). Typical synthetic procedures are as follows:

5,6-*O*-Octylidene-L-ascorbic acid (2a): A mixture of L-ascorbic acid (4.23 g, 24 mmol), 1,1-dimethoxyoctane **1a** (3.49 g, 20 mmol), *p*-toluenesulfonic acid monohydrate (0.76 g, 4 mmol), DMF (20 mL) and *n*-hexane (30 mL) was placed in a round-bottom flask equipped with a Dean-Stark trap. The mixture was refluxed for 7 h; approximately 1 mL of methanol was collected in the Dean-Stark trap. After addition of sodium hydroxide (0.16 g, 4 mmol) in methanol (5 mL) at room temperature to neutralize *p*-toluenesulfonic acid, the solvent was evaporated off *in vacuo*. The residue was extracted with brine (50 mL) and Et_2O (3 x 80 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by recrystallization from benzene (76 % yield, m.p. 128~130 ℃). The isolated product was found to consist of a mixture of two diastereomers (ratio 1:1) by the NMR spectroscopic analyses. Analytical data for compound **2a** are as follows: IR (KBr): 3420, 3050, 2930, 2850, 1760, 1680, 1470, 1330, 1130 cm^{-1}. Mass[m/e, rel. intens.]: 286[M^+, 4], 187[100], 171[35], 141[36], 111[35], 69[57]. ^{1}H-NMR[acetone-d_6, TMS as an internal standard, δ, *J* (Hz)]: Diastereomer A; 0.88 (t, 3H, *J* = 6.8), 1.28-1.38 (m, 10H), 1.54-1.60 (m, 2H), 3.90 (dd, 1H, *J* = 7.3, 8.3), 4.26 (dd, 1H, *J* = 7, 8.5), 4.34 (m, 1H), 4.76 (d, 1H, *J* = 2.9), 4.89 (t, 1H, *J* = 4). Diastereomer B; 0.88 (t, 3H, *J* = 6.8), 1.28-1.38 (m, 10H), 1.54-1.60 (m, 2H), 3.99 (dd, 1H, *J* = 7.3, 8.3), 4.06 (dd, 1H, *J* = 5.4, 8.3), 4.32 (m, 1H), 4.72 (d, 1H, *J* = 3.9), 4.87 (t, 1H, *J* = 4).

1-3-3. Results and Discussion

First, L-ascorbic acid was allowed to react with an appropriate aliphatic aldehyde or ketone in DMF-benzene, in the presence of *p*-toluenesulfonic acid, under reflux conditions in order to eliminate condensed water into the Dean-Stark trap. In this case the desired 5,6-*O*-alkylidene- or alkenylidene-L-ascorbic acids were obtained in low yields, perhaps because L-ascorbic acid and the resulting acetal derivatives, which were both very heat-labile, decomposed to a considerable extent. So carbonyl compounds were preliminarily converted into the corresponding dimethyl acetals, and the target acetal compounds were synthesized under milder conditions using transacetalization of the dimethyl acetals with L-ascorbic acid. The dimethyl acetal derivatives **1** were almost quantitatively prepared according to the previously reported method.[11,12] These acetals **1** were made to react with L-ascorbic acid in



Scheme 1-5. Preparation of acetal derivatives of L-ascorbic acid

Table 1-9. Yields and Elemental Analyses of Compounds **2a-g**

Compound	R^1	R^2	Yield[a] %	E. A.[b] Found (Calcd)
2a	C_7H_{15}	H	76 (46)	C: 56.66 (56.94) H: 7.67 (7.85)
2b	$C_{11}H_{23}$	H	65 (32)	C: 61.23 (61.52) H: 8.55 (8.89)
2c	CH_2=$CH(CH_2)_8$	H	58 (26)	C: 60.63 (60.88) H: 8.12 (8.11)
2d[c]	R^C	H	50 (30)	C: 60.92 (61.52) H: 7.75 (7.74)
2e	C_6H_{13}	CH_3	48 (27)	C: 58.66 (58.73) H: 7.40 (7.74)
2f	$C_{11}H_{23}$	CH_3	47 (21)	C: 63.75 (64.02) H: 8.93 (9.05)
2g[d]	R^G	CH_3	35 (22)	C: 64.46 (64.75) H: 7.98 (8.00)

[a]Isolated yields. Yields in parentheses are ones obtained by the reactions of L-ascorbic acid with aliphatic aldehyde or ketone.
[b]Calculated values for **2a-d** are based on the assumption that these contain 0.5 mol of water.
[c]R^C : $(CH_3)_2C$=$CH(CH_2)_2CH(CH_3)CH_2$
[d]R^G : $(CH_3)_2C$=$CH(CH_2)_2C(CH_3)$=$CH(CH_2)_2$

DMF-*n*-hexane at the reflux temperature, as illustrated in Scheme 1-5. Methanol generated during the reaction was removed into the Dean-Stark trap. The yields of products are shown in Table 1-9. Compared with the first method, this method using transacetalization gave the desired compounds in better yields. The real yields of compounds **2a-g** should be much higher than the isolated yields reported in the Table, judging from TLC analyses of the crude products. However, a slight amount of DMF, the unreacted dimethyl acetals or carbonyl compounds generated by hydrolysis of **1** caused lowering of the yields purified by recrystallization. Especially for the products **2e-g** derived from ketone dimethyl acetals, it was very difficult to completely remove the unreacted **1** from the crude compounds before recrystallization, and so their isolated yields became lower than those of the compounds **2a-d** derived from aldehyde dimethyl acetals. The ^{1}H-NMR, ^{13}C-NMR, H-H COSY and C-H COSY spectra of compounds derived from aldehyde dimethyl acetals (**2a-d**) indicated that they consisted of a mixture of two diastereomers (ratio ~1:1) which had different configurations at the acetal carbon atom on the 1,3-dioxolane ring. On the contrary, all spectral data showed that the isolated **2e-g** derived from ketone dimethyl acetals apparently comprised only one diastereomer, although the presence of other diastereomers in the crude products should be possible.

1-3-4. References

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Chapter 2. Preparation, Properties, and Micellar Catalysis of Surfactants Bearing Sugar-Amide Head Groups

2-1. Preparation and Properties of Nonionic Surfactants with One Alkyl Chain and Two Sugar-Amide Head Groups

2-1-1. Introduction

Surfactants bearing sugar head groups, such as alkyl glycosides[1-6] and sucrose fatty acid esters,[7,8] have gained a wide technical interest, since they are derived from renewable resources and have good surface-active properties as well as low toxicity and high biodegradability. These surfactants have also been utilized in the biological field as detergents to solubilize membrane proteins[9-12] and as receptors for sugar-binding proteins such as lectins.[13-16] The surfactants bearing sugar-amide head groups[17-24] are among the most useful and attractive sugar-derived surfactants from an industrial point of view, since they can be easily prepared in good yields without tedious operations such as protection and deprotection of the hydroxyl groups in the sugar molecule and without use of expensive reagents. However, most of the previous sugar-amide surfactants, for example *N*-alkylgluconamides[20] and dialkylbisgluconamides,[23,24] showed low water solubility, and this property limited the application range of these surfactants. That prompted the author to prepare a new structural type of sugar-amide surfactant possessing excellent water solubility as well as excellent surface-active properties. Here the author describes the preparation of a homologous series of nonionic surfactants bearing one alkyl chain and two sugar-amide groups (gluconamides, maltobionamides, lactobionamides, maltotrionamides) and their surface-active properties. Furthermore, as a part of investigation of the biological function of these surfactants bearing two sugar-amide head groups, the author examined their binding properties to a lectin, Concanavalin A.

2-1-2. Experimental Section

Materials. Tetrahydrofuran (THF) and diethyl ether were purified before use. All other reagents used were of commercially available reagent grade. Concanavalin A [from Canavalia

ensiformis (Jack Bean), Type IV] was purchased from Sigma Chemical Co.

Analytical Methods. ^{1}H NMR spectra were recorded in DMSO-d_6 with a JEOL JNM-GSX-400 (400 MHz) or a Varian UNITY INOVA-600 (600 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were measured on a HORIBA FT-710 spectrometer. Mass spectra were measured on a JEOL JMS-DX-303 mass spectrometer. Elemental analyses were measured with a Yanagimoto CHN-Corder. Melting points were measured with a Yanaco MP-S3 apparatus. Gas-liquid chromatography (GLC) was performed with a Hitachi G-3000 equipped with a fused-silica capillary column (liquid phase, DB-1; film thickness, 0.25 μm; column dimensions, 5m x 0.25 mm; J&W Scientific, Folsom, CA).

2-1-2-1. Preparation of surfactants with two sugar-amide head groups

Monoalkylation of malononitrile with alkyl bromide. Sodium amide (7.8 g, 200 mmol) was gradually added to a mixture of alkyl bromide (100 mmol), malononitrile (13.21g, 200 mmol), and tetra-*n*-butylammonium bromide (6.45 g, 20 mmol) in THF (150 mL) at 60 ℃. The reaction mixture was heated under reflux for 3 h. After the completion of the reaction was ascertained by GLC analysis, the reaction system was cooled to room temperature and water (20 mL) was then added to deactivate the unreacted sodium amide. After THF was removed *in vacuo* from the reaction mixture, the residue was extracted with diethyl ether (150 mL) – water (100 mL) and the separated ether layer was washed with water (100 mL x 2). The ether layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The resulting oil was purified by Kugelrohr distillation under reduced pressure (for **1a** and **1b**) or by silica-gel column chromatography with a dichloromethane/*n*-hexane (1:1, vol/vol) eluent (for **1c**) to give the pure product.

1a: yield 60%. bp 70 ℃/0.08 Torr. Mass(m/e, relative intensity): 179[$(M+1)^+$, 100]. IR(neat): 2900, 2850, 2250, 1460, 1370, 710 cm^{-1}.

1b: yield 67%. bp 80 ℃/0.03 Torr. Mass(m/e, relative intensity): 207[$(M+1)^+$, 100]. IR(neat): 2900, 2850, 2250, 1460, 1360, 700 cm^{-1}.

1c: yield 50%. Mass(m/e, relative intensity): 235[$(M+1)^+$, 100]. IR(neat): 2900, 2850, 2250, 1470, 1350, 720 cm^{-1}.

Reduction of 2-alkyl-1,3-propanedinitrile (1). A mixture of lithium aluminum hydride (1.14g, 30 mmol) and aluminum chloride (4.0 g, 30 mmol) was stirred in diethyl ether (40 mL) at

ambient temperature for 30 min. To this mixture was dropped 2-alkyl-1,3-propanedinitrile **1** (2.06 g, 10 mmol) at ambient temperature, and the reaction mixture was stirred for 2 h. After disappearance of the peak of compound **1** on GLC was confirmed, 5 wt% NaOH aqueous solution (80 mL) was added to the reaction mixture. This mixture was extracted with diethyl ether (100 mL x 3). The combined ether layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a desired compound **2**.

2a: yield 75%. Mass(m/e, relative intensity): 187[$(M+1)^+$, 100]. IR(neat): 3300, 2900, 1600, 1450, 1370, 1300, 810, 730 cm^{-1}.

2b: yield 80%. Mass(m/e, relative intensity): 215[$(M+1)^+$, 100]. IR(neat): 3300, 2900, 1600, 1460, 1370, 1300, 850, 730 cm^{-1}.

2c: yield 65%. Mass(m/e, relative intensity): 243[$(M+1)^+$, 100]. IR(neat): 3300, 2900, 1600, 1460, 1380, 1100, 840, 730 cm^{-1}.

Reaction of 2-alkyl-1,3-propanediamine (2) with sugar lactone. Alkyl diamine **2** (20 mmol) and sugar lactone (50 mmol), which was prepared from the corresponding sugar according to the previously reported method,[17, 19, 25] were stirred in methanol (20 mL) at ambient temperature for 4 h. After the removal of methanol from the reaction system *in vacuo*, the residue was purified by recrystallization from ethanol (for C_8G, $C_{10}G$, and $C_{12}G$) or methanol-ethanol (1/5, v/v) (for C_8Mb, $C_{10}Mb$, $C_{12}Mb$, $C_{12}L$, and $C_{12}Mt$) to yield the end product as a white powder.

C_8G: yield 77%. decomposition point 147 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.12-1.25(m, 14H), 1.56(m, 1H), 2.96-3.00(m, 2H), 3.09-3.13(m, 2H), 3.39(m, 2H), 3.48(m, 4H), 3.57-3.59(m, 2H), 3.92(m, 2H), 4.01(m, 2H), 4.33(OH, 2H), 4.37-4.42(OH, 2H), 4.47 (OH, 2H), 4.54(OH, 2H), 5.41(OH, 2H), 7.82-7.87(NH, 2H). IR(KBr) 3350, 2950, 2850, 1650, 1540, 1440, 1080 cm^{-1}. FAB-MS (m/e, relative intensity) 543[$(M+1)^+$, 50], 155[100]. Anal. Found: C, 49.56; H, 8.59; N, 4.97%. Calcd for $C_{23}H_{46}N_2O_{12}\cdot H_2O$: C, 49.27; H, 8.55; N, 5.16%.

$C_{10}G$: yield 79%. decomposition point 147 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.25-1.30(m, 18H), 1.56(m, 1H), 2.95-3.01(m, 2H), 3.09-3.15(m, 2H), 3.39(m, 2H), 3.48(m, 4H), 3.57-3.59(m, 2H), 3.92(m, 2H), 4.00(m, 2H), 4.33(OH, 2H), 4.38-4.43(OH, 2H), 4.48 (OH, 2H), 4.54(OH, 2H), 5.41(OH, 2H), 7.81-7.86(NH, 2H). IR(KBr) 3300, 2950, 2850, 1640, 1430, 1050 cm^{-1}. FAB-MS (m/e, relative intensity) 571[$(M+1)^+$, 28], 185[100]. Anal. Found: C, 52.03; H, 8.99; N, 4.83%. Calcd for $C_{25}H_{50}N_2O_{12}\cdot 0.5H_2O$: C, 51.80; H, 8.87; N, 4.83%.

$C_{12}G$: yield 59%. decomposition point 150 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.14-1.24(m, 22H), 1.56(m, 1H), 2.98(m, 2H), 3.10(m, 2H), 3.38(m, 2H), 3.48(m, 4H), 3.57 (m, 2H), 3.91(m, 2H), 4.01(m, 2H), 4.33(OH, 2H), 4.38-4.42(OH, 2H), 4.47 (OH, 2H), 5.54(OH, 2H), 5.41(OH, 2H), 7.84(NH, 2H). IR(KBr) 3350, 2950, 2850, 1650, 1540, 1440, 1090 cm^{-1}. FAB-MS (m/e, relative intensity) 599[$(M+1)^+$, 55], 211[100]. Anal. Found: C, 53.68; H, 9.23; N, 4.57%. Calcd for $C_{27}H_{54}N_2O_{12}\cdot 0.5H_2O$: C, 53.36; H, 9.12; N, 4.61%.

C_8Mb: yield 70%. mp 124-126 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.24-1.30(m, 14H), 1.55(m, 1H), 2.99(m, 2H), 3.06-3.12(m, 4H), 3.25(m, 2H), 3.38-3.50(m, 6H), 3.55(m, 2H), 3.60-3.70(m, 8H), 4.02(m, 4H), 4.44-4.52(OH, 6H), 4.67(OH, 2H), 4.88(m, 2H+4OH), 5.41(OH, 2H), 5.57(OH, 2H), 7.82(NH, 2H). IR(KBr) 3300, 2900, 1630, 1040 cm^{-1}. FAB-MS (m/e, relative intensity) 867[$(M+1)^+$, 14], 105[100]. Anal. Found: C, 47.00; H, 7.34; N, 3.00%. Calcd for $C_{35}H_{66}N_2O_{22}\cdot 1.5H_2O$: C, 47.03; H, 7.78; N, 3.13%.

$C_{10}Mb$: yield 75%. decomposition point 146 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.12-1.30(m, 18H), 1.52(m, 1H), 2.99(m, 2H), 3.07-3.12(m, 4H), 3.25(m, 2H), 3.38-3.51(m, 6H), 3.55(m, 2H), 3.60-3.69(m, 8H), 4.02(m, 4H), 4.44-4.50(OH, 6H), 4.67(OH, 2H), 4.88(m, 2H+4OH), 5.41(OH, 2H), 5.55(OH, 2H), 7.82(NH, 2H). IR(KBr) 3300, 2950, 1620, 1030 cm^{-1}. FAB-MS (m/e, relative intensity) 895[$(M+1)^+$, 5], 85[100]. Anal. Found: C, 49.02; H, 7.94; N, 3.20%. Calcd for $C_{37}H_{70}N_2O_{22}\cdot H_2O$: C, 48.68; H, 7.95; N, 3.07%.

$C_{12}Mb$: yield 68%. decomposition point 148 ℃. ^1H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.12-1.30(m, 22H), 1.52(m, 1H), 2.99(m, 2H), 3.07-3.12(m, 4H), 3.26(m, 2H), 3.39-3.51(m, 6H), 3.57(m, 2H), 3.60-3.68(m, 8H), 4.02(m, 4H), 4.43-4.51(OH, 6H), 4.67(OH, 2H), 4.88(m, 2H+4OH), 5.41(OH, 2H), 5.55(OH, 2H), 7.82(NH, 2H). IR(KBr) 3350, 2900, 1620, 1030 cm^{-1}. FAB-MS (m/e, relative intensity) 923[$(M+1)^+$, 8], 65[100]. Anal. Found: C, 49.05; H, 7.83; N, 2.72%. Calcd for $C_{39}H_{74}N_2O_{22}\cdot 2H_2O$: C, 48.84; H, 8.20; N, 2.92%.

$C_{12}L$: yield 67%. decomposition point 141 ℃. ^1H NMR(DMSO-d_6) δ 0.85(t, 3H), 1.09-1.28(m, 22H), 1.50(m, 1H), 2.97(m, 2H), 3.07-3.11(m, 2H), 3.29-3.40(m, 6H), 3.49(m, 6H), 3.59(m, 4H), 3.69(m, 4H), 4.00(m, 3H), 4.10(m, 1H), 4.26(m, 2H), 4.45-4.48(OH, 4H), 4.64(OH, 3H), 4.75(OH, 5H), 5.13(OH, 2H), 5.19(OH, 2H), 7.81(NH, 2H). IR(KBr) 3300, 2900, 1620, 1020 cm^{-1}. FAB-MS (m/e, relative intensity) 923[$(M+1)^+$, 20], 307[100]. Anal. Found: C, 49.87; H, 7.87;

N, 2.78%. Calcd for $C_{39}H_{74}N_2O_{22}\cdot H_2O$: C, 49.78; H, 8.14; N, 2.98%.

C_{12}Mt: yield 53%. decomposition point 168 ℃. ^{1}H NMR(DMSO-d_6) δ 0.86(t, 3H), 1.22-1.27(m, 22H), 1.52(m, 1H), 3.03-3.20(m, 6H), 3.30(m, 2H), 3.42-3.60(m, 14H), 3.61-3.74(m, 14H), 4.02(m, 4H), 4.45(OH, 2H), 4.52-4.60(OH, 6H), 4.66(OH, 2H), 4.87(OH, 4H), 4.91(m, 2H), 5.01(m, 2H), 5.41-5.49(OH, 6H), 5.64(OH, 2H), 7.82(NH, 2H). IR(KBr) 3350, 2900, 1620, 1020 cm^{-1}. FAB-MS (m/e, relative intensity) 1247[$(M+1)^+$, 4], 79[100]. Anal. Found: C, 47.37; H, 7.34; N, 1.89%. Calcd for $C_{51}H_{94}N_2O_{32}\cdot 2H_2O$: C, 47.73; H, 7.70; N, 2.18%.

2-1-2-2. Surface-active properties

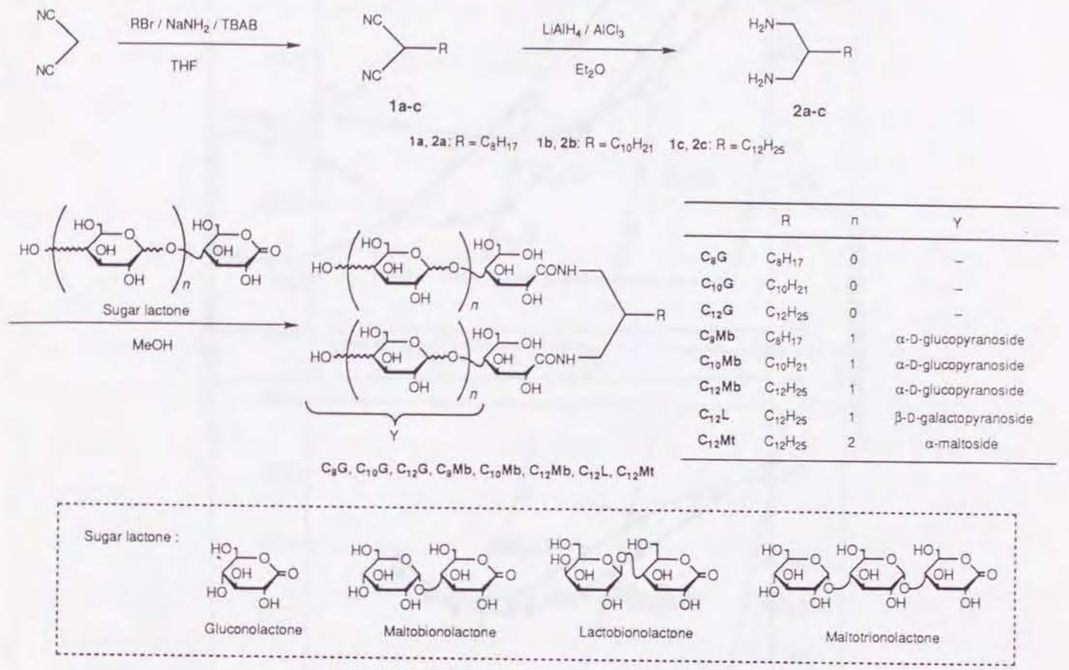
The Krafft point (T_{cp}) was determined by the naked eye from a 1 wt% aqueous solution. The surface tension of the surfactant solutions was measured at 20 ℃ with a Wilhelmy tensiometer (Shimazu ST-1; glass plate). The critical micelle concentration (CMC) was determined by the dye method using pinacyanol chloride as a dye probe.[26] Visible spectra of different concentrations of surfactant solutions including 5 x 10^{-6} M pinacyanol chloride were measured with a Hitachi U-2000 spectrophotometer.

2-1-2-3. Binding properties to Lectin (Concanavalin A)

The binding properties of the surfactants bearing two sugar-amide head groups to lectin (Concanavalin A) were estimated using a modification of the precipitation reaction reported by So and Goldstein.[27] Concanavalin A (750 μg) and different concentrations of surfactant (0.01 – 1 mM) were dissolved in an aqueous buffer (6 mL, 0.05 M potassium dihydrogenphosphate, 0.5 M NaCl, 0.1 mM $MnCl_2$, 0.1 mM $CaCl_2$, pH 7.2). Each solution was gently shaken at 25 ℃ for 48 h and the resulted precipitate was separated by centrifugation. The precipitate was dissolved in 0.05 M NaOH aqueous solution (6 mL) and the protein content was determined by a semimicro Lowry method.[28] Inhibition experiments were carried out at 25 ℃ by addition of increasing amounts of methyl α-D-glucopyranoside or methyl α-D-galactopyranoside as an inhibitor to the above buffer solution containing Concanavalin A (125 μg/mL) and surfactant **C_{12}Mb** or **C_{12}Mt** (0.35 mM).

2-1-3-4. Results and Discussion

Preparation of surfactants with one alkyl chain and two sugar-amide head groups.



	R	n	Y
C_8G	C_8H_{17}	0	–
$C_{10}G$	$C_{10}H_{21}$	0	–
$C_{12}G$	$C_{12}H_{25}$	0	–
C_8Mb	C_8H_{17}	1	α-D-glucopyranoside
$C_{10}Mb$	$C_{10}H_{21}$	1	α-D-glucopyranoside
$C_{12}Mb$	$C_{12}H_{25}$	1	α-D-glucopyranoside
$C_{12}L$	$C_{12}H_{25}$	1	β-D-galactopyranoside
$C_{12}Mt$	$C_{12}H_{25}$	2	α-maltoside

Scheme 2-1. Preparation of surfactants bearing one alkyl chain and two sugar-amide head groups

Surfactants bearing one alkyl chain and two sugar-amide head groups were prepared according to the routes in Scheme 2-1. Monoalkylation of malononitrile was carried out in THF by use of alkyl bromide and sodium amide as an alkylating reagent and a base, respectively. Here the product yields increased from 31-50% to 50-67% by the addition of a phase-transfer catalyst, tetra-*n*-butylammonium bromide (TBAB), into this reaction system. Reduction of alkyl dinitriles **1** with $LiAlH_4/AlCl_3$ in diethyl ether gave alkyl diamines **2** in good yields. The reaction of **2** with sugar lactones in methanol afforded the end surfactants bearing one alkyl chain and two sugar-amide groups. No protection of sugar hydroxyl groups was needed in the routes of preparation of these surfactants, similarly to those of the conventional gluconamide surfactants. The purification of these surfactants was carried out by recrystallization from ethanol (for **C_8G**, **$C_{10}G$**, **$C_{12}G$**) or methanol-ethanol (1/5, v/v) (for **C_8Mb**, **$C_{10}Mb$**, **$C_{12}Mb$**, **$C_{12}L$**, and **$C_{12}Mt$**).

Surface-active properties.

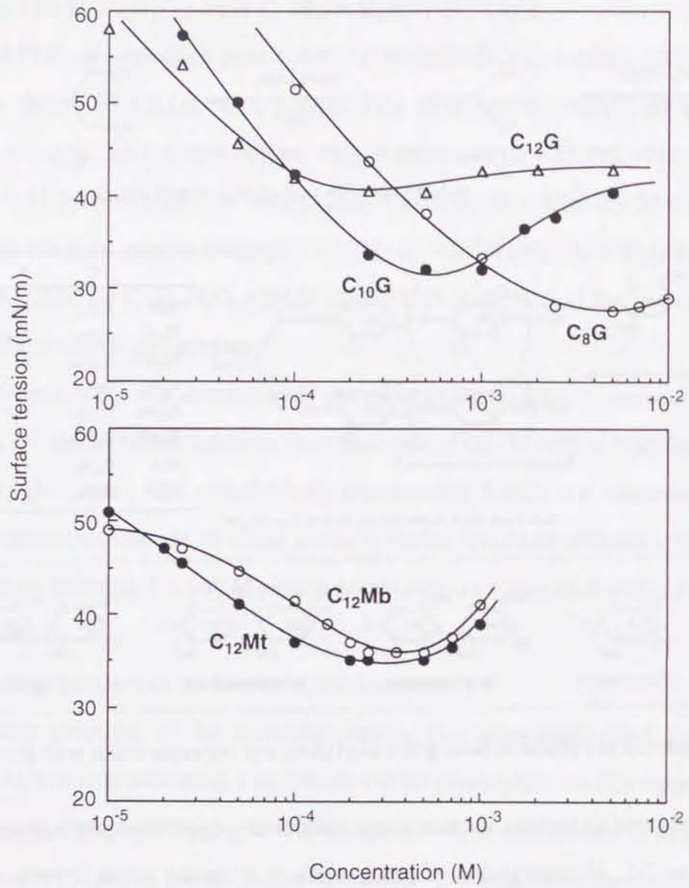


Figure 2-1. Plots of surface tension *vs.* concentration for C_8G, $C_{10}G$, $C_{12}G$, $C_{12}Mb$, and $C_{12}Mt$ at 20 °C.

The plots of the surface tension (γ) *vs.* the concentration (log C) for C_8G, $C_{10}G$, $C_{12}G$, $C_{12}Mb$, and $C_{12}Mt$ at 20 ℃ are shown in Figure 2-1. A clear break point in the γ–log C curve corresponding to the CMC was not observed for these compounds. So the CMCs of C_8G, $C_{10}G$, $C_{12}G$, C_8Mb, $C_{10}Mb$, $C_{12}Mb$, $C_{12}L$, and $C_{12}Mt$ were determined by the dye method with pinacyanol chloride as a dye probe.[26] Figure 2-2 shows the plots of the wave length of maximal absorption (λ_{max}) of pinacyanol chloride *vs.* the concentration (log C) of C_8G, $C_{10}G$, $C_{12}G$, C_8Mb, $C_{10}Mb$, and $C_{12}Mb$. Since the λ_{max} of pinacyanol chloride shifts to a longer wave length when it is incorporated into the

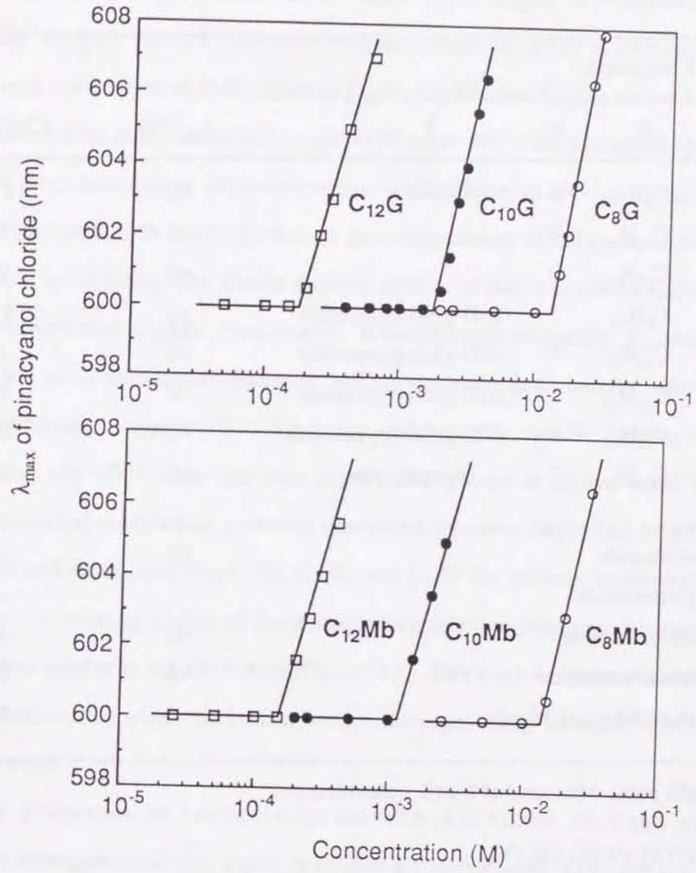


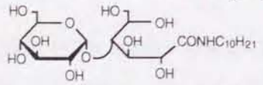
Figure 2-2. Plots of wave length of maximal absorption (λ_{max}) of pinacyanol chloride *vs.* concentration of C_8G, $C_{10}G$, $C_{12}G$, C_8Mb, $C_{10}Mb$, and $C_{12}Mb$ at 20 °C.

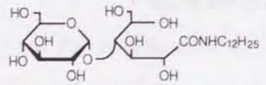
hydrophobic region of micelles from the bulk aqueous phase, a break point on the λ_{max}–log C curve can be defined as the CMC of the surfactant. The CMC and the Krafft point (T_{Kp}) measured at 1 wt% concentration are summarized in Table 2-1. C_8G, $C_{10}G$, $C_{12}G$, C_8Mb, $C_{10}Mb$, $C_{12}Mb$, $C_{12}L$, and $C_{12}Mt$ were freely soluble in water at any temperature at 1 wt% concentration. Concerning *N*-octylgluconamide and dioctylbisgluconamide as the reference surfactants, the T_{Kp} of the former was

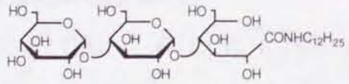
Table 2-1. Surface-Active Properties

Compound					
	R	n	Y	T_{Kp}[a] (°C)	CMC[b] (mM)
C_8G	C_8H_{17}	0	–	<0	14
$C_{10}G$	$C_{10}H_{21}$	0	–	<0	1.9
$C_{12}G$	$C_{12}H_{25}$	0	–	<0	0.18
C_8Mb	C_8H_{17}	1	α-D-glucopyranoside	<0	14
$C_{10}Mb$	$C_{10}H_{21}$	1	α-D-glucopyranoside	<0	1.2
$C_{12}Mb$	$C_{12}H_{25}$	1	α-D-glucopyranoside	<0	0.15
$C_{12}L$	$C_{12}H_{25}$	1	β-D-galactopyranoside	<0	0.15
$C_{12}Mt$	$C_{12}H_{25}$	2	α-maltoside	<0	0.17
N-octylgluconamide[c]				69	–
dioctylbisgluconamide[d]				–[e]	–
N-decylmaltobionamide[f]				<0	1.8
N-dodecylmaltobionamide[f]				<0	0.20
N-dodecylmaltotrionamide[f]				<0	0.19

[a] T_{Kp} = Krafft point. Measured at 1 wt% concentration.
[b] At 20 °C.
[c] $C_8H_{17}NHCO(CHOH)_4CH_2OH$
[d] $(C_8H_{17})_2C(CH_2NHCO(CHOH)_4CH_2OH)_2$ See ref.24.
[e] This compound was hardly soluble in water up to 100 °C even at 0.1 wt% concentration.
[f] These surfactants were prepared according to the method in ref.17.


N-decylmaltobionamide


N-dodecylmaltobionamide


N-dodecylmaltotrionamide

69 °C and the latter was hardly soluble in water up to 100 °C even at 0.1 wt% concentration. These results clearly show that the surfactants bearing single alkyl chain and two gluconamide groups have higher water solubility than those of the conventional gluconamide surfactants bearing the same alkyl

chain length. Concerning bisgluconamide series (**C_8G**, **$C_{10}G$**, **$C_{12}G$**) or bismaltobionamide series (**C_8Mb**, **$C_{10}Mb$**, **$C_{12}Mb$**), the CMC decreased with an increase of carbon number in the alkyl chain. On the other hand, comparison of CMC values of **$C_{12}G$**, **$C_{12}Mb$**, and **$C_{12}Mt$** showed that the CMCs of these surfactants were independent of the number of sugar unit in the hydrophilic part. Moreover, the CMC was also independent of the anomeric configuration of the glycosidic linkage from comparison of cmcs of **$C_{12}Mb$** and **$C_{12}L$**, though the configurations of OH group at the 4' position in those compounds are different. The micelle forming abilities of decylbismaltobionamide **$C_{10}Mb$** and dodecylbismaltobionamide **$C_{12}Mb$** (furthermore, dodecylbismaltotrionamide **$C_{12}Mt$**) were almost equal to those of *N*-decylmaltobionamide and *N*-dodecylmaltobionamide (furthermore, *N*-dodecylmaltotrionamide), respectively. This result indicates the micelle forming ability of the surfactant bearing one alkyl chain and two sugar-amide groups is almost equal to that of the conventional monoalkyl sugar-amide surfactant possessing the same alkyl chain length. Comparison of the minimum surface tensions that **C_8G**, **$C_{10}G$**, and **$C_{12}G$** can achieve, respectively, shows that the surface tension-lowering ability of these bisgluconamide-type compounds decreased with an increase of carbon number in the alkyl chain (Figure 2-1). This trend is contrary to that observed on the dialkylbisgluconamide, where the surface tension-lowering ability increased with an increase of the alkyl chain length.[24]

Binding properties to Lectin (Concanavalin A). Lectins are highly specific sugar-binding proteins that agglutinate cells and/or precipitate glycoconjugates. Concanavalin A (Con A) is one of the representative lectins and a tetramer with four sugar-binding sites. It specifically binds to the glucopyranoside or mannopyranoside residue at the end of oligo- and polysaccharides. Precipitation reaction with Con A has been used as a method for evaluating the binding property of the surfactant possessing sugar head groups to Con A,[17,19,29,30] since the precipitation occurs as a result of the cross-linking between Con A and the aggregate formed by the surfactant molecules. The precipitation curves of surfactants **$C_{12}G$**, **$C_{12}Mb$**, **$C_{12}L$**, and **$C_{12}Mt$** with Con A are shown in Figure 2-3. Precipitation with Con A was observed on **$C_{12}Mb$** and **$C_{12}Mt$** bearing the terminal glucopyranoside residues in their hydrophilic parts. The quantity of Con A precipitated had the maximum value at surfactant concentrations of 0.35–0.40 mM. These precipitation reactions occurred at concentrations much lower than their cmcs: at 0.03 mM and 0.01 mM for **$C_{12}Mb$** and **$C_{12}Mt$**,

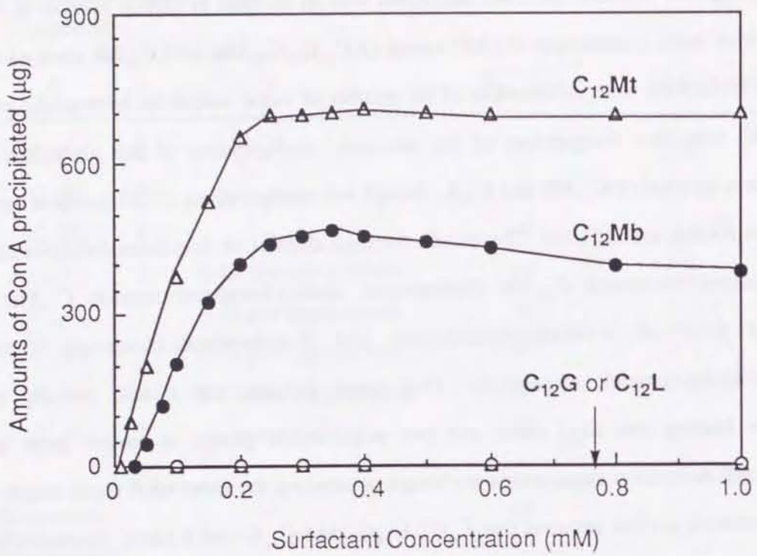


Figure 2-3. Plots of amounts of Con A precipitated *vs.* surfactant concentration

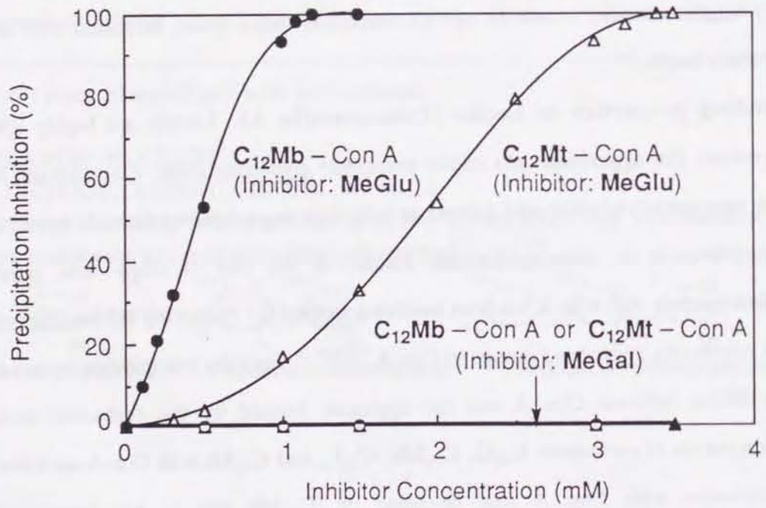


Figure 2-4. Inhibition of C_{12}**Mb**–Con A or C_{12}**Mt**–Con A precipitation by methyl α-D-glucopyranoside (**MeGlu**) or methyl α-D-galactopyranoside (**MeGal**)

respectively. This result is different from the case of conventional surfactants bearing only one sugar-amide groups, where the precipitation began to occur at concentrations near their CMCs.[17] This phenomenon can be explained as follows: even as a monomer, the surfactant which possesses two terminal glucopyranoside residues can precipitate Con A through cross-linking, analogously to the case of the polysaccharides possessing plural terminal glucopyranoside residues.[27] On the other hand, the monomers of conventional surfactants which possess only one terminal glucopyranoside residue can not form the corresponding cross-linked network with Con A leading to the precipitation.

The precipitation reactions between Con A and C_{12}**L** bearing terminal galactopyranoside residues, on the contrary, were not observed. Additionally, the precipitation reaction between the bisgluconamide-type surfactant C_{12}**G** and Con A was also not observed. These results indicate that the terminal sugar residues in the bis(sugar amide)-type surfactants were specifically discriminated by Con A. Inhibition of Con A-surfactant precipitation by methyl glucopyranoside, which competes with the surfactant for the binding site of Con A, further demonstrates the specificity of the precipitation reaction. Methyl α-D-glucopyranoside completely inhibited the formation of the C_{12}**Mb**–Con A complex and the C_{12}**Mt**–Con A complex at the 1.2 mM and 3.4 mM concentrations, respectively (Figure 2-4). On the other hand, methyl α-D-galactopyranoside showed no inhibitory effect on the formation of these Con A–surfactants complexes even at the concentration of 5 mM.

2-1-4. References

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2-2. Enantioselective Hydrolysis of an α-Amino Acid Ester in Sugar-Derived Surfactant Micelles

2-2-1. Introduction

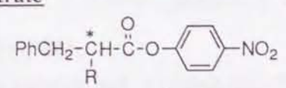
Over the past few decades, the enantioselective micellar catalysis has attracted much attention because of its usefulness as a model for enzyme catalysis. In most of such studies, the enantioselectivity has been attained by a combination of chiral nucleophiles and achiral surfactant micelles.[1-7] On the other hand, only a few studies have been reported on the enantioselective reaction in a simpler system which contains only chiral surfactant micelles.[8-12] In particular, there is no report on enantioselective reaction systems consisting of only the micelles formed with sugar-derived surfactants possessing no additional chiral center other than those from the parent sugar. Such enantioselective micellar systems consisting of sugar surfactants alone would be useful not only as a new enzyme model but also for elucidating the functions of sugar chains of the cell surface. In this section, the author wishes to report the first enantioselective hydrolysis of an α-amino acid ester in the micelles formed with the sugar-derived surfactants.

2-2-2. Experimental Section

Substrates *p*-nitrophenyl *N*-(benzyloxycarbonyl)-D- or L-phenylalaninate **1** and *p*-nitrophenyl ester of D- or L-phenylalanine hydrogen bromide **2** were prepared according to previously reported methods.[13] Sugar-amide surfactants **3**, **4**, and **5** were prepared by the reactions of sugar lactones with alkylamine or alkyldiamine.[14,15] Their critical micelle concentrations (cmcs), which were determined by the dye method using pinacyanol chloride as a dye probe,[16] at 20 ℃, are as follows: **3a**: 1.8 mM, **3b**: 0.20 mM, **3c**: 4.2×10^{-2} mM, **3d**: 0.19 mM, **4**: 1.9 mM, **5**: 0.15 mM. Dodecyl β-D-maltoside **6** (cmc = 0.16 mM)[17] and Triton X-100 (cmc = 0.33 mM)[18] as a reference surfactant were purchased from commercial sources. The hydrolysis was carried out at 25 ℃, pH 7.2 in 0.05 M potassium dihydrogenphosphate buffer solution which contains 5.0×10^{-5} M chiral substrate, 0.1 M LiCl, and 3 vol.% acetonitrile. Hydrolysis of the substrates was spectrophotometrically monitored by measuring

absorbance of the released *p*-nitrophenolate ion at 400 nm to determine the reaction rates. Each experiment was repeated at least three times to ensure the reproducibility (± 10%).

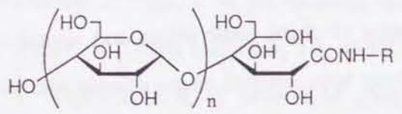
Substrate



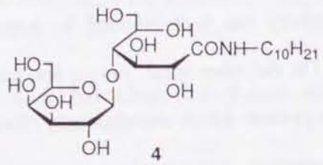
D- or L-**1** : R = NH–C(=O)–OCH_2Ph

D- or L-**2** : R = $NH_3^+ Br^-$

Surfactant



3a : R = $C_{10}H_{21}$, n = 1 **3b** : R = $C_{12}H_{25}$, n = 1
3c : R = $C_{14}H_{29}$, n = 1 **3d** : R = $C_{12}H_{25}$, n = 2



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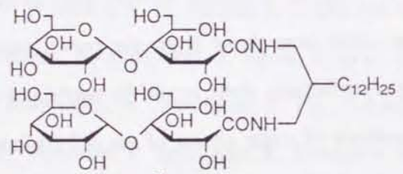

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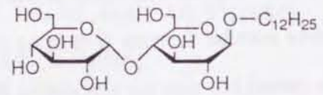
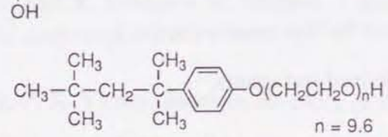


6



Triton X-100

2-2-3. Results and Discussion

Table 2-1 shows the observed pseudo-first-order rate constants for the hydrolysis of the substrates **1** and **2** in the absence (entries 1 and 8) and the presence of sugar-derived surfactant micelles (entries 2-6 and 9-18), together with the results using Triton X-100 micelles (entries 7 and 19). The rates of hydrolysis of D- and L-**1** were somewhat increased by the sugar-amide surfactant micelles (entries 2-5), while they were markedly decreased by dodecyl β-D-maltoside **6** (entry 6) and Triton X-100 (entry 7) micelles. In these cases, no enantioselectivity for the hydrolysis was observed. These results are in accordance with our expectation based on the locus of solubilization of **1** in these surfactant micelles. The less polar substrate **1** would be solubilized in the hydrophobic cores of the dodecyl β-D-maltoside **6** and Triton X-100 micelles, so that the nucleophilic attack by water

molecules or hydroxide ions from the aqueous bulk phase is largely retarded. On the other hand, in the cases of sugar-amide surfactants **3** and **4**, **1** is most likely solubilized near the hydrophilic layer of the micelles through the hydrogen bonding between the amide hydrogen of the surfactant and the

Table 2-1. Kinetic data[a] for hydrolysis of 1 and 2

	Surfactant			k_{obs}[b]($10^{-3}s^{-1}$)		Enantioselectivity
Entry	Substrate	Concentration (mM)		D-Substrate	L-Substrate	D/L
1	**1**	None		1.4	1.4	1.0
2	**1**	**3a**	5.0	1.5	1.5	1.0
3	**1**	**3b**	5.0	2.7	2.7	1.0
4	**1**	**3d**	5.0	5.0	4.9	1.0
5	**1**	**4**	5.0	2.4	2.4	1.0
6	**1**	**6**	5.0	0.061	0.061	1.0
7	**1**	Triton X-100	5.0	0.038	0.038	1.0
8	**2**	None		7.5	7.5	1.0
9	**2**	**3a**	5.0	28	15	1.9
10	**2**	**3b**	2.5	32	12	2.7
11	**2**	**3b**	5.0	39	12	3.3
12	**2**	**3b**	10	44	12	3.7
13	**2**	**3b**	20	51	14	3.6
14	**2**	**3c**	5.0	33	11	3.0
15	**2**	**3d**	5.0	39	12	3.3
16	**2**	**4**	5.0	9.8	9.3	1.1
17	**2**	**5**	5.0	46	19	2.4
18	**2**	**6**	5.0	10	7.9	1.3
19	**2**	Triton X-100	5.0	11	11	1.0

[a] [substrate] = 5.0×10^{-5} M.

[b] Observed pseudo-first-order rate constant.

carbonyl group of the solubilized substrate. At this site, the nucleophilic attack by both the sugar hydroxyl groups of the surfactant and the water molecules (or hydroxide ions) may have occurred, giving rise to the acceleration of the hydrolysis of **1**. However, no enantioselectivity was observed in

those systems, suggesting that **1** does not approach the chiral sugar head groups closely enough, and thus it is necessary to locate the substrate closer to the chiral sugar head groups for the enantioselective hydrolysis with the sugar surfactant micelles to occur. On the basis of this hypothesis, D- and L-**2** bearing an intensively hydrophilic ammonium group, which should be located between the hydrophilic head groups of the micelles, were chosen as the substrate. Surprisingly, in all the cases using the sugar surfactant micelles, D-**2** was hydrolyzed faster than L-**2** (entries 9-18). Among the surfactant micelles examined in this work, the highest enantioselectivity was attained with *N*-dodecylmaltobionamide **3b** or *N*-dodecyl-maltotrionamide **3d** micelles. Concerning the monomaltobionamide-type surfactants **3**, the increase of the alkyl chain length from C10 to C12 remarkably increased the enantioselectivity, whereas the change from C12 to C14 slightly lowered it (entries 9, 11, and 14). Entries 10-13 showed that the enantioselectivity increased with the increase of concentration of surfactant **3b** in the range of 2.5 to10 mM, but decreased slightly with the increase from 10 to 20 mM. Below the cmc (0.2 mM), **3b** showed no enantioselectivity (for example, $k_{obs(D)} = k_{obs(L)} = 8.7 \times 10^{-3}$ s^{-1} at 0.10 mM), indicating that the existence of the micelles is essential for the enantioselective hydrolysis of **2**. The comparison of entries 11 and 17 showed that the increase of the number of the hydrophilic branches having the same sugar units enhanced the hydrolysis rates of both D- and L-substrates but decreased the enantioselectivity. The increase of the sugar chain length had no effect on either the hydrolysis rate or the enantioselectivity (entries 11 and 15). Interestingly, large differences in both the hydrolysis rate and the enantioselectivity between **3a** and **4**, which have different terminal sugar residues, were observed. Furthermore, only a slight enantioselectivity was observed in the case of dodecyl β-D-maltoside **6** micelles even for **2**, in contrast to dodecyl maltobinamide **3b** micelles. These results indicate that the enantioselectivity for hydrolysis of **2** depends largely on the structure of the sugar moiety of the surfactant as well as the presence of amide linkage. The enantioselectivity in these micellar systems can be explained by considering the selective nucleophilic attack on the D-substrate and/or selective stabilization of the resulting intermediate by sugar hydroxyl groups in the micelle, similarly to the previous cases in which the enantioselective hydrolysis of the *p*-nitrophenyl esters was carried out using the micellar systems formed with the chiral surfactants bearing hydroxyl groups, such as D-ephedrinium derivative[8] and sodium deoxycholate.[10] Work on the detailed mechanism of the enantioselective hydrolysis in these systems

and the development of a sugar surfactant micellar system with higher enantioselectivity is now in progress.

2-2-4. References

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Chapter 3. Preparation and Unique Interfacial Properties of Novel Triple-chain Amphiphiles Bearing Three Hydrophilic Groups Derived from Polyols

3-1. A Facile Synthesis of Polyglycidyl Ethers from Polyols and Epichlorohydrin

3-1-1. Introduction

Glycidyl compounds have been widely used as valuable intermediates in organic syntheses.[1] Previously we have developed an useful method for the synthesis of glycol diglycidyl ethers[2] and have demonstrated that these compounds are valuable intermediates for the preparation of crown ether derivatives[3] and new surfactants.[4] Recently, new types of highly functionalized compounds such as starburst dendrimers[5] and cascade molecules[6] have been developed and noted in the field of supramolecular chemistry.[7] From this point of view, polyglycidyl ethers having more than three oxirane rings are considered to be potentially useful as their starting materials. However, previously reported synthetic approaches to polyglycidyl ethers consisted of two reaction steps and required tedious operations.[8] In this section, the author reports a facile, one-step synthesis of polyglycidyl ethers from polyols bearing three or four hydroxyl groups and epichlorohydrin.

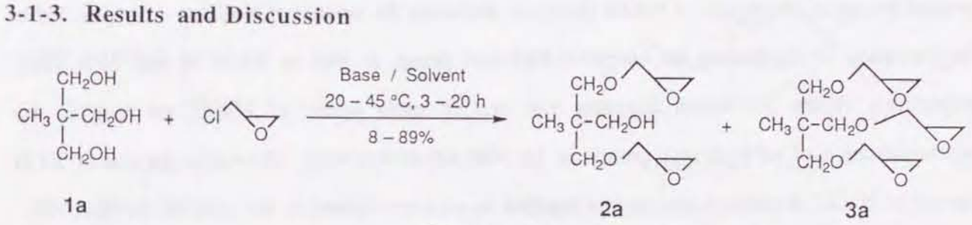
3-1-2. Experimental Section

All reagents were of reagent grade and were used without further purification. IR spectra were recorded on a Hitachi infrared spectrometer 260-10. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer using TMS as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 303 HF spectrometer. Elemental analyses were obtained using a Perkin-Elmer 240C analyzer. GC analyses were performed using a Shimadzu Gas Chromatograph GC-8APF equipped with a 3% Silicone SE-30 on Celite 545 1 m x 3.2 mm glass column. TLC was done on silica gel (Merck Silica 60F_{254} sheets). Column chromatography was carried out with Kiesel gel 60 (70-230 mesh ASTM, Merck).

Preparation of Polyglycidyl ether (2a, 3a-f); General procedure:

To a stirred mixture of polyol (0.03 mol) dissolved in DMSO (30 mL) and KOH (10.10 g, 0.18 mol; in the case of **1c**, 13.47 g, 0.24 mol), epichlorohydrin (24.98 g, 0.27 mol; in the case of **1c**, 33.31 g, 0.36 mol) was added dropwise over a period of 1 h at 20-35 ℃. After the completion of addition, stirring was continued for 5-18 h at 20-45 ℃. The solid material was filtered off and washed with dichloromethane (300 mL). The solvent was evaporated off under reduced pressure. The residue was partitioned between Et_2O (2 x 150 mL) and saturated aq NaCl (80 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated. The products were purified as follows: For **2a**, **3a**, **3b**, **3d**, and **3e**, the resulting oil was purified by Kugelrohr distillation under reduced pressure (as listed in Table 3) to give the pure product. For **3c** and **3f**, the purification was performed by silica gel column chromatography with acetone/hexane (3:7) and acetone/toluene (1:8), respectively, as an eluent.

3-1-3. Results and Discussion



1a **2a** **3a**

Scheme 3-1

Table 3-1. Yields of **16a** and **17a** under Various Conditions

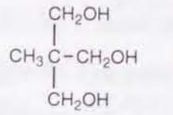
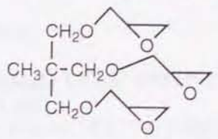
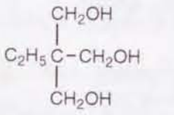
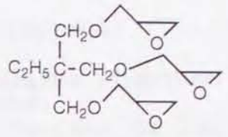
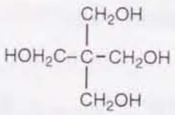
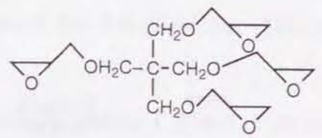
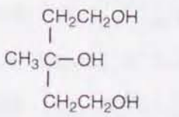
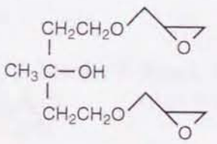
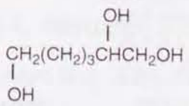
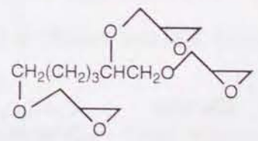
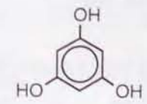
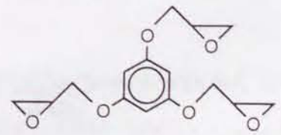
Entry	Reaction Conditions				Yield[a] (%)	
	Base [OH eqiv. [b]]	Solvent	Temp (°C)	Time (h)	**16a**	**17a**
1	NaOH [3.0]	——— [c]	45	5	1	9
2	NaOH [5.0]	Benzene/H_2O[c]	40	18	3	5
3	NaOH [2.0]	Dioxane/H_2O[d]	45	20	17	35
4	NaOH [2.0]	DMF	40	20	18	23
5	NaOH [1.3]	DMSO	40	15	36 (30)	30 (25)
6	NaOH [2.0]	DMSO	40	3	2	62 (53)
7	KOH [2.0]	DMSO	40	0.5	polymerized	
8	KOH [2.0]	DMSO	20	8	0	89 (81)

[a]Determined by GC using diphenylmethane as an internal standard. Yields in parentheses are isolated ones. The yields of monoglycidyl ether were 0% in all cases.
[b]Equivalent to OH group of **15a**.
[c](n-$C_4H_9)_4N^+HSO_4^-$ (5 mol% to **15a**) was added.
[d](n-$C_8H_{17})_3N^+(CH_3)Cl^-$ (5 mol% to **15a**) was added.

First, the reactions of 1,1,1-tris(hydroxymethyl)ethane **1a** with epichlorohydrin were carried out under various conditions to explore the optimum conditions for the preparation of polyglycidyl ethers (Scheme 3-1, Table 3-1). When the procedures for the preparation of glycol diglycidyl ethers[2] were applied to this case, the reaction barely proceeded to afford the corresponding diglycidyl ether **2a** or triglycidyl ether **3a** (Entry 1). A two-phase reaction consisting of benzene-H_2O in the presence of a phase-transfer catalyst (PTC) also gave a poor yield (Entry 2). In the 1,4-dioxane/H_2O system including a PTC, however, **2a** and **3a** were obtained in 17 and 35% yield, respectively (Entry 3). These results indicate that solvents capable of dissolving both **1a** and epichlorohydrin are necessary for the success of the reaction. Therefore, aprotic polar solvents such as DMF and DMSO, were examined in the following runs. When DMF was used, the formation of approximately equimolecular amounts of **2a** and **3a** was observed (Entry 4). However, the product ratio changed little even in the presence of further excess NaOH (3 equiv. to OH group of **1a**. In DMSO **3a** was obtained as a main product by use of two equiv. of NaOH (Entry 6). Reducing the amount of NaOH to 1.3 equiv. led to the formation of **2a** bearing an unreacted hydroxyl group as well as **3a** in 36 and 30% yield, respectively (Entry 5), which suggests that two or more equiv. of NaOH are required for functionalization of all hydroxyl groups in **1a** with epichlorohydrin. Moreover, the use of KOH instead of NaOH at ambient temperature resulted in an improvement in the yield of **3a** (Entry 8) , while at 40 ℃ polymerization of epichlorohydrin occurred (Entry 7) because of its higher reactivity. When NaOH was used, the polymerization took place only above 60 ℃. Using this KOH/DMSO system, the reactions of other polyols **1b-f** with epichlorohydrin were carried out (Table 3-2). From 2-ethyl-2-(hydroxymethyl)-1,3-propanediol **1b** and pentaerythritol **1c** containing only primary hydroxyl groups, the corresponding tri- and tetraglycidyl ethers **3b** and **3c** were obtained in high yield, respectively. The reaction of 3-methyl-1,3,5-pentanetriol **1d**, which possesses both primary and tertiary hydroxyl groups, with epichlorohydrin afforded only the diglycidyl ether derivative **3d** in 65% yield. In this case, the tertiary hydroxyl group did not react with epichlorohydrin even when the reaction temperature was raised to 50 ℃. 1,2,6-Hexanetriol **1e** having a secondary hydroxyl group in addition to primary ones gave the corresponding triglycidyl ether **3e** in 72% yield. 1,3,5-Trihydroxybenzene **1f** reacted with epichlorohydrin in the presence of a PTC to give the corresponding triglycidyl ether **3f** in 28% yield. This result indicates that the KOH/DMSO system is

also applicable to the preparation of phenolic polyglycidyl ethers.

Table 3-2. Reactions of Polyols with Epichlorohydrin under the KOH/DMSO System

	Substrate	Reaction Conditions			Product	Yield(%)
		Temp (°C)	Time (h)			
15a		20	8	**17a**		81
15b		30	7	**17b**		76
15c		35	7	**17c**		79[a]
15d		40	6	**17d**		65
15e		40	5	**17e**		72
15f		45	18	**17f**		28[a,b]

[a] Determined by GLC.

[b] $C_{12}H_{25}N^+(CH_3)_3\,Cl^-$ was added.

Table 3-3. Polyglycidyl Ethers **2a, 3a-f** Prepared

Product	mp (°C) or bp (°C / Torr)	Molecular Formula[b]	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS m/z (%)
2a	130 / 0.05	$C_{11}H_{20}O_5$ (232.3)	3300-3600 2930, 2870, 1100	0.89 (s, 3H), 2.62 (m, 2H), 2.73 (t, -OH, *J*=6), 2.80 (m, 2H), 3.14(m, 2H), 3.37-3.57 (m, 8H), 3.74 (dd, 1H, *J* = 3, 4), 3.77(dd, 1H, *J* = 3,4)	233(M^++1, 100)
3a	135 / 0.05	$C_{14}H_{24}O_6$ (288.3)	2870, 1090	0.96(s, 3H), 2.60(dd, 3H, *J* = 2.4, 4.9), 2.78(dd, 3H, *J* = 4.4, 4.9), 3.13(m, 3H), 3.34-3.41(m, 9H), 3.70(dd, 3H, *J* = 2.9, 11.7)	289(M^++1, 36), 141(100)
3b	160 / 0.04	$C_{15}H_{26}O_6$ (302.2)	2900, 1120	0.86(t, 3H, *J* = 7), 1.42(q, 2H, *J* = 7), 2.59(dd, 3H, *J* = 2.4, 4.9), 2.78(dd, 3H, *J* = 4.4, 4.9), 3.12(m, 3H), 3.37 (m, 9H), 3.69(dd, 3H, *J* = 2.9 ,11.7)	303(M^++1, 6), 155(100)
3c	syrup	$C_{17}H_{28}O_8$ (360.4)	2870, 1090	2.59(dd, 4H, *J* = 2.4, 4.9), 2.77(dd, 4H, *J* = 4.4, 4.9), 3.12(m, 4H), 3.37(dd, 4H, *J* = 5.9,11.7), 3.49(m, 8H), 3.70(dd, 4H, *J* = 2.9, 11.7)	361(M^++1, 4), 83(100)
3d	140 / 0.05	$C_{12}H_{22}O_5$ (246.3)	3480, 2930, 1120	1.23(s, 3H), 1.75-1.89(m, 4H), 2.60(dd, 2H, *J* = 3.5), 2.80(dd, 2H, *J* = 4, 5), 3.12 -3.16(m, 2H), 3.36(s, -OH), 3.38(dd, 1H, *J* = 2.0, 5.9), 3.41(dd, 1H, *J* = 2.4, 5.9), 3.67-3.77(m, 6H)	247(M^++1, 29), 81(100)
3e	170 / 0.04	$C_{15}H_{26}O_6$ (302.4)	2870, 1100	1.36-1.63(m, 6H), 2.59-2.62(m, 3H), 2.78-2.80 (m, 3H), 3.13-3.15(m, 3H) ,3.29-3.81(m, 11H)	303(M^++1, 77), 229(100)
3f	59-62	$C_{15}H_{18}O_6$ (294.3)	2920, 2870, 1600, 1160	2.74(dd, 3H, *J*=2,5), 2.90 (dd, 3H, *J*=4,5), 3.33(m, 3H), 3.88(dd, 3H,*J*=6,11), 4.19(dd, 3H, *J*=3,11), 6.14 (s, 3H)	294(M^+,100)

[a]Kugelrohr distillation

[b]Satisfactory microanalyses obtained: C±0.35, H±0.11.

3-1-4. References

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3-2. Unique Interfacial Properties of a Homologous Series of Novel Triple-chain Amphiphiles Bearing Three Anionic Head Groups Derived from 1,1,1-Tris(hydroxymethyl)ethane

3-2-1. Introduction

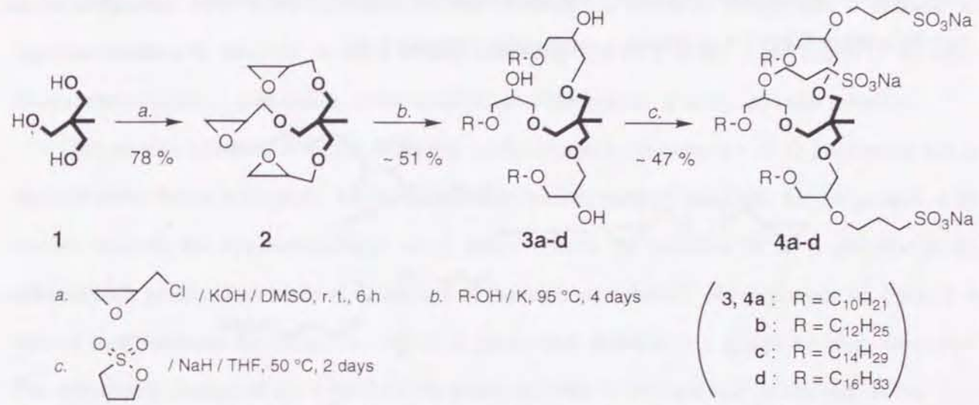
Almost all the established surfactants are amphipathic molecules consisting of one lipophilic chain and one hydrophilic head group. The relation between the interfacial properties and the structural factors of such surfactants has been already systematically summarized in detail.[1] So, if someone designs an unknown surfactant molecule on paper by combining a lipophilic group and a hydrophilic group, he should be able to speculate on the surface-active properties of the supposed compound.

Okahara *et al.* have found, however, the double-chain amphiphiles bearing two ionic head groups, of which the molecular structure is apparently shaped as a bundle of two typical single-chain surfactants, exhibit various interesting interfacial properties.[2] These properties are not on the extension of the relation between the interfacial properties and the structural factors of conventional surfactants. So we have been investigating the preparation and properties of new amphiphiles consisting of two or three lipophilic chains, two hydrophilic head groups and an appropriate connecting group between the lipophilic part and the head groups.[3,4] Especially, among these compounds, triple-chain amphiphiles bearing two anionic groups derived from glycerol have very small CMC values and high ability to lower surface tension, both of which cannot be achieved by the simple modification of the structure of general single-chain monoanionic surfactants.[3] In this section, the author used trimethylolethane (**1**) as a starting material and synthesized novel triple-chain amphiphiles bearing three sulfonate groups (**4**). Here the author reports unusual and interesting interfacial properties observed among these homologues.

3-2-2. Results and Discussion

Scheme 3-2 shows the synthetic route for the target triple-chain tris(sulfonate) compounds **4a-d**.

The synthetic intermediate, trimethylolethane tris(glycidyl ether) **2**, was prepared according to the previously reported method.[5] Pure compounds **4a-d** were finally isolated as white solids by silica gel column chromatography with a chloroform:methanol eluent.[6]



Scheme 3-2

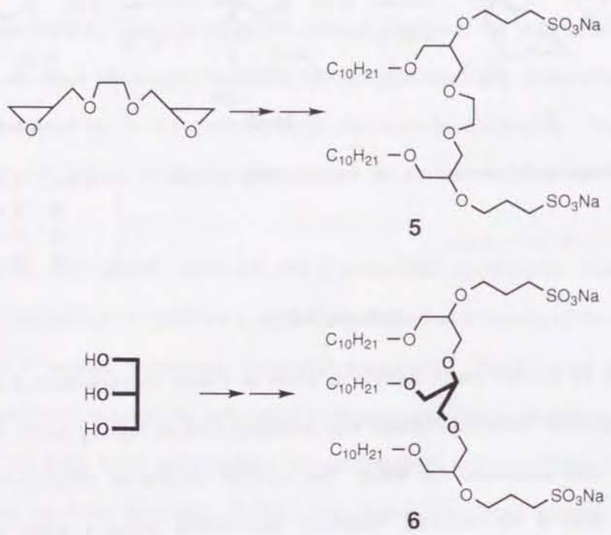
Although compounds **4a-c** were freely soluble in water at 1 wt% concentration at any temperature, compound **4d** bearing three hexadecyl chains was insoluble even in boiling water. So the interfacial properties in water were measured for **4a-c**. The surface tension of amphiphile solutions was measured at 20 ℃ with a conventional Wilhelmy tensiometer using a glass plate. Table 3-4

Table 3-4. The CMC, γCMC, and pC_{20} values of amphiphiles **4a-c** and the reference compounds measured by the Wilhelmy method at 20 ℃ in water

Amphiphile	CMC / M	γCMC / mN m^{-1}	pC_{20}
4a	6.8 x 10^{-6}	31.5	7.4[a]
4b	5.0 x 10^{-5}	33.0	5.8
4c	2.5 x 10^{-4}	34.0	4.8
5[b]	3.2 x 10^{-5}	30.0	5.2
6[c]	1.4 x 10^{-5}	28.0	6.6[a]

[a]Estimated value. [b]Ref. 7. [c]Ref. 3.

summarizes the data of their CMC, γCMC (the surface tension at CMC) and pC_{20} (the efficiency of adsorption at the air/water interface)[7] values which are obtained from each surface tension vs. concentration (on log scale) curve. The corresponding data for double-chain bis(sulfonate) (**5**) derived from ethylene glycol diglycidyl ether[8] and triple-chain bis(sulfonate) (**6**) derived from glycerol[3] are also included in Table 3-4 as reference amphiphiles (Scheme 3-3).



Scheme 3-3

Surprisingly, in the homologous series of compounds **4**, the increasing order of CMC is: **4a** < **4b** < **4c**, indicating that the CMC values increase with an increase in the length of the lipophilic alkyl chain. This result is contrary to the common recognition that the CMC values for the homologous series of general single-chain surfactants decrease with an increase in the length of the alkyl chain till about hexadecyl group.[9] In the case of the homologous series of reference compound **5** or **6**, this unusual tendency for the CMC values was not observed within the range of our study.[3,8]

Moreover, there are two noteworthy points concerning the measurement of surface tension for compounds **4a-c** by the Wilhelmy method. First, very long aging time was required (from 24 h to 48 h) until the surface tension of the aqueous solution of these compounds reached a constant value at lower concentrations than their each CMC. Second, the pC_{20} values decreased with an increase in the

length of the alkyl chain as shown in Table 3-4. The pC_{20} value is proportional to a standard free energy of adsorption at the air/water interface, $-\Delta G^{\circ}_{ad}$.[7] The pC_{20} values generally increase linearly with an increase in the number of carbons in a straight-chain lipophilic group of conventional single-chain surfactants.[7] But the pC_{20} values for the homologous series of compounds **4** showed an opposite tendency to this rule, in other words, indicating that an increase in the length of the alkyl chain makes a negative contribution to the adsorption of compounds **4** at the air/water interface.

Information obtained from the Wilhelmy method reflects the behavior of an amphiphile not in the bulk phase but at the surface. So we additionally tried to measure the CMC for compounds **4** by another method, the dye-method,[10] of which result reflects the behavior of an amphiphile in the aqueous bulk phase. Ultra-violet (UV) spectra of the aqueous solutions of compounds **4a-c** and **5** at various concentrations including 5 x 10^{-7} M of pinacyanol chloride as a dye-probe were measured. The absorbance change of the γ-band of the probe at λmax = 490 nm was monitored. It has been reported that the absorbance of the γ-band decreases with a formation of aggregation of amphiphiles in

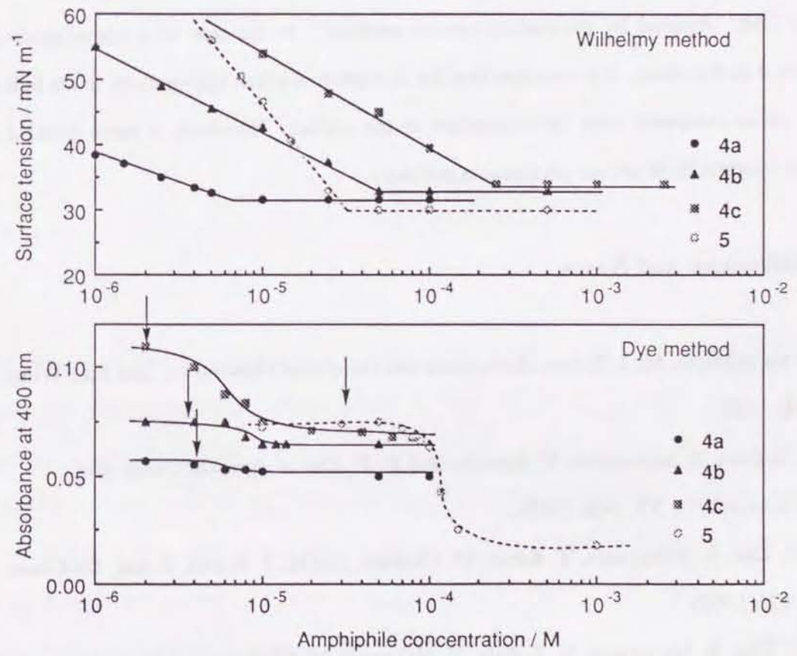


Figure 3-1. CMC measurement by the Wilhelmy method (upper) and by the dye method (lower). Arrows indicate estimated CMC values.

the bulk phase.[10] The determination limit of the amphiphile concentration was about 2 x 10^{-6} M under experimental conditions of this work. The relation between the amphiphile concentration and the surface tension (measured by the Wilhelmy method) or the absorbance at 490 nm (measured by the dye method) for compounds **4a-c** and **5** is shown in Figure 3-1.

For compound **5**, the CMC values obtained by the two different methods are almost the same. For compounds **4a-c**, however, the absorbance change attributed to the formation of aggregation in water was observed at much lower concentration than each CMC estimated from the Wilhelmy method. It appears that the absorbance of **4c** is already changing at the minimum amphiphile concentration of this experiment.

These results strongly indicate that compounds **4a-c** could form some molecular aggregations, such as "pre-micelles", even at lower concentration than their each CMC shown by the Wilhelmy method. Recently, Menger *et al.* have also reported that some "gemini surfactants", which are amphiphiles possessing, in sequence, a long lipophilic chain, an ionic head group, a rigid spacer, a second ionic group, and another lipophilic hydrocarbon tail, would be substantially preassembled well below the CMC obtained by the surface tension method.[11] In the case of a homologous series of compounds **4** in this study, it is surmised that the formation of some aggregations in the bulk phase is relatively easier compared with the adsorption at the surface. However, a more detailed study is required to interpret these unique phenomena precisely.

3-2-3. References and Notes

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6. Satisfactory spectral and microanalytical data were obtained for all purified **4**. Selected spectroscopic data for **4** are as follows: for **4a**; ^{1}H-NMR [JEOL JNM-GSX-400 (400 MHz)] δ 0.88 (t, 12H), 1.09-1.47 (m, 42H), 1.50-1.67 (m, 6H), 1.97 (m, 6H), 2.72-3.08 (m, 6H), and 3.20-3.97 (m, 33H); IR(KBr) 2900, 2860, 1450, 1170, 1110, and 1070 cm^{-1}. Anal. calcd for $C_{53}H_{105}O_{18}S_3Na_3.2H_2O$: C, 51.69; H, 8.92; S, 7.81. Found: C, 51.65; H, 8.86; S, 8.30.
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Chapter 4. Selective Transport of Saccharides through a Bulk Liquid Membrane Using Reversed Micelle Carriers

4-1. Introduction

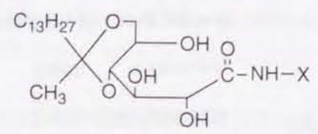
Recently, a system for selective saccharide transport through a liquid membrane including an artificial carrier has been developed and has attracted much attention, since such system is useful not only as a separation method for a particular saccharide but also as a model for clarifying the mechanism of action of saccharide transporter in a cell membrane. Until now, several researchers have reported the transport of monosaccharides or glycosides through an organic liquid membrane by use of phenylboronic acid or its analogues, which can covalently complex with saccharides to give cyclic boronate esters, as the carriers.[1] However, no other carrier for saccharide transport has been presented. The author has a great interest in developing a new carrier for saccharide transport through a liquid membrane. In this chapter, the author reports selective transport of saccharides using reversed micelle carriers. While the selective liquid-liquid extraction[2] and the transport[3] through a liquid membrane using reversed micelle systems have been described as good separation methods for proteins, there has been no report on transport of saccharides using the reversed micelle carrier to the best of my knowledge.

4-2. Experimental Section

Transport experiments were carried out using a U tube apparatus (1.5 cm internal diameter, 14.6 cm high, 2 cm distance between two arms) equipped with a stirring rod and a magnetic stirrer (500 rpm) at 25 ℃. An organic solution (15 mL) containing an amphiphilic compound was placed in the bottom of the tube, and two portions of aqueous solutions (both 3 mL) were carefully added on the tops of the organic solution. The details of transport conditions are summarized in the footnotes of Table 4-1. The concentration of saccharide in the receiving phase was determined by HPLC (Asahipack column, 4.6 mm internal diameter x 250 mm, acetonitrile/water = 75/25 as an eluent) using ethylene glycol as an internal standard. Water content in an organic liquid membrane after the

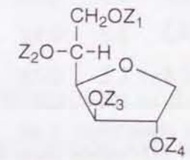
transport experiment (1 day) was measured by Karl-Fischer titration method. Centrifugal partition chromatography (CPC) was performed by using a Sanki Engineering Centrifugal Partition Chromatograph Model-NMF. The separation conditions are as follows: flow rate = 2.0 mL/min, rotational speed = 1000 rpm. Each experiment was repeated at least three times to ensure reproducibility (± 10%).

4-3. Results and Discussion



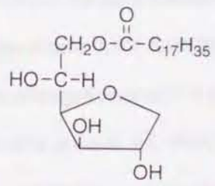
1a-c

1a : X = -$(CH_2)_2OH$
1b : X = -C_3H_7
1c : X = -$(CH_2)_2OCH_3$

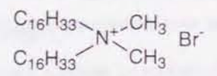


Z_1~ Z_4 =
$C_{17}H_{33}COO$-, $C_{17}H_{33}COO$-,
$C_{17}H_{33}COO$-, -$(C_2H_4O)_{20}H$

Tween 85



Span 60



DHDMAB

On the basis of the idea that the water pool formed in a reversed micelle may be an actual carrier for the transport of hydrophilic guest compounds across a liquid membrane, the author designed amphiphiles **1a-c** bearing a highly lipophilic alkyl group and hydrophilic amide and polyhydroxyl groups that were supposed to be effective for forming a water pool, as reversed micelle-forming compounds. These compounds were prepared by acetalization of glucono-1,5-lactone with 2-pentadecanone, followed by amidation with the appropriate amines.[4] For the purpose of comparison, polyoxyethylene sorbitan trioleate (Tween 85), sorbitan stearate (Span 60), Aerosol–OT (AOT), dihexadecyldimethylammonium bromide (DHDMAB), and cetyltrimethylammonium bromide (CTAB)

which are commercially available were selected as the typical reversed micelle-forming compounds.[5] Among them, AOT and CTAB were found to be inadequate for this transport because their good water solubilities caused them to leak from the organic liquid membrane into the aqueous phases during the transport.

Table 4-1. Competitive Transport Data[a]

Entry	Amphiphile	Transport Rate[b]			Water Content[c]
		Ri	Glu	Fru	
1	**1a**	6.3	1.1	1.3	1050
2	**1b**	2.7	1.0	1.2	880
3	**1c**	2.3	0.96	1.0	840
4	Tween 85	1.5	0.96	0.70	1050
5	Span 60	4.3	1.3	0.92	1040
6	DHDMAB	2.8	1.2	0.75	820

[a]Transport conditions: source phase (H_2O, 3 mL, [D-ribose] = [D-glucose] = [D-fructose] = 1.5 M); organic phase ($CHCl_3$, 15 mL, [amphiphile] = 1 x 10^{-2} M); receiving phase (H_2O, 3 mL), 25 °C, 500 rpm. [b]mM/day, Ri = D-Ribose, Glu = D-Glucose, Fru = D-Fructose. [c]ppm, after 1 day.

Table 4-1 shows the results of competitive transport toward D-ribose, D-glucose, and D-fructose using various reversed micelle carriers and water content in the organic liquid membrane after the transport experiments (1 day). These water content values were approximately equal to those obtained after the transport experiments over 4 days, indicating that the water content in the liquid membrane has come to equilibrium fully after 1 day. D-Ribose was transported faster than D-glucose and D-fructose, regardless of the type of carrier employed. The reversed micelle carrier formed by amphiphile **1a** bearing a terminal hydroxyl group in the hydrophilic moiety showed the highest D-ribose/D-glucose selectivity as well as the fastest transport rate for D-ribose among all types of carriers examined. On the other hand, when amphiphile **1b** (or **1c**), which has a CH_3 (or OCH_3) group in the terminal, was used as the reversed micelle-forming compound, both the transport rates for three types of saccharides and the D-ribose selectivity decreased. Concerning the carriers formed by the gluconamide-type amphiphiles **1a-c**, transport rates for these saccharides increased with an increase in water content in the liquid membrane. Since the water content relates to the amount of water pool formed in the reversed micelle, there should exist the close relationship between transport rates for saccharides and the amount of water pool in the liquid membrane. The D-ribose selectivity in the reversed micelle transport system may be explained by assuming that the more lipophilic the saccharide tends to transfer the faster from the source aqueous phase to the water pool (and from the water pool to the receiving aqueous phase)

across a lipophilic region of the reversed micelle.

The competitive transports[6] toward monosaccharides (D-ribose, D-glucose, D-arabinose, D-xylose, D-mannose, D-fructose, D-galactose), disaccharides (D-maltose, D-sucrose), and glucosides (methyl α-D-glucoside, methyl β-D-glucoside) using the carriers formed by compounds **1a** resulted in clarifying the following order of increasing transport rate:

D-ribose (30) > methyl α-D-glucoside (27) > methyl β-D-glucoside (18) > D-arabinose (5.7) > D-xylose (3.4), D-fructose (3.4) > D-mannose (1.8) > D-glucose (1.0) > D-galactose (0.29) > maltose (0.19) > sucrose (0.18)

where the relative transport rate for each saccharide (or glucoside) to that of D-glucose (0.3~0.6 mM/48 h) is shown in the parenthesis. This order is in agreement with the increasing order of the elution rate of saccharide molecule in centrifugal partition chromatography (CPC) using 1-butanol-ethanol-water (4 : 1 : 4, vol/vol/vol) as the solvent system (stationary phase: lower) , that is, the increasing order of the partition coefficent of saccharide molecule from water to 1-butanol phase. This result indicates that the hydrophobicity of saccharide molecule is an important factor among those affecting saccharide discrimination by the reversed micelle system.

4-4. References and Notes

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6. These transport experiments were carried out under the following conditions: source phase (H_2O, 3 mL, [saccharide or glucoside] = 1.5 M); organic phase ($CHCl_3$, 15 mL, [**1a**] = 1 x 10^{-2} M); receiving phase (H_2O, 3 mL), 25 ℃, 300 rpm.

Chapter 5. Amphiphilic Cycloinulohexaose: Preparation, Surface-Active Properties, and Complexing Abilities toward Various Metal Chlorides

5-1. Introduction

Cyclodextrins are a class of cyclic oligosaccharides consisting of several α-(1,4)-linked D-glucopyranose units and have a cone-shaped cavity. Their abilities to form inclusion complexes with a wide range of organic guests have found applications in many areas.[1] Recently, cyclic oligosaccharides other than cyclodextrins have attracted much attention as new host compounds.[2-7] Cycloinulohexaose,[2] which is a β-(2,1)-linked cyclohexaose of D-fructofuranose, is among them. This compound is prepared from inulin by using cycloinulo-oligosaccharide fructanotransferase. The molecule possesses a chiral 18-crown-6 skeleton. The chemical modification using an appropriate reagent is expected to afford a promising artificial receptor. Indeed, cycloinulohexaose has been reported to have a high complexing ability toward Ba^{2+}.[8,9] Additionally, Sawada *et al.* have found that permethylated cycloinulohexaose has a selectivity toward K^+ and Ba^{2+} among alkali metal and alkaline earth metal cations, like that of 18-crown-6.[10]

In this study, the author describes the preparation of amphiphilic cycloinulohexaoses by the reaction of cycloinulohexaose with long-chain acyl chloride or long-chain alkyl bromide, their surface-active properties, and their complexing abilities toward metal cations such as Li^+, Na^+, K^+, Rb^+, and Ba^{2+}. Similarly to amphiphilic cyclodextrins[11] and amphiphilic crown ethers,[12] both of which have been extensively studied up to now, the amphiphilic cycloinulohexaoses or their aggregates are potentially useful as carriers of ions or organic compounds in membrane systems and as sensors for a variety of

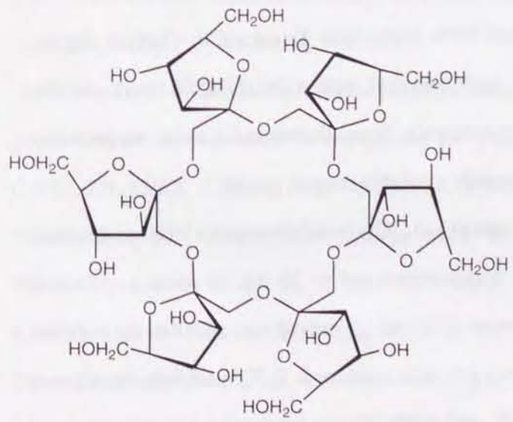


Figure 5-1. Structure of cycloinulohexaose

chemical species. To the best of our knowledge, this is the first example of an amphiphilic compound bearing cycloinulohexaose as a hydrophilic part.

5-2. Experimental Section

^{1}H NMR spectra were recorded with a JEOL JNM-GSX-400 (400 MHz) spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. IR spectra were measured on a HORIBA FT-710 spectrometer. Mass spectra were measured on a JEOL JMS-DX-303 mass spectrometer. Elemental analyses were measured with a Yanagimoto CHN-Corder. Melting points were measured with a Yanaco MP-S3 apparatus. Cloud points (T_{cp}) were determined by the naked eye with a 1wt% aqueous solution. Critical micelle concentrations (cmcs) were determined by a dye method using pinacyanol chloride as a dye probe.[13] Visible spectra of different concentrations of surfactant solutions including 5.0 x 10^{-6} M pinacyanol chloride were measured with a Hitachi U-2000 spectrophotometer. Micellar aggregation numbers were determined by a static method in which pyrene and hexadecylpyridinium chloride (HPC) were used as a fluorescence probe and a quencher, respectively.[14] Fluorescence measurements were carried out on a Shimadzu fluorescence spectrophotometer RF-1500. Fluorescence intensities of 1.0 x 10^{-7} M pyrene in 1.0 x 10^{-4} M surfactant solution were measured at 380 nm (excitation wavelength: 335 nm) as a function of the quencher concentration.

Materials. Cycloinulohexaose was obtained from Mitsubishi Kagaku Co. (Tokyo, Japan). Triethylamine, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled before use. Pyrene and HPC were purified by recrystallization from ethanol and acetone, respectively, before use. All other reagents used were of commercially available reagent grade.

Mono(6-*O*-dodecanoyl)cycloinulohexaose(1a). Cycloinulohexaose (1.03 g, 1 mmol) was dissolved in DMF (50 mL) and the solution was concentrated to 30 mL *in vacuo* to eliminate water bonded to cycloinulohexaose. After triethylamine (0.70 mL, 5 mmol) was added to the solution, dodecanoyl chloride (0.22 g, 1 mmol) was dropped into this mixture at 0 ℃, and then the mixture was stirred for 2 h at room temperature. After DMF and triethylamine were removed under reduced pressure, the residue was purified by a reversed-phase column chromatography (Column: ULTRA

PACK$_{TM}$ ODS-A-40B ϕ26 x 300 mm, Yamazen Co.) with methanol as an eluent to give pure mono(6-*O*-dodecanoyl)cycloinulohexaose (0.30 g, 26% yield), mp 140-142 ℃. ^{1}H NMR(DMSO-d_6) δ 0.85(t, 3H, CH_3), 1.24(m, 16H, -(CH_2)$_8$-), 1.50(m, 2H, CH_2CH$_2$C=O), 2.31(t, 2H, CH_2C=O), 3.37-3.47(m, 5H, H-6a'), 3.47-3.59(m, 16H, H-1a+H-6b'+H-5'+H-1a'), 3.59-3.71(m, 6H, H-1b+H-1b'), 3.71-3.77(m, 1H, H-5), 3.77-3.86(m, 6H, H-4+H-4'), 3.86-4.00(m, 6H, H-3'+H-3), 4.04(dd, 1H, *J* = 7 and 12 Hz, H-6a), 4.24(dd, 1H, *J* = 2 and 12 Hz, H-6b), 4.43-4.50(m, 4H, OH-3'), 4.57(d, 1H, *J* = 6.2 Hz, OH-3'), 4.62(d, 1H, OH-3, *J* = 6.2 Hz), 4.63-4.70(m, 5H, OH-6'), 5.23(d, 5H, *J* = 5.5 Hz, OH-4'), 5.44(d, 1H, *J* = 5.5 Hz, OH-4). IR(KBr) 3380, 2925, 1724, 1030 cm^{-1}. FAB-MS (m/z, relative intensity) 1177[(M+Na)$^+$, 83], 89(100). Found: C, 46.38; H, 7.07%. Calcd for $C_{48}H_{82}O_{31}\cdot 5H_2O$: C, 46.30; H, 7.45%.

Mono(6-*O*-tetradecanoyl)cycloinulohexaose(1b). This compound was prepared and purified in the same manner as compound **1a**: yield 30%. mp 192-195 ℃. ^{1}H NMR(DMSO-d_6) δ 0.85(t, 3H, CH_3), 1.24(m, 20H, -(CH_2)$_{10}$-), 1.51(m, 2H, CH_2CH$_2$C=O), 2.32(t, 2H, CH_2C=O), 3.38-3.47(m, 5H, H-6a'), 3.47-3.59(m, 16H, H-1a+H-6b'+H-5'+H-1a'), 3.59-3.71(m, 6H, H-1b+H-1b'), 3.71-3.77(m, 1H, H-5), 3.77-3.86(m, 6H, H-4+H-4'), 3.88-4.00(m, 6H, H-3'+H-3), 4.04(dd, 1H, *J* = 7 and 12 Hz, H-6a), 4.24(dd, 1H, *J* = 2 and 12 Hz, H-6b), 4.43-4.50(m, 4H, OH-3'), 4.57(d, 1H, *J* = 6.2 Hz, OH-3'), 4.62(d, 1H, *J* = 6.2 Hz, OH-3), 4.63-4.70(m, 5H, OH-6'), 5.23(d, 5H, *J* = 5.5 Hz, OH-4'), 5.44(d, 1H, *J* = 5.5 Hz, OH-4). IR(KBr) 3380, 2925, 1728, 1030 cm^{-1}. FAB-MS (m/z, relative intensity) 1205[(M+Na)$^+$, 100]. Found: C, 48.94; H, 7.38%. Calcd for $C_{50}H_{86}O_{31}\cdot 2H_2O$: C, 49.26; H, 7.44%.

Mono(6-*O*-hexadecanoyl)cycloinulohexaose(1c). This compound was prepared and purified in the same manner as compound **1a**: yield 26%. mp 219-222 ℃. ^{1}H NMR(DMSO-d_6) δ 0.84(t, 3H, CH_3), 1.22(m, 24H, -(CH_2)$_{12}$-), 1.50(m, 2H, CH_2CH$_2$C=O), 2.30(t, 2H, CH_2C=O), 3.37-3.46(m, 5H, H-6a'), 3.46-3.59(m, 16H, H-1a+H-6b'+H-5'+H-1a'), 3.59-3.69(m, 6H, H-1b+H-1b'), 3.69-3.75(m, 1H, H-5), 3.75-3.86(m, 6H, H-4+H-4'), 3.86-3.99(m, 6H, H-3'+H-3), 4.04(dd, 1H, *J* = 7 and 12 Hz, H-6a), 4.24(dd, 1H, *J* = 2 and 12 Hz, H-6b), 4.40-4.50(m, 4H, OH-3'), 4.53(d, 1H, *J* = 6.2 Hz, OH-3'), 4.57(d, 1H, *J* = 6.2 Hz, OH-3), 4.59-4.68(m, 5H, OH-6'), 5.21(d, 5H, *J* = 5.5 Hz, OH-4'), 5.43(d, 1H, *J* = 5.5 Hz, OH-4). IR(KBr) 3390, 2925, 1728, 1030 cm^{-1}. FAB-MS (m/z, relative intensity) 1233[(M+Na)$^+$, 54], 89(100). Found: C, 48.12; H, 7.44%.

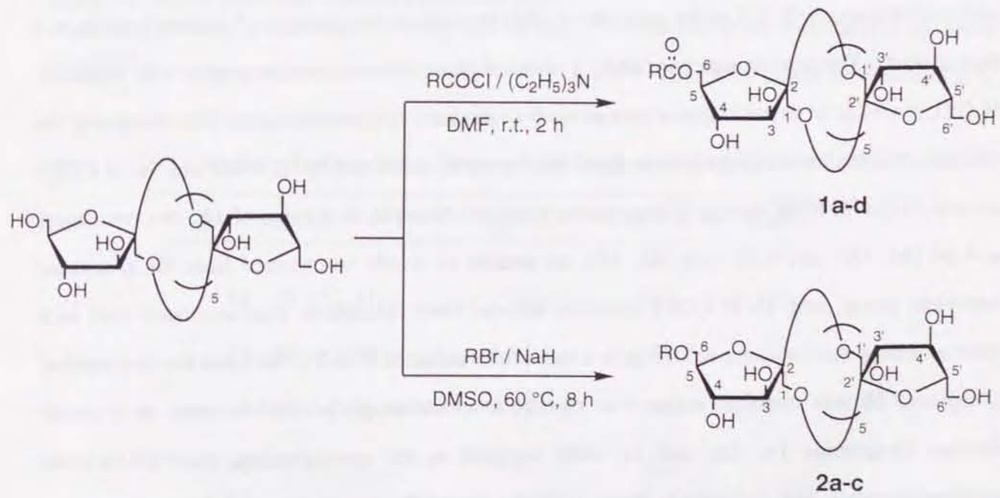
Calcd for $C_{52}H_{90}O_{31}\cdot 5H_2O$: C, 47.99; H, 7.75%.

Mono(6-*O*-octadecanoyl)cycloinulohexaose(1d). This compound was prepared and purified in the same manner as compound **1a**: yield 28%. mp 164-166 ℃. ^{1}H NMR(DMSO-d_6) δ 0.85(t, 3H, CH_3), 1.24(m, 28H, -$(CH_2)_{14}$-), 1.51(m, 2H, CH_2CH_2C=O), 2.32(t, 2H, CH_2C=O), 3.37-3.47(m, 5H, H-6a'), 3.47-3.59(m, 16H, H-1a+H-6b'+H-5'+H-1a'), 3.59-3.70(m, 6H, H-1b+H-1b'), 3.70-3.76(m, 1H, H-5), 3.76-3.84(m, 6H, H-4+H-4'), 3.84-3.99(m, 6H, H-3'+H-3), 4.04(dd, 1H, J = 7 and 12 Hz, H-6a), 4.24(dd, 1H, J = 2 and 12 Hz, H-6b), 4.41-4.50(m, 4H, OH-3'), 4.52(d, 1H, J = 6.2 Hz, OH-3'), 4.57(d, 1H, J = 6.2 Hz, OH-3), 4.58-4.68(m, 5H, OH-6'), 5.21(d, 5H, J = 5.5 Hz, OH-4'), 5.43(d, 1H, J = 5.5 Hz, OH-4). IR(KBr) 3380, 2924, 1731, 1030 cm^{-1}. FAB-MS (m/z, relative intensity) 1261[(M+Na)$^+$, 63], 107(100). Found: C, 49.17; H, 7.52%. Calcd for $C_{54}H_{94}O_{31}\cdot 5H_2O$: C, 48.79; H, 7.89%.

Mono(6-*O*-dodecyl)cycloinulohexaose(2a). Dodecyl bromide (0.37 g, 1.5 mmol)/ DMSO (10 mL) was dropped into a mixture of cycloinulohexaose (1.03 g, 1 mmol) and NaH (60%) (0.07 g net, 3 mmol) in DMSO (40 mL) at 60 ℃ under an argon atmosphere. The mixture was stirred at 60 ℃ for 8 h. After methanol was added into this reaction system to deactivate the unreacted NaH, the solvent was removed under reduced pressure. The residue was purified by a reversed-phase column chromatography (Column: ULTRA PACK$_{TM}$ ODS-A-40B ϕ26 x 300 mm, Yamazen Co.) with methanol-H_2O (1:1, v/v) as an eluent to give pure mono(6-*O*-dodecyl)cycloinulohexaose (0.22 g, 19% yield). mp 168-170 ℃. ^{1}H NMR(DMSO-d_6) δ 0.85(t, 3H, CH_3), 1.23(m, 18H, -$(CH_2)_9$-), 1.48(m, 2H, CH_2CH_2O), 3.36-3.47(m, 7H, CH_2O+H-6a'), 3.47-3.62(m, 19H, H-6a+H-6b+H-6b'+H-5+H-5'+H-1a+H-1a'), 3.62-3.72(m, 6H, H-1b+H-1b'), 3.71-3.85(m, 6H, H-4+H-4'), 3.85-3.96(m, 6H, H-3+H-3'), 4.40-4.52(m, 6H, OH-3+OH-3'), 4.58-4.69(m, 5H, OH-6'), 5.21(d, 5H, J = 5.5 Hz, OH-4'), 5.29(d, 1H, J = 5.5 Hz, OH-4). IR(KBr) 3380, 2927, 1026 cm^{-1}. FAB-MS (m/z, relative intensity) 1179[(M+K)$^+$, 100]. Found: C, 47.87; H, 7.29%. Calcd for $C_{48}H_{84}O_{30}\cdot 4H_2O$: C, 47.52; H, 7.64%.

Mono(6-*O*-tetradecyl)cycloinulohexaose(2b). This compound was prepared and purified in the same manner as compound **2a**: yield 19%. mp 172-176 ℃. ^{1}H NMR(DMSO-d_6) δ 0.84(t, 3H, CH_3), 1.23(m, 22H, -$(CH_2)_{11}$-), 1.47(m, 2H, CH_2CH_2O), 3.35-3.47(m, 7H, CH_2O+H-6a'), 3.47-3.62(m, 19H, H-6a+H-6b+H-6b'+H-5+H-5'+H-1a+H-1a'), 3.62-3.72(m, 6H, H-1b+H-1b'), 3.73-3.86(m, 6H, H-4+H-4'), 3.86-3.97(m, 6H, H-3+H-3'), 4.42-4.56(m, 6H, OH-3+OH-3'), 4.60-4.71(m, 5H, OH-6'), 5.22(d, 5H, J = 5.5 Hz, OH-4'), 5.30(d, 1H, J = 5.5 Hz, OH-4). IR(KBr) 3380, 2927, 1026 cm^{-1}. FAB-MS (m/z, relative intensity) 1207[(M+K)$^+$, 100]. Found: C, 47.84; H, 7.56%. Calcd for $C_{50}H_{88}O_{30}\cdot 5H_2O$: C, 47.69; H, 7.84%.

Mono(6-*O*-hexadecyl)cycloinulohexaose(2c). This compound was prepared and purified in the same manner as compound **2a**: yield 15%. mp 176-179 ℃. ^{1}H NMR(DMSO-d_6) δ 0.85(t, 3H, CH_3), 1.23(m, 26H, -$(CH_2)_{13}$-), 1.48(m, 2H, CH_2CH_2O), 3.36-3.47(m, 7H, CH_2O+H-6a'), 3.47-3.62(m, 19H, H-6a+H-6b+H-6b'+H-5+H-5'+H-1a+H-1a'), 3.62-3.70(m, 6H, H-1b+H-1b'), 3.73-3.84(m, 6H, H-4+H-4'), 3.86-3.96(m, 6H, H-3+H-3'), 4.37-4.50(m, 6H, OH-3+OH-3'), 4.58-4.68(m, 5H, OH-6'), 5.21(d, 5H, J = 5.5 Hz, OH-4'), 5.29(d, 1H, J = 5.5 Hz, OH-4). IR(KBr) 3390, 2927, 1026 cm^{-1}. FAB-MS (m/z, relative intensity) 1235[(M+K)$^+$, 100]. Found: C, 49.43; H, 7.54%. Calcd for $C_{52}H_{92}O_{30}\cdot 4H_2O$: C, 49.20; H, 7.94%.



	1a	1b	1c	1d	2a	2b	2c
R :	$C_{11}H_{23}$	$C_{13}H_{27}$	$C_{15}H_{31}$	$C_{17}H_{35}$	$C_{12}H_{25}$	$C_{14}H_{29}$	$C_{16}H_{33}$

Scheme 5-1

5-3. Results and Discussion

Preparation of Amphiphilic Compounds Containing a Cycloinulohexaose as a Hydrophilic Moiety. Mono-6-*O*-acylated and mono-6-*O*-alkylated cycloinulohexaoses were prepared according to Scheme 5-1. It is noteworthy that the preparation of these amphiphilic cycloinulohexaoses was accomplished without protection and deprotection processes of the hydroxy groups in the cycloinulohexaose molecule. Mono-6-*O*-acylated cycloinulohexaose was prepared by the reaction of cycloinulohexaose with an equimolar amount of acyl chloride in the presence of triethylamine for 2 h at ambient temperature. Either prolonging the reaction time or raising the reaction temperature led to an increase of diacylated products. The mono-6-*O*-acylated product was isolated from the reaction mixture, which also includes the diacylated product and unreacted cycloinulohexaose, by a reversed-phase column chromatography with methanol as an eluent. On the other hand, mono-6-*O*-alkylated cycloinulohexaose was prepared by the reaction of cycloinulohexaose with 1.5 molar amounts of alkyl bromide in the presence of sodium hydride as a base at 60 ℃. The product was purified by a reversed-phase column chromatography with methanol-H_2O (1:1, v/v) as an eluent to give a pure mono-6-*O*-alkylated cycloinulohexaose. The structure of the obtained cycloinulohexaose derivatives **1a-d** and **2a-c** was confirmed by ^{1}H NMR and ^{1}H-^{1}H COSY spectra. In the ^{1}H NMR spectra of compounds **1a-d**, for example, in the case of **1b**, two resonances at 4.04 (dd, 1H) and 4.24 ppm (dd, 1H) are present as would be expected from the *O*-acylated methylene group, and ^{1}H-^{1}H COSY spectrum showed these resonances were associated with each other as well as the resonance at 3.73 ppm which can be assigned to H-5 of the same fructose residue. Compound **1b** was therefore assigned as mono(6-*O*-tetradecanoyl)cycloinulohexaose. In a similar manner, compounds **1a**, **1c**, and **1d** were assigned as the corresponding mono-6-*O*-acylated cycloinulohexaose. For compounds **2a-c**, a doublet (one OH proton) around 5.3 ppm is present, which can be assigned to OH-4 of the alkylated fructose residue on the basis of the assignment results of compounds **1a-d**. The assignment based on this resonance and ^{1}H-^{1}H COSY spectrum proved that compounds **2a-c** are mono-6-*O*-alkylated cycloinulohexaoses.

Surface-Active Properties. The cmcs of compounds **1** and **2** were determined by a dye method[13] with pinacyanol chloride as a dye probe. Figure 5-2 shows the plots of the wavelength of maximal absorption (λ_{max}) of pinacyanol chloride vs. the logarithm of concentration (log C) for compounds **1b** and **2b**. Since the λ_{max} of pinacyanol chloride shifts to a longer wavelength when it is incorporated into the hydrophobic region of micelles from the bulk phase, the break point on the λ_{max}- log C curve can be regarded as the cmc of the surfactant. The cmcs and the cloud points (T_{cp}) measured at 1 wt% concentration are summarized in Table 5-1. The cloud points of compounds **1**

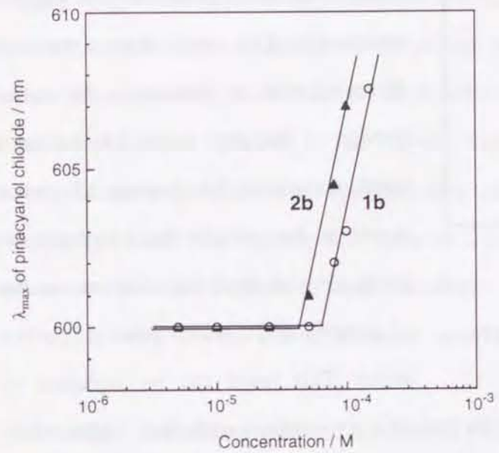


Figure 5-2. Plots of wavelength of maximal absorption (λ_{max}) of pinacyanol chloride vs. concentration of compounds **1b** and **2b** at 20 °C.

Table 5-1. Surface-Active Properties of Compounds **1** and **2**

Compound	T_{cp}[a] (℃)	CMC[b] (x 10^{-5} mol/L)
1a ($R = C_{11}H_{23}$)	> 95	21
1b ($R = C_{13}H_{27}$)	> 95	6.6
1c ($R = C_{15}H_{31}$)	> 95	1.8
1d ($R = C_{17}H_{35}$)	> 95	2.2
2a ($R = C_{12}H_{25}$)	> 95	14
2b ($R = C_{14}H_{29}$)	> 95	4.1
2c ($R = C_{16}H_{33}$)	> 95	1.4

[a] T_{cp} = cloud point. Measured at 1wt% concentration.
[b] At 20 ℃.

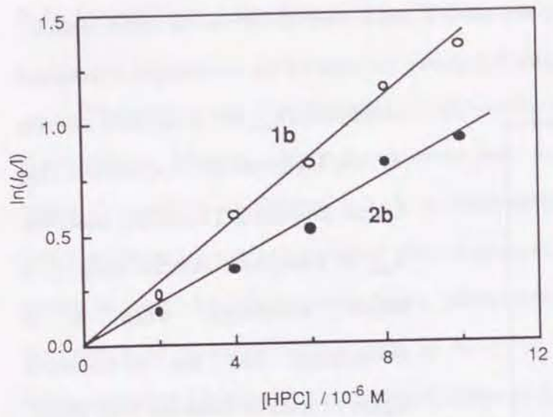


Figure 5-3. Plots of $\ln(I_0/I)$ vs. [HPC] for 1.0 x 10^{-4} M surfactant aqueous solutions.

and **2** were more than 95 ℃ at 1 wt% concentration, which clearly show that they have good water solubility. As regards compounds **1a-c** and **2a-c**, the cmc decreased with an increase in the carbon number of the alkyl chain. On the other hand, compound **1d** bearing 17 carbon atoms in the straight-chain hydrophobic group showed about the same cmc as that of compound **1c** which bears 15 carbon atoms. This result can be explained by coiling of the long C17 alkyl chain, similarly to the case of a conventional surfactant.[15] Meanwhile, micelle-forming ability of monoalkylated cycloinulohexaose **2** was higher than that of monoacylated cycloinulohexaose **1** bearing the same carbon number in the hydrophobic part. The cmc value of mono(6-*O*-dodecyl)cycloinulohexaose **2a** was almost equal to that of dodecyl β-D-maltoside (1.6 x 10^{-4} M).[16]

Micellar Aggregation Number. Micellar aggregation number (N) was determined from the slope of the plot of the logarithm of I_0/I of pyrene vs. the quencher concentration as follows:

$$\ln(I_0/I) = [\text{HPC}]N/\{[\text{Surfactant}] - \text{cmc}\} \qquad (1)$$

where I and I_0 are fluorescence intensities of pyrene in a surfactant solution in the presence and absence of the quencher, respectively, and [HPC] and [Surfactant] are concentrations of HPC and the surfactant, respectively.[14] Figure 5-3 shows that a linear relationship exists between $\ln(I_0/I)$ and [HPC] for each surfactant solution. The aggregation numbers of compounds **1b** and **2b** determined from this relation were 4.8 and 6.5, respectively. These values were much smaller than the aggregation numbers of octyl β-D-glucoside and dodecyl β-D-maltoside, which are 87[17] and 110[18], respectively. This result may be attributed to the large molecular size of cycloinulohexaose as the hydrophilic part of compounds **1b** and **2b**, compared to the sizes of glucose and maltose.

Complexation Properties. Previously, Okahara et al. reported that the cmcs of amphiphilic crown ethers were raised selectively by the addition of alkali metal salts when the crown ethers can strongly complex with the cations.[19] Based on this finding, the change in the cmcs was regarded to be an important method for estimating the complexing ability of the crown ethers in water toward alkali metal cations. According to this method for crown ethers, the complexation properties of compounds **1** and **2** with Li^+, Na^+, K^+, Rb^+, or Ba^{2+} in water were evaluated from the changes in their cmc values in the presence and absence of the corresponding metal chloride. Table 5-2 shows the cmc values of compounds **1b** and **2b**, together with those of Triton X-100 as a reference compound, both in the presence and absence of the above metal chlorides.

It is well known that alkali metal or alkaline earth metal salts diminish the cmcs of

Table 5-2. Effect of Metal Chlorides on CMCs of Compounds **1b** and **2b**

	CMC (x 10^{-5} mol/L)		
Metal chloride[a]	**1b** (Δ^b)	**2b** (Δ^b)	Triton X-100 (Δ^b)
None	6.6	4.1	35
LiCl	6.0 (-0.6)	3.0 (-1.1)	28 (-7)
NaCl	5.0 (-1.6)	1.5 (-2.6)	19 (-16)
KCl	7.4 (+0.8)	5.0 (+0.9)	23 (-12)
RbCl	7.2 (+0.6)	4.6 (+0.5)	23 (-12)
$BaCl_2$	9.2 (+2.6)	5.5 (+1.4)	25 (-10)

[a]Concentration of metal chloride = 0.1 M
[b]Δ = (CMC in the presence of metal chloride) – (CMC in the absence of metal chloride)

polyoxyethylene-type nonionic surfactants by the salting-out effect, except when special counter-anions are used.[20] Indeed, the cmc of Triton X-100 bearing a poly(oxyethylene) chain as the hydrophilic part was decreased by the addition of any of these metal chlorides, as reported. On the other hand, the cmc of compound **1b** was increased by the addition of either KCl or RbCl, and more greatly by the addition of $BaCl_2$, while it was decreased by the addition of either LiCl or NaCl. The

cmc of compound **2b** in the presence of the metal chlorides also showed a tendency similar to the case of compound **1b**. These results can be explained by considering the salting-in effect due to the complexation of the cycloinulohexaose ring, as the hydrophilic part of surfactants **1b** and **2b**, with K^+, Rb^+, or Ba^{2+}. On the other hand, the surfactants **1b** and **2b** were salted out by the addition of Li^+ or Na^+ because of their low complexing abilities toward such cations. The observed complexation properties of the amphiphilic cycloinulohexaoses with alkali metal or alkaline earth metal cations are consistent with that of unsubstituted cycloinulohexaose in water, which has been estimated by Yoshie *et al.*[9] using the ^1H NMR titration method.

5-4. References

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Conclusion

This thesis mainly deals with the preparation, properties, and functions of new amphiphilic compounds derived from polyols including sugars. The results obtained through this work are summarized as follows.

In chapter 1, novel amphiphilic compounds were prepared from glucono-1,5-lactone, *N*-acetyl-D-glucosamine, and L-ascorbic acid as starting materials *via* several reaction steps which include acetalization of two hydroxyl groups of the sugars (or the related compounds) with aldehyde or ketone dimethyl acetal. The surfactants derived from glucono-1,5-lactone and *N*-acetyl-D-glucosamine showed good water solubility and good surface-active properties. Especially, the nonionic surfactants derived from glucono-1,5-lactone and the anionic surfactants derived from *N*-acetyl-D-glucosamine showed excellent ability to lower surface tension. They can be utilized as cleavable surfactants, because they decompose into non-surface-active species under acidic conditions. Furthermore, the anionic compounds derived from *N*-acetyl-D-glucosamine showed good biodegradability comparable to that of sodium dodecanoate.

In chapter 2, *p*-nitrophenyl ester of D-phenylalanine hydrogen bromide was found to be hydrolyzed faster than the corresponding L-isomer in the presence of micelles formed with the sugar-amide surfactants. Particularly, a high enantioselectivity for the hydrolysis was attained in the presence of *N*-dodecylmaltobionamide surfactant micelles. The hydrolysis rate and the enantioselectivity were influenced by the alkyl chain length and the structure of the sugar moiety of the surfactant.

In chapter 3, polyglycidyl ethers were prepared in high yields by the reaction of polyols with epichlorohydrin using DMSO and KOH as a solvent and a base, respectively. A novel triple-chain amphiphile bearing three anionic head groups was derived from 1,1,1-tris(glycidyloxymethyl)ethane thus obtained. Interestingly, the critical micelle concentration (cmc) of this compound in water, which was evaluated by the common surface tension method using a Wilhelmy tensiometer, increased along

with an increase in the number of carbon atoms in the alkyl chain, in contrast to the tendency reported for the cmc values of conventional surfactants.

In chapter 4, the reversed micelles formed with various types of amphiphilic compounds were found to be useful as a carrier for selective transport of saccharides through a bulk liquid membrane. Among the amphiphilic compounds examined in this study, a gluconamide-type amphiphile formed the best carrier from the point of both selectivity and velocity. The selectivity for transport of saccharides in these systems was found to be closely related to the hydrophobicity of the saccharide molecule.

In chapter 5, novel amphiphilic cycloinulohexaoses, mono-6-*O*-acylated cycloinulohexaoses and mono-6-*O*-alkylated cycloinulohexaoses, were prepared from cycloinulohexaose which is a β-(2,1)-linked cyclohexaose of D-fructofuranose. These compounds were found to complex with K^+, Rb^+, and Ba^{2+} in water, but negligibly with Li^+ and Na^+, on the basis of the changes in their cmcs in the presence and absence of the corresponding metal chloride.

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