REVIEW

Ether Lipids Based on the Glyceryl Ether Skeleton: Present State, Future Potential

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ABSTRACT: Lipids from natural sources consist mainly of saponifiable substances, such as glycerides, along with some unsaponifiable lipids, some of which are ether lipids. Typical ether lipids are monoalkyl ethers of glycerin, also called alkyl/alkenyl glyceryl ethers. Alkyl/alkenyl glyceryl ethers have also been reported in marine organisms and in human feces. Several chemical syntheses of such ether lipids have been reported. Typical examples are alkyl glyceryl ether formation by the addition reaction of alkyl glycidyl ether and the telomerization reaction of butadiene with glycerin and a transition metal catalyst. Characteristic chemical structures, such as terpene alkyl glyceryl ethers, archaebacterial macrocyclic ether lipids, and glyceryl ethers of condensed cyclic planar molecules, have been obtained as well. Over the past few decades, industry has shown much interest in the chemistry and application of highly branched fatty acids. For example, isostearyl glyceryl ether (GE–IS) with methyl branching in the middle chain was already known, but it is now prepared at an industrial scale by proprietary alkyl glycidyl ether methods. The characteristic behavior of GE–IS toward water, such as formation of water-in-oil emulsions containing large amounts of water and of liquid crystals, has made it applicable for use in hair and skin-care cosmetics. Based on these studies and considerations, glyceryl ether lipids, which are rarely investigated, may become one of the most important and useful lipids in the industry.

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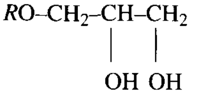
KEY WORDS: Ether lipids, GE–IS, glyceryl ether, glycidyl ether, isostearic acid, isostearyl glyceryl ether, liquid crystal, W/O emulsion.

Saponification of lipids from tissues and organs of many marine animals results in water-soluble soaps that have high levels of some unsaponifiable substances, which chiefly include hydrocarbons, such as squalene, sterols, and long-chain alcohols with one or more hydroxyl groups (1,2). Typical long-chain alcohols that contain one or more hydroxyl groups are particularly present as monoalkyl ethers of glycerin:



$$\begin{array}{llll} RO\text{–}CH_2\text{–} & CH & \text{–} & CH_2 \\ & | & & | \\ & OH & & OH \end{array}$$

[1]

For example, it is well known that lipids in the liver oils of sharks, rays, etc. contain palmityl glyceryl ether (called "chimyl alcohol"), stearyl glyceryl ether (called "batyl alcohol"), and oleyl glyceryl ether (called "selachyl alcohol").

Another typical glycerin derivative, monoglyceride, which contains two OH groups and an ester bond in place of the ether bond, is well known and is utilized extensively in many industries throughout the world. The usefulness and chemical and physical properties of monoglycerides, especially in the food industry, have been well studied and reviewed (3). However, little has been reported on the distribution, chemical and physical properties, preparation, and uses of glyceryl ethers.

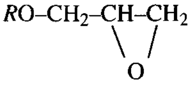
Mangold (1,5) and Mangold and Weber (4) conducted a detailed overview of the synthesis and biosynthesis of alkoxylipids that contained glyceryl ether compounds. Moreover, in 1983, Mangold and Paltauf (6) edited "Ether Lipids: Biochemical and Biomedical Aspects," in which they reviewed and discussed analytical studies, chemical syntheses and biosyntheses, human and animal dietary uses, and research on biological and model membranes of ether lipids. Several special ether lipid groups, such as glycolipids, macrocyclic ethers, steryl ethers, vinyl ethers, and platelet-activating factor (PAF), were reviewed as well.

Based on prior knowledge and our own experience, encountered in the industrial development of glyceryl ethers, we will now review glyceryl ethers and discuss in detail the potential for future use of these lipids in our everyday lives and in industry.

DISTRIBUTION OF GLYCERYL ETHERS

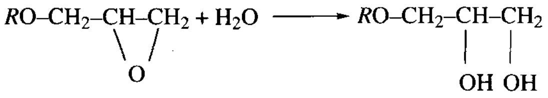
Glyceryl ethers found in marine organisms. In 1922, Tsujimoto and Toyama discovered batyl and selachyl alcohols in the liver oils of sharks and rays (1). Recently, free alkyl glyceryl monoethers have been found in some marine sponges. For example, free chimyl alcohol was found in *Stylopus australis* (7), *Tethya aurantia* (8), and *Tedania ignis* (9), and free batyl alcohol was found in *Ulosa ruetzleri* (10) and *T. ignis* (11). Quijano *et al.* (12) have reported on chimyl alcohol, heptadecyl glycerol, and batyl alcohol as the major constituents in a mixture of free alkyl glyceryl ethers isolated from the sponge *Desmapsamma anchorata*, harvested in the Gulf of Mexico, and minor components consisted of C_{15}, C_{19}, C_{20}, and C_{21} alkyl glyceryl ethers (12). They also found that sponges such as *D. anchorata* contain methyl-branched (*iso*, *anteiso* type) C_{17} and C_{19} alkyl glyceryl ethers, which might be a good source of phospholipids with methyl-branched fatty acids, which are typically not found in terrestrial systems (13).

Glyceryl ethers obtained from glycidyl ethers. Alkyl glycidyl ethers are compounds that have a chemically stable ether bond and a highly reactive epoxy bond separated by a methylene ($-CH_2-$) unit:



[2]

The reactive epoxy ring is readily opened into corresponding alkyl glyceryl ether derivatives through an attack by various nucleophiles, especially by a water molecule, which gives alkyl glyceryl ethers (14–16):



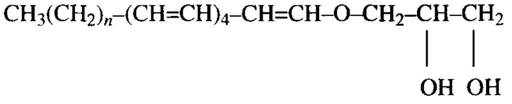
[3]

The synthetic method for glyceryl ethers *via* glycidyl ether compounds creates some advantages over products from natural sources: (i) alkyl glycidyl ethers can now be prepared at both laboratory and industrial scales from an alcohol (C_1–C_{18} and longer alkyl chains) by the phase-transfer catalytic Williamson ether synthesis process (14,17); (ii) alkyl glycidyl ethers that contain not only natural straight-chain moieties, but also unique branched alkyl chains or sterically bulkier molecules, such as cholesterol and derivatives, can be designed and obtained artificially. Thus, several kinds of strategic trials for the molecular construction of ether lipids, based on alkyl glycidyl ethers, are now in progress in our laboratory.

Glyceryl ethers by transition metal-catalyzed conversion. The global production of glycerin, which mainly comes from oleochemicals (~80%), has reached over 600,000 tons/year (18). Research and development of glycerin applications in industry are of great importance. Glycerin is obtained from fats and oils, so some work on the development of tensides based on glycerin for application to washing and cosmetic materials is now in progress. Researchers of Henkel KGaA have discovered the transition metal-catalyzed conversion (telomerization) of glycerin and butadiene to give glyceryl unsaturated octyl and dioctyl ethers on an industrial scale (18) (Scheme 1).

The transition metal catalyst is $Pd(acac)_2/PPh_3$. The catalytic system $Pd(acac)_2/PPh_3$/butadiene/glycerin (1:2:75000:18000) gave glyceryl octyl ether/diether/triether (38:53:9) with a 90–100% conversion. After hydrogenation, the mixture gave the corresponding saturated octyl mono- and dioctyl glyceryl ethers. The corresponding ether sulfates are obtained by the reaction of these ethers with SO_3 (gas), followed by neutralization with NaOH. They are interesting anionic surfactants for use in detergents and cosmetics.

Polyunsaturated glyceryl ethers found in human feces. Fecapentaenes, polyunsaturated glyceryl ethers (4), as shown later are effective, directly acting mutagens present in the feces of a large portion of the European and North American communities, and are suspected of being colon carcinogens (19). Baptista *et al.* (20) have reported the absolute configuration of fecapentaene by means of high-performance liquid chromatography (HPLC) and ^1H nuclear magnetic resonance (NMR):



$$CH_3(CH_2)_n\text{–}(CH{=}CH)_4\text{–}CH{=}CH\text{–}O\text{–}CH_2\text{–}\underset{\substack{|\\ OH}}{CH}\text{–}\underset{\substack{|\\ OH}}{CH_2} \qquad [4]$$

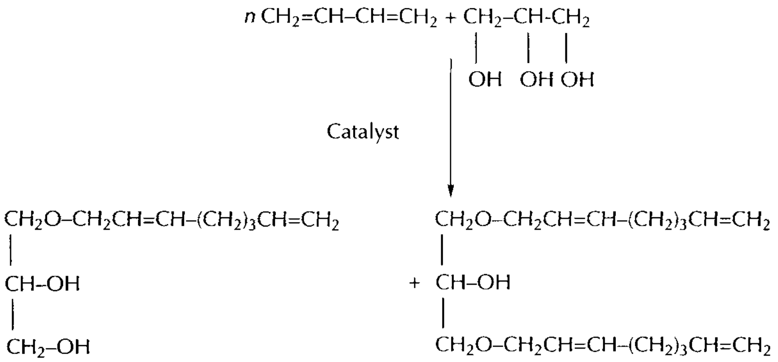
Also, synthetic all-*trans*-fecapentaenes by the Horner-Wittig reaction have been reported (21). The structural comparison exhibited identical HPLC retention times between fecapentaenes from feces and the synthetic version of the same.

In the next section, usefulness and properties of some alkyl glyceryl ethers of unique molecular structure will be mentioned.

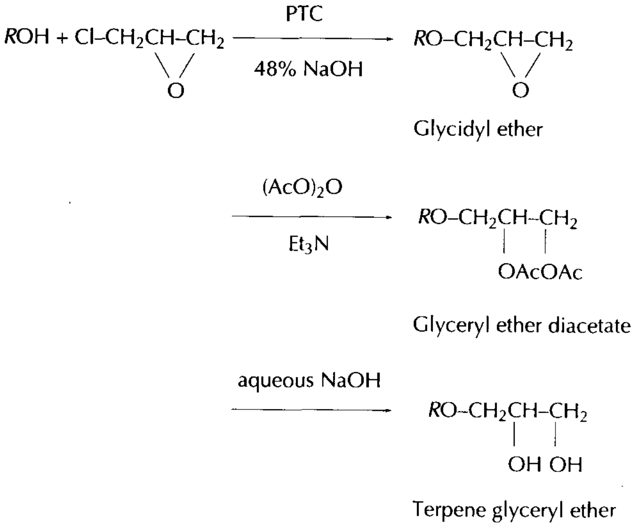
SOME ETHER LIPIDS WITH CHARACTERISTIC CHEMICAL STRUCTURES

Lipids found in plants and animals play an important role in maintaining life among organisms and in the evolution of the species. Among these lipids, some ether lipids with unique structures have been discovered or synthesized and shown to behave in a more unusual manner than was thought.

Terpene glyceryl ethers. Many types of terpene glyceryl



SCHEME 1



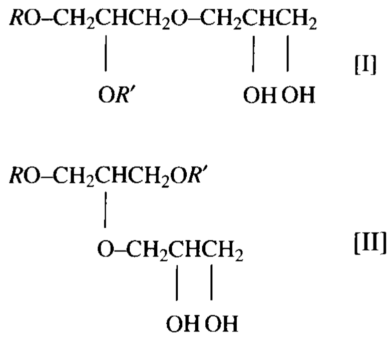
R = farnesyl ($C_{15}H_{25}$–), phytyl ($C_{30}H_{39}$–)

SCHEME 2

ether compounds have been isolated, and their physical and chemical properties have been established. Among these terpene glyceryl ethers, alicyclic terpene glyceryl ether was invented as an insecticide (22), and mono-/diphytanyl glyceryl ethers were separated from the methanolyzed lipids of the extreme halophile, *Halobacterium cutirubrum,* and their chemical structures were shown to be identical with those of synthetic ethers (23,24). We also prepared terpene alkyl glyceryl ethers, such as farnesyl- and phytyl glyceryl ethers, *via* glyceryl ether formation (Scheme 2; PTC, phase-transfer catalyst) (25).

These glyceryl ethers are liquid at 25°C, and the latter compound tends to form liquid crystals both at 25 and 70°C. They had stronger lipophilicity, offered resistance to washing, and survived longer on the skin-upon-skin coating. They are useful as emollients or moisturizers for skin cosmetics.

As an extension of our studies on terpene glyceryl ethers, we also prepared novel diglycerin alkyl ethers of terpene alcohols and used them in cosmetics as emulsifiers, emollients, humectants, etc. A typical example was diglycerin alkyl ethers of terpene alcohols of formula [I] (Eq. 5), which were applied onto the skin and exhibited high resistance to washing. Terpene glyceryl ethers (26) and isodiglycerin dialkyl ethers of terpene alcohols of formula [II] (Eq. 5) exhibited less irritation to the skin and were useful as emulsifiers, emolients, humectants, or viscosity-increasing agents (Eq. 5) (27).

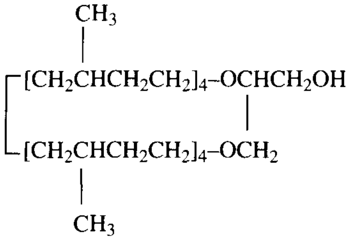


$$R\text{O–CH}_2\underset{\displaystyle OR'}{\underset{|}{\text{CH}}}\text{CH}_2\text{O–CH}_2\underset{\displaystyle OH}{\underset{|}{\text{CH}}}\underset{\displaystyle OH}{\underset{|}{\text{CH}_2}} \quad [\text{I}]$$

$$R\text{O–CH}_2\underset{\displaystyle \text{O–CH}_2\underset{\displaystyle OH}{\underset{|}{\text{CH}}}\underset{\displaystyle OH}{\underset{|}{\text{CH}_2}}}{\underset{|}{\text{CH}}}\text{CH}_2\text{O}R' \quad [\text{II}] \qquad [5]$$

R = farnesyl ($C_{15}H_{25}$–), phytyl ($C_{30}H_{39}$–);
R' = C_1–C_{24} alkyl or alkenyl group

Archaebacterial macrocyclic ether lipid. Archaebacteria exhibit unusual resistance to adverse environmental conditions, such as high temperatures (up to 100°C), high pressure, or low/high pH. Archaebacterial membrane lipids contain unique structures in which glycerin is linked to macrocyclic isoprenoid chains with etherial bonding (5). Woese *et al.* (28) have classified procaryotes into two types—*eubacteria* and *archaebacteria*. The former contain ester bonds and the latter contain ether bonds in their lipids. It is thought that the existence of an etherial linkage and a macrocyclic chain allows archaebacteria to resist the drastic environmental conditions mentioned previously. Thus, these unusual macrocyclic ether lipids have attracted attention, and several researchers have been attempting their synthesis. For example, Eguchi *et al.* (29) reported the first synthesis of a 36-membered macrocyclic diether lipid after more than 15 steps (Eq. 6):



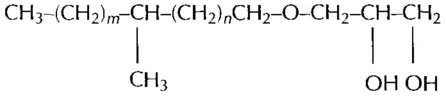
$$\left[\begin{array}{l}[\text{CH}_2\overset{\displaystyle CH_3}{\overset{|}{\text{C}}}\text{HCH}_2\text{CH}_2]_4\text{–OCHCH}_2\text{OH}\\ [\text{CH}_2\underset{\displaystyle CH_3}{\underset{|}{\text{C}}}\text{HCH}_2\text{CH}_2]_4\text{–OCH}_2\end{array}\right. \qquad [6]$$

Recently, macrocyclic etherial lipids have been found interesting as bolaamphiphiles, which are defined as molecules in which two or more hydrophilic groups are connected by hydrophobic functional groups (30). Bolaamphiphiles have gained much attention recently because they offer insight into both micellar and liposomal systems that can mimic enzymes, act as therapeutic agents, complement previous observations of unusual thermotropic properties, enhance liposomal stability, or serve as tools in the investigation of molecular recognition and assemblage (31).

Ether lipids from condensed cyclic plane molecules. Cholesterol or cholestanol and abietyl alcohol are molecules with condensed cyclic plane structures that can form the corresponding glycidyl ethers by proprietary glycidyl ether formation. These steroidal glycidyl ethers or abietyl glycidyl ether gave the corresponding glyceryl ethers (14). Skin preparations containing these compounds improved water retention in the corneum to control or prevent skin chapping or skin roughening (32,33).

ISOSTEARYL GLYCERYL ETHERS (GE–IS) AS NOVEL ETHER LIPIDS

It has been reported that palmityl glyceryl ether (chimyl alcohol), stearyl glyceryl ether (batyl alcohol), and oleyl glyceryl ether (selachyl alcohol) have excellent properties as emulsifiers, particularly for water-in-oil type emulsions. They also



$$CH_3\text{-}(CH_2)_m\text{-}\underset{CH_3}{CH}\text{-}(CH_2)_nCH_2\text{-}O\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}\underset{OH}{CH_2}$$

m is an integer of 2–14, *n* is an integer of 2–10, and total of *m* + *n* is 10–16

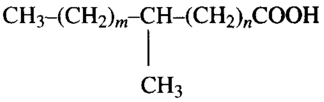
SCHEME 3

have medicinal activities, such as an acceleration effect on blood cell formation in the marrow, an anti-inflammatory effect, and an antitumor activity. However, these known monoalkyl glyceryl ethers have certain drawbacks, as being solids with high melting points, their lipophilicity is too high, and those having unsaturated bonds, such as selachyl alcohol, are chemically unstable.

There has always been a need for an emulsifier that is liquid at room temperature, is chemically stable, and gives good emulsion stability. These requirements were attained by our company in 1979 when it provided a novel mono (methyl-branched alkyl) glyceryl ether, represented by the formula shown in Scheme 3 (34).

Here we list some alkyl glyceryl ethers with alkyl-branched chains that have resulted from our research.

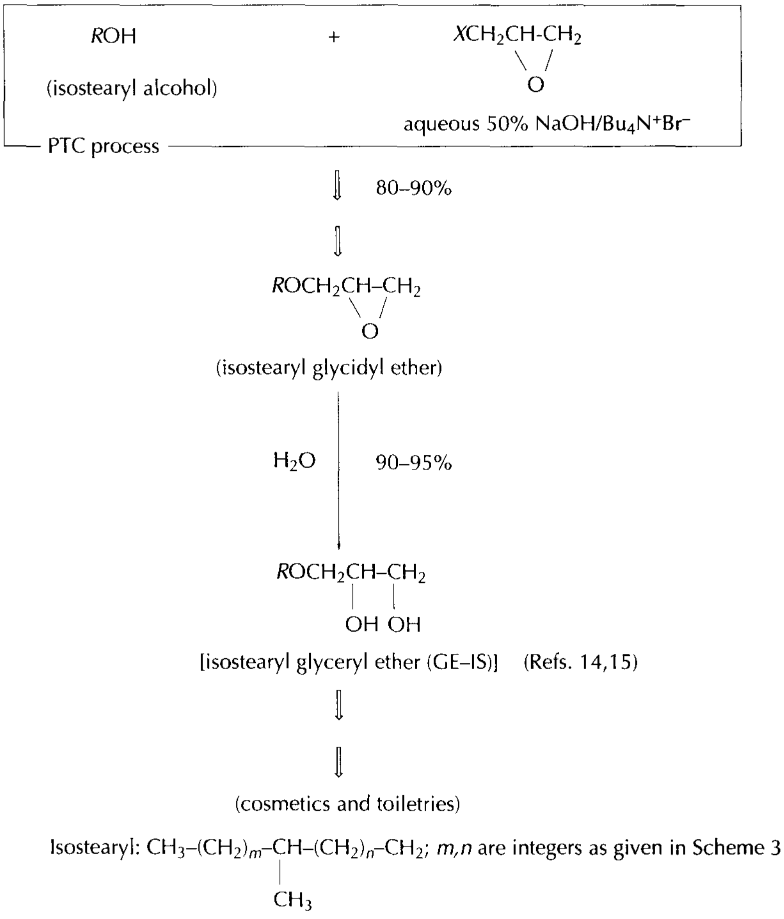
Methyl-branched isostearic acid. During the acid clay-catalyzed dimerization of oleic, elaidic, or tall oil fatty acids to obtain so-called "dimer acids," the monomeric product was gained in moderate yield (~35% of the total) (35). Both Den Otter (36–38) and researchers at Unichema Chemie B.V. (39) characterized the methyl-branched isostearic acid structure:



$$CH_3\text{-}(CH_2)_m\text{-}\underset{CH_3}{CH}\text{-}(CH_2)_nCOOH \qquad [7]$$

The methyl-branched isostearic acid contains about 75% or more of the acid with a total of 18 carbon atoms (i.e., the total of *m* and *n* being 15 in Eq. 7), and the rest was composed of acids with a total of 14, 16, or 20 carbon atoms. The branched methyl groups are located at the central position of the main alkyl chain (35,39–41).

Methyl-branched GE–IS. Methyl-branched isostearic acid or its alkyl esters can be reduced to form the corresponding alcohol in quantitative yields under high pressure (200–250 atm) and high temperature (150–200°C) with the use of a hydrogenation catalyst, e.g., a copper-chromium catalyst. The thus-obtained methyl-branched isostearyl alcohol gave the corresponding glyceryl ether, GE–IS, as shown in Scheme 4 (14,15).



Isostearyl: $CH_3\text{-}(CH_2)_m\text{-}\underset{CH_3}{CH}\text{-}(CH_2)_n\text{-}CH_2$; *m,n* are integers as given in Scheme 3

where PTC is phase-transfer catalyst; *X* represents chlorine.

SCHEME 4

Some physical properties of GE–IS. The solubility of GE–IS in water was investigated by polarizing microscopy, differential scanning calorimetry, electrical conductivity, and binary-phase diagrams of GE–IS and water. GE–IS has a melting point of 23°C, a specific gravity at 30°C of 0.912, and a viscosity at 30°C of 856cP. GE–IS is a surfactant with low solubility in water and forms a lyotropic liquid crystal with a reversed hexagonal structure, even at a low concentration, e.g., GE–IS/water (8–23 wt%:77–92 wt%) in the binary phases (42,43). Further investigation on emulsification of GE–IS showed that GE–IS produced water-in-oil type emulsions, even though the water content of the emulsion was extremely high. Water-in-oil emulsions containing GE–IS had a characteristic stability as the water concentration was increased. The ternary phase diagram, consisting of GE–IS/water/paraffin, showed the formation of a water-in-oil emulsion region with a high concentration of water, where only the reversed hexagonal liquid crystalline and water phases existed. All of the paraffin was completely solubilized into the crystalline phase, and no separation of water and oil occurred (42–44). The electron microscopic studies showed that the interfacial layer between oil and water phases in the emulsion was the liquid crystal. And for higher water concentrations, the continuous phase itself was composed of the liquid crystal. These interfacial layers were mechanically so stable that the water droplets did not coalesce. Thus, water-in-oil emulsions stabilized with GE–IS are water-in-liquid crystal emulsions.

It was reported that polyhydroxyl amphiphiles that form lamellar or columnar liquid crystalline macrostructures are an important class of compounds whose mesogenicity depends on the ability to form hydrogen bonds (45). Amphiphilic alkyl glyceryl ethers may be regarded as the simplest compounds of this type, and the hydroxyl groups are linked through a dynamic network of cooperative hydrogen bonding. So, the stability of liquid crystalline phases is raised considerably by the introduction of the 1,2-diol unit into the molecules (46). Also, in the formation of liquid crystalline phases, molecular self-organization through hydrogen bonding plays an important role, and the phenomenon represents a state of matter characterized by the order and mobility at the molecular level. Recently, Shioya *et al.* (47) observed, by means of electron spin resonance spectra, the increment in the mobility of nitroxy radicals that were modified by stearic acid in reversed hexagonal liquid crystalline phases, formed by the binary system of GE–IS and water.

The water-in-oil emulsion containing GE–IS thus-obtained as a lipophilic surfactant could be utilized for both skin- and hair care cosmetics. Based on the characteristic properties, high concentrations of water in the water-in-oil emulsion could be attained for many types of cosmetics. So, in the following section, we will summarize typical applications of the water-in-oil emulsion with GE–IS as an emulsifier.

Applications of GE–IS for skin and hair cosmetics. This section lists patent applications filed by Kao Corp. of GE–IS for preparations for skin and hair cosmetics (Table 1). The basic concept of our discovery was the formation of stable water-in-oil emulsions based on GE–IS, even in a high concentration of water.

GE–IS could be applied not only for skin and hair cosmetics but also for detergents and pharmaceuticals.

Utilization of dimer acids and their derivatives. GE–IS is a derivative of isostearic acid, which is the by-product in acid-catalyzed dimerization of unsaturated fatty acids. The chemical structures of the dimer acids are now being studied, but have not been fully determined and characterized yet (48–50). However, both the preparation and applications of dimer acid derivatives have attracted much attention. Below, we refer to dimer acid derivatives.

Fuhrhop *et al.* (51) reported that the addition of cyclohexylamine or of the amide formed with aniline-2-sulfonic acid converted dimer acid, the acid itself being water-insoluble, into a vesicle-forming bolaamphiphile. Dimer acid derivatives may be candidates for large-scale applications of vesicles. Related bolaamphiphiles from the reaction of a reduction product of a dimer acid with chlorosulfonic acid and subsequent neutralization tend to form three-dimensional open multilamellar structures (52). Dimer acids can be converted to betaines through a reaction with 3-dimethyl-amino-1-propyl amine, followed by treatment with sodium chloroacetate (53). The detailed study of rheological properties of aqueous dimer acid betaine solutions showed that these systems exhibit strong elastic properties, even at low concentrations. In contrast to cationic and anionic surfactant solutions, the average lifetime of anisometric dimer acid betaine micelles is long. In industry, several applications have been developed over the past three decades. For examples, meadowfoam dimer acids, prepared in a thermal clay-catalyzed reaction (54), and their esters have color, viscosity, and wear-preventive characteristics comparable to those of commercial dimer acids and their esters (55). These dimer acids and their esters have been long used as lubricants (56). Recently, researchers at Henkel KGaA reported the preparation of C_{36}-dimer fatty alcohols with two primary OH-groups by fatty acid hydrogenation technology. The thus-obtained C_{36}-dimer fatty alcohols have no ester groups and are therefore useful for the preparation of polyurethanes resistant to saponification (57).

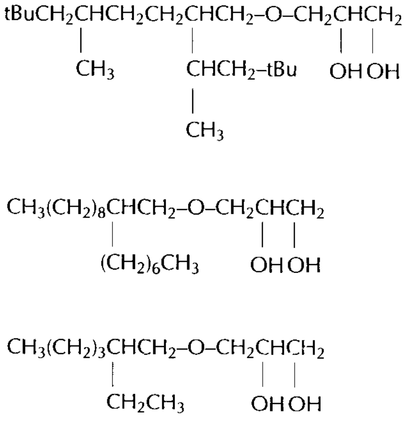
HIGHLY BRANCHED ALKYL GLYCERYL ETHERS

The oxo-reaction of long-chain α-olefins from petroleum can produce alkyl carboxylic acid (known as "oxo-acid") with a one-carbon extension. Oxo-acids, which are now commercially available, can be converted to the corresponding oxo-alcohols by hydrogenation. They, in turn, undergo a Guerbet reaction to give Guerbet alcohols with β-positional alkyl-branching (so-called highly alkyl-branched alcohol) (58). The thus-obtained Guerbet alcohols react, by proprietary synthetic methods with alkyl glyceryl ethers, to obtain the corresponding Guerbet glyceryl ethers at a high yield (59). Typical examples are shown in Scheme 5.

TABLE 1
Isostearyl Glyceryl Ether (GE–IS) Patent Applications Filed by Kao Corporation[a]

Component	Inventions	Patents
Skin cosmetics		
GE–IS	GE–IS as stable nonirritating emulsifier for skin-care compounds	EP25302B US4634719 JP82036260
Salts	Water-in-oil emulsions containing GE–IS and salts	EP25654B US4425329 JP85026366
Esters salts	Cosmetics prepared by emulsifying esters, GE–IS, and salts	JP89009283
Water-insoluble salts	Cosmetic composition comprised of GE–IS and water-insoluble inorganic or organic salts	JP85026367
Waxes	Stick-shaped cosmetic containing GE–IS and beeswax, carnaubawax	JP85003362
Surfactant	Oil-in-water emulsions prepared by GE–IS and hydrophilic surfactants (hydrophilic–lipophilic balance $\ll$10)	JP88014684
Triglyceride	Solid cosmetic preparation comprised cosmetic components, triglyceride, and GE–IS	EP194887B US5011680 JP89044165
Amino acid salts	Oil-in-water emulsion composition comprised of a basic amino acid salt of alkaliphosphate and GE–IS	EP245756B US4776976 JP91033376
Hair cosmetics		
Ammonium salts	Ammonium salt and GE–IS as hair cosmetics	US4486406 JP87001368
Surfactant	Shampoo containing GE–IS and anionic, nonionic, or amphoteric	JP89015482
Alkyl glycoside	GE–IS, alkyl glycoside, and polyol esters for hair treatment	JP87009565
Surfactant polymer	Permanent wave second component containing GE–IS, anionic, or amphoteric surfactant and cationic polymer	JP88052007
Surfactant glyceride	Pearlizing dispersion liquid containing GE–IS, cationic surfactant, and glycerine fatty acid ester	JP92043043
Nonione	Nonsticky hair dressing composition containing GE–IS and polyoxyalkylene alcohol	EP168574B JP92075203
Quaternary ammonium salt	Hair cosmetic composition containing branched quaternary ammonium salt and GE–IS	EP242792B JP94015456
Miscellaneous applications		
Surfactant	Detergent composition for kitchen and tableware containing GE–IS and anionic, nonionic, or amphoteric surfactant	JP84040878
Cation higher-alcohol	Pearlescent liquid suspension comprised of cationic surfactant, higher alcohol, and GE–IS	EP130609B US4544498 JP89041123
Medicine	Xerodermia and other skin disease treatment by transdermal penetration using GE–IS, physiological active material, and oil	EP216303B US4879274 JP90044815
Medicine alcohol	Composition for treatment of mouth disease, containing GE–IS, active ingredient, and alcohol	JP89011613
Cooling agent	Cosmetic material for cooling skin, containing GE–IS, and cooling agents	JP63208505
Silicone oil	Water-in-oil type emulsified material, containing GE–IS and silicone oil	JP93024123

[a] Kao Corp. (Toyko, Japan); EP, European Patent; U.S., United States Patent; JP, Japanese Patent.



$$\mathrm{tBuCH_2\underset{\underset{\displaystyle CH_3}{|}}{C}HCH_2CH_2\underset{\underset{\displaystyle \underset{\underset{\displaystyle CH_3}{|}}{C}HCH_2\text{–}tBu}{|}}{C}HCH_2\text{–}O\text{–}CH_2\underset{\underset{\displaystyle OH}{|}}{C}H\underset{\underset{\displaystyle OH}{|}}{C}H_2}$$

: 5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl glyceryl ether

$$\mathrm{CH_3(CH_2)_8\underset{\underset{\displaystyle (CH_2)_6CH_3}{|}}{C}HCH_2\text{–}O\text{–}CH_2\underset{\underset{\displaystyle OH}{|}}{C}H\underset{\underset{\displaystyle OH}{|}}{C}H_2}$$

: 2-heptylundecyl glyceryl ether

$$\mathrm{CH_3(CH_2)_3\underset{\underset{\displaystyle CH_2CH_3}{|}}{C}HCH_2\text{–}O\text{–}CH_2\underset{\underset{\displaystyle OH}{|}}{C}H\underset{\underset{\displaystyle OH}{|}}{C}H_2}$$

: 2-ethylhexyl glyceryl ether

SCHEME 5

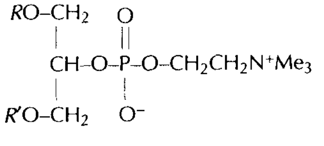
The Guerbet glyceryl ethers obtained with sterically bulky hydrophobic groups, such as branched alkyl chains, which hinder the aggregation of molecules, formed no mesomorphic phases, and no mutual interaction between water and glyceryl ether was observed. Thus, there was no formation of liquid crystals as there was in the case of GE–IS (42). The former two Guerbet glyceryl ethers obtained had high viscosities of 1200–1350 cP at 30°C and are useful as oil components, moisturizers, or emollients for skin cosmetics.

USEFUL ETHER LIPIDS WITH MODIFIED GLYCERYL ETHERS

The two OH-groups present in the glyceryl ether can react with different groups; so, multifunctionalized ether lipids can be obtained. Recent approaches to multifunctionalized ether lipids based on functionally modified glyceryl ether are discussed here in some detail.

PAF and related glyceryl ether phospholipids. PAF interacts with platelets to induce aggregation and secretion of granular constituents. Moreover, it has been established that PAF lowers the blood pressure of artificially hypertensive animals and may be a potent antihypertensive agent (60). Structural elucidation, by examining the effects of enzymic and simple chemical modification on its chromatographic behavior, and its pharmacological action on rabbit platelets were reported in 1979 by Demopoulos *et al.* (61) and Chignard *et al.* (62). On the basis of these data, the structure of PAF was proposed as 1-*O*-alkyl-2-*O*-acetyl-*sn*-3-glyceryl-3-phosphorylcholine with an alkyl chainlength of mainly C_{16} and C_{18}. After these basic approaches, several researchers have been trying to synthesize stereospecific analogs of PAF or of the more pharmacologically active substances similar to PAF. In the course of such approaches to PAF and homologs, the key materials for the syntheses are alkyl or alkenyl glyceryl ethers. van Boeckel *et al.* (63) reported the synthesis of the enantiomer of PAF, 2-*O*-acetyl-3-*O*-hexa-decyl-*sn*-1-glycerylphosphorylcholine, starting from 3-*O*-hexadecyl-*sn*-glycerol and a further phosphorylation process. Researchers for F. Hoffmann-La Roche & Co. have synthesized several types of PAF, starting from long alkyl (64) or alkenyl (65) glyceryl ethers, with *sn*-glycerol skeletons *via* several steps.

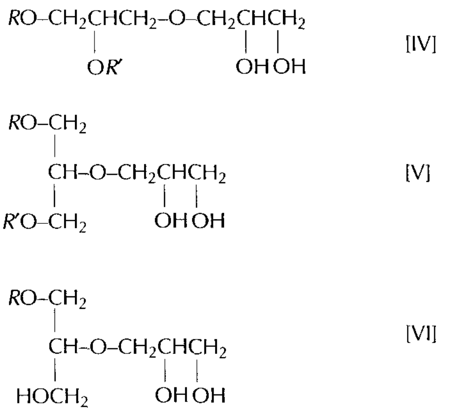
Some comparative studies on the properties of water binding of the ether type of phosphatidylcholine (PC) have also been conducted. Tirri *et al.* (66) reported differences in hydrogen bonding between diether and diester PC and cholesterol. They found that lipid–lipid hydrogen bonding has become difficult or impossible in the diether-PC/cholesterol membrane. The cholesterol-OH can neither approach the phosphate because the hydrophilic character of the glyceryl ether system forces the cholesterol to retreat into the membrane, nor can it easily bond to the ether oxygens because they are weaker hydrogen bond acceptors than the ester C=O bond and are sterically not as readily accessible; space-filling molecular models make this apparent. As a result, the cholesterol O–H bond is no longer mostly latitudinally oriented, the alignment of the water molecules is upset, and the entropy content of the system is increased, they speculated (66). Analogous evidence concerning the difference in the water-binding properties between ether- and ester-PC compounds has been reported by Wong and Mantsch (67). They rearranged a lipid in which the *sn*-ester linkage of *sn*-1,2-dipalmitoylphosphatidylcholine (DPPC) was replaced by a ether linkage—1-*O*-hexadecyl-2-*O*-palmitoylphosphatidylcholine(HPPC). This experiment indicated that no hydrogen bonding occurred between the water molecules and the ether oxygen bond of HPPC. Ruocco *et al.* (68) reported that calorimetric, X-ray diffraction, and ^{31}P NMR studies of aqueous dispersions of 1,2-dihexadecyl-*sn*-glycero-3-phosphorylcholine (DHPC) gel phases at low temperatures (–60 to 22°C) showed thermal, structural, and dynamic differences when compared to aqueous dispersions of DPPC gel phases at corresponding temperatures. Differential scanning calorimetry of DHPC dispersions demonstrated a reversible, low-enthalpy "subtransition" at 4°C, in contrast to the conditionally reversible, high-enthalpy subtransition observed at 17°C for annealed DPPC bilayers. A comparison of X-ray diffraction and ^{31}P NMR spectral data between DHPC and DPPC suggested the presence of fast axial diffusion of DHPC in the lamellar gel-phase bilayers at all temperatures below the pretransition point. In contrast to this, the motion of DPPC in the lamellar gel-phase bilayers was frozen at ~0°C. Some choline glycerophospholipids were isolated from the marine annelid *Marphysa sanguinea* (69). These lipids contained lyso-PAF and 1-hexadecyl-2-arachidonyl- and 1-hexadecyl-2-eicosapentaenoyl-*sn*-glycero-3-phosphocholine, which are regarded as stored precursor forms of PAF. We have also been interested in the ether-type phospholipids for pharmacological uses. We focused on ether phospholipids based on 1,3-di-*O*-alkyl-glycerol-2-PC, different from natural forms. These di-*O*-alkylglycerol-2-PC (Scheme 6) were prepared by phosphorylation of 1,3-di-*O*-alkyl-glycerols according to known methods (70). These novel ether phospholipids [III] (Scheme 6) exhibited anti-inflammatory, analgesic, and antimicrobial activities (70). No mortality occurred at a dose of 2 g/kg in ICR mice. [III] (Scheme 6) may be administered orally, externally, by injection, or in the form of suppositories, at 0.1–1000 mg/kg/day orally, 0.01–1000 mg/kg/day by injection, or 0.01–10 wt% preparations for external applications. Ether lipids and analogs related to PAF have been tested for direct cytotoxicity in cells from human solid tumors and leukemias by using [^{3}H]thymidine uptake, trypan blue dye exclusion, human tumor clonogenic assays, and cell morphology as criteria. Certain 1-*O*-alkyl-lysophospholipids and *sn*-2-analogs



$$\begin{array}{l} RO\text{–}CH_2 \quad\;\; O \\ \quad | \qquad\quad\;\; \| \\ CH\text{–}O\text{–}P\text{–}O\text{–}CH_2CH_2N^+Me_3 \\ \quad | \qquad\quad\;\; | \\ R'O\text{–}CH_2 \quad\;\; O^- \end{array}$$

[III]

SCHEME 6



SCHEME 7

of PAF were found to be cytotoxic in a dose- and time-dependent fashion (71–74).

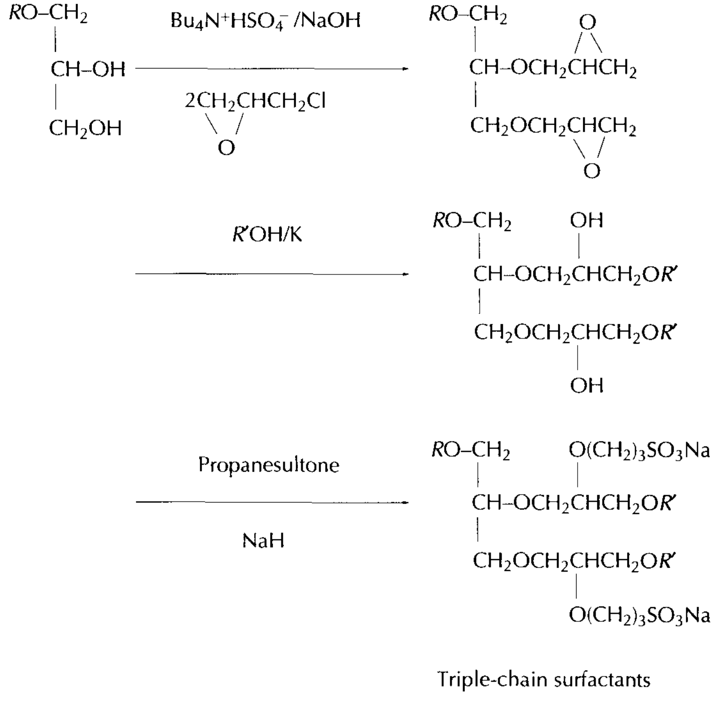
Recently, Ladika *et al.* (75) have reported highly stable liposomes, made from macrocyclic diyne phospholipids. These phospholipids are similar to those lipids of thermoacidophilic bacteria, which are fully functional at temperatures of up to 90°C and at external pH values as low as 0.5. Lipids of those bacteria have hydrocarbon chains that are linked to the glycerol backbone by means of ether groups, and those chains are frequently joined to form macrocycles.

Surfactants based on alkyl glyceryl ethers with hydroxyl groups as hydrophilic moiety. Alkyl glycerol homologues, diglyceryl alkyl ethers [IV]–[VI] (Scheme 7), were derived through the reaction of alkyl glycidyl ethers with glycerol (15). Typical compounds are shown in Scheme 7. The solution behavior in water of [IV]–[VI] was investigated by determining their binary phase diagrams. Each alkyl diglyceryl ether formed a lamellar liquid crystalline phase, even at a low concentration. However, their solution behavior was different (76).

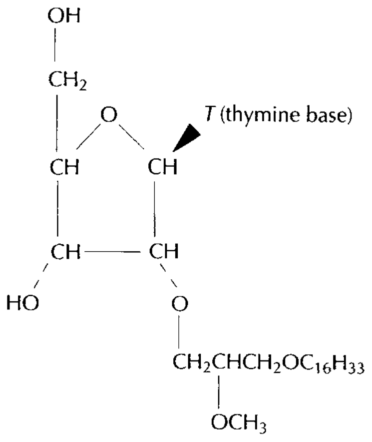
Also, in connection with further extension to the ether lipids of glycosides, stereoselective syntheses of long-chain 1-*O*-(β-D-maltosyl)-3-*O*-*sn*-glycerols (alkyl glyceryl ether lysoglycolipids) were reported (77). Some properties of these amphiphilic compounds with nonionic carbohydrate head groups do not differ much (critical micelle concentration, hemolytic activity), whereas other properties differ greatly (antitumor efficiency) from those of analogous compounds with Zwitterionic phosphorylcholine head groups.

Glycerol-based double- or triple-chain surfactants with two hydrophilic ionic groups. A novel series of glycerol-based double- or triple-chain surfactants with two sulfonate, two sulfate, or two carboxylate groups have been prepared, and their surface-active properties were determined by researchers at Osaka University (78–81). For example, triple-chain surfactants with two sulfonate groups could be obtained from alkyl glyceryl ether as shown in Scheme 8.

The triple-chain surfactants exhibited excellent surface-active properties, such as micelle-forming and surface tension-lowering ability, compared not only with the corresponding single-chain anionic surfactants, but also with the corresponding double-chain surfactants. The group at Osaka University is now making progress toward preparation and analyses of homologous series of novel multichain-containing amphiphiles that bear multi-ionic head groups derived from polyols (80).



SCHEME 8

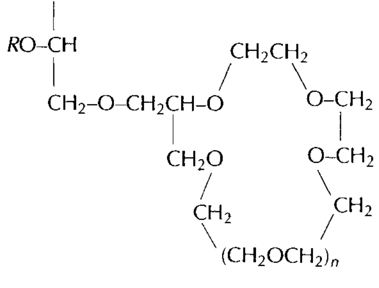


SCHEME 9

Membrane mimetic chemistry based on glyceryl ether. Moss *et al.* (82,83), with much interest in membrane mimetic chemistry based on pseudoglyceryl lipids, have studied the correlation of lipid molecular structure with various properties of the assembled aggregates in relation to the parts of the lipid structure—chain, backbone, head group, and the chain-backbone linkage unit. They found that pseudoglycerylammonium ion lipids bearing ether linkages displayed less resistance to thermally driven lipid flip-flop than liposomes constructed of similar lipids with ester linkages. They proposed that superior dynamic resistance of the ester lipids was attributable to the stabilization of their bilayers *via* C=O/water H-bonding networks that originate at the acyl moieties. This conclusion is the same as that mentioned earlier (66).

Miscellaneous modified glyceryl ethers. Recently, researchers at Ciba AG (Basel, Switzerland) invented a novel nucleoside with a long-chain alkyl glyceryl ether skeleton, which is particularly useful for studying gene expression in a selective and well-defined manner (84) (Scheme 9).

Crown ethers are well known as chelating or enveloping compounds of several types of inorganic or organic substances. Okahara and Masuyama (85) prepared novel surfactants with complexing ability, such as amphiphilic crown ether compounds, based on an alkyl glyceryl ether skeleton (Scheme 10).



SCHEME 10

ETHER LIPIDS IN THE DIET OF HUMANS

Ether lipids that occur in various tissues of animals, such as rats and mice, have been well characterized. In contrast to this, little is known regarding the ether lipids found in human food and animal feed. A survey of the literature on ether lipids in food and feedstuff was published by Mangold in 1983 (86). Also, dietary ether lipid incorporation into tissue plasmalogens of humans and rodents has been reported (87).

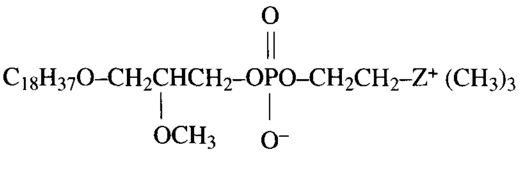
There is no doubt that ether lipids are present in plant foods only in trace amounts. However, it is as yet unknown why ether lipids are ubiquitous constituents of human and animal tissues, and also of a large variety of microorganisms, but not of plants. Large proportions of neutral ether lipids are present in the liver of some sharks, as already mentioned. For example, alkyl-di-acyl glycerols occur in high proportions in the liver of some selachian fish, such as *Squalus acanthias* and *S. suckleyi,* which consist of about 45% neutral ether lipids. The liver lipids of the Atlantic and Pacific ratfish, *Chimaera monstrosa* and *Hydrolagus colliei,* respectively, consist of 60–70% ether lipids, as well. Ratfish liver oil is the richest source of alkyl (or alkenyl) diacylglycerols known. Shark meat is used as human food and animal feed in many parts of the world. In Europe, for example, smoked fillets prepared from dogfish and dusky shark are well known and accepted as seafood. Some reports claim that ratfish and some other sharks, such as the Greenland shark, are unfit for human consumption. Mangold (86) reviewed other reports on ether lipids in human food and animal feed.

Trialkyl glycerols with long alkyl chains are neither cleaved in the alimentary canal nor absorbed intact. But trialkyl glycerols are nontoxic and, because they do not affect the absorption of fats and fat-soluble vitamins, edible fats can be diluted with ether lipids to reduce their caloric content without significantly changing their physical or organoleptic properties (86). Knowledge of nonnutritional factors found in ether lipids has been extended to nonfattening fats that are made from fully esterified sorbitol and sucrose. They appear to be the compounds most suitable for use as nonfattening fats (88,89).

FUTURE POSSIBILITIES FOR ETHER LIPIDS AS POTENTIAL LIPIDS

Over the last several decades, most researchers in oleochemistry have shown interest in lipids that are essentially based on glycerides (mono-, di-, and tri-). However, as mentioned previously, many types of naturally occurring lipids as minor components are not as well known. Alkyl glyceryl ether compounds are just one type of such unique lipids used in our daily lives. The existence of ether bonds which are resistant to hydrolysis and chemically stable makes it possible to apply this class of materials under drastic environmental conditions (90). Alkyl glyceryl ether lipids that are found in membranes of archaebacteria are such typical lipid molecules. The high resistance to hydrolysis, because of the ether linkage, makes it possible to apply alkyl glyceryl ether as emulsifier in both water-in-oil and oil-in-water emulsions. Especially the stable liquid crystalline phase, based on the reversed or lamellar state in water-in-oil emulsions, induced much progress in the cosmetic industry.

We anticipate many new uses of ether lipids based on the alkyl glyceryl ether skeleton and propose how to solve problems in some detail: (i) We can now produce special fatty acids, such as branched fatty acids, artificially on an industrial scale. These artificial special fatty acids add unique properties not found in natural fatty acids. Branched alkyl glyceryl ethers derived from these artificial special fatty acids might have more interesting chemical, physical, or pharmacological properties. (ii) Phospholipids based on the alkyl glyceryl ether skeleton, such as PAF, have been of much interest in the medical field. However, until now, few researchers have found applications in medicines or phamaceuticals in our daily lives. The search for physiologically active phospholipids should be continued. In this connection, Stekar *et al.* (91) have recently reported novel phospholipids with nitrogen homologues:



$$C_{18}H_{37}O{-}CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2{-}O\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle O^-}{|}}{P}}}O{-}CH_2CH_2{-}Z^+(CH_3)_3$$

[8]

Phospholipids with Z=P or As have been demonstrated to have antineoplastic activity comparable to that of the N-containing parent phospholipids, *in vitro* and in rats with dimethylbenz[a]anthracene-induced tumors. Phospholipids containing arsenic (Z=As) are less toxic to mice than cholinephospholipids (Z=N), despite the fact that arsenic compounds are generally quite poisonous. (iii) Amphiphilic surfactants with a glycerol-based double- or triple-alkyl chain (so-called "Geminis surfactants") have been of much interest in surface chemistry in recent years. This suggests the possibility that alkyl glyceryl ether lipids may reform hitherto known surfactants. (iv) Liquid crystals formed by alkyl glyceryl ether may be useful as display materials in the electric and computer industries. We have already discovered that aqueous solutions of 1–2% of 1,3-di-*O*-alkyl-2-*O*-glycerol-glycerin showed coloration that changed with surfactant concentration. These surfactants form lamellar liquid crystals, and the coloration appears to arise from the interference of light reflected at the interface of lamellar layers whose thickness is comparable to that of the wavelength of visible light (92). These facts suggest that the alkyl glyceryl ether can be used as a color display material in place of hitherto known liquid crystals. Further molecular modifications of the ether lipids based on alkyl glyceryl ether skeletons should be attempted.

Ether lipids have great potential for use in our daily lives and in industry, but more research and development needs to be conducted on a worldwide scale.

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