New speciality surfactants with natural structural motifs

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The interest in designing highly specialised synthetic surfactants incorporating natural structural motifs has increased remarkably during the last few years. The variety of naturally occurring structures used as parts of such "designer surfactants" ranges from simple amino acids and short peptides over carbohydrates to steroids. Surely, one of the most prominent examples in this respect and probably the breakthrough for tailor-made surfactants in highly specialised applications was the use of a surfactant for the first successful crystallisation of a membrane protein, a great feat for which the Nobel Prize in Chemistry was awarded in the year 1988. Moreover, the ability of certain specialised surfactants to accelerate the transport of genetic material or drugs through biological membranes is widely taken advantage of in biotechnology and pharmacy. The most important applications for surfactants, however, are related to their self-organisation in solution. Self-organisation leads to the formation of micelles, liposomes, lyotropic liquid crystalline phases, and microemulsions. These self-organised structures are used for solubilisation, transport, and separation processes, as templates for nanoparticles, as models for biomembranes, and as reaction media, to mention just a few. In all these applications surfactants designed on the basis of natural compounds are either desirable or even indispensable. An overview of some of our recent synthetic work in the field of "new speciality surfactants with natural structural motifs", partly taking advantage of the "chiral pool", will be given and future perspectives will be discussed.

1 Introduction

The global output of surfactants is tremendous. The total production of surface active agents (surfactants) was about 17

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million tonnes in the year 2000.[1] The large demand for surfactants urgently calls for sustainable surfactants made from renewable raw materials to reduce the impact on the environment and to save fossil resources. Thus, it is not astonishing that in the last two decades academic institutions and industry have focused on surfactants containing natural structural motifs. The low toxicity, the good biocompatibility and fast biodegradation of many surfactants that are made of natural building blocks like amino acids, sugars and fatty acids, together with the possibility of a sustainable production from renewable sources are the main reasons for the increasing industrial interest in these compounds. The major part of surfactants currently produced is used in cleaning and washing agents. It is the self-organisation that leads to the wetting of surfaces, to foaming, and to the dispersion of solid particles, *i.e.* to processes that are central to cleaning and washing. Apart from these everyday uses, several surfactants containing natural structural motifs lend themselves to highly specialised applications. Again, the exceptional characteristics of surfactants in all these applications are closely related to their ability to organise themselves in supramolecular architectures.

We will start this perspective by outlining the most important principles of self-organisation of surfactants. After that we will describe a number of advanced applications of specialised surfactants. In all these applications surfactants derived from natural compounds are of utmost importance because of their relatively low impact on the environment (see *e.g.* the studies on alkyl polyglycosides[2]). It is worth mentioning that there are a number of interesting and useful examples of oligo- and polymeric carbohydrate- and amino acid-derivatives surfactants, some of which are gained solely from natural sources[3] (*e.g.* Surfactin®, an acylpeptide produced by *Bacillus subtilis*). This area, however, will not be dealt with in the present paper. What we will concentrate on are selected low molecular weight surfactants containing structural motifs of natural compounds. Examples will be given where either the hydrophilic head group or the hydrophobic tail is made of a natural compound. Considering the syntheses routes presented in the paper at hand it is clear that large scale production is impossible in view of the high costs. Thus the suggested surfactants are examples of speciality surfactants and should find their use in high-price, specific applications. However, once we know more about the properties of the terpene- and/or inositol-based surfactants a demand for large-scale production might arise. In this case, routes to synthesise these—or similar—surfactants on a large scale need to be developed.

2 Self-organisation of surfactants

The outstanding properties of surfactants are closely related to their exceptional ability to self-organise. While it is clearly beyond the scope of this perspective to provide an in-depth insight into molecular self-organisation it is inevitable to outline at least the most relevant supramolecular principles (without any claim to, or attempt at, completeness) to facilitate an understanding of later discussions. It is mainly the amphiphilicity of surfactants that determines their ability to build complex supramolecular structures like micelles, liposomes, lyotropic liquid crystalline phases or microemulsions, all of which will be described in the following. Of particular interest from a synthetic chemistry point of view is the fact that the amphiphilicity can be tuned *via* the molecular structure, *i.e. via* the balance of hydrophilic and hydrophobic parts.

2.1 Micelles and vesicles

In aqueous solutions surfactants usually adsorb at the water/air surface, thus lowering the surface tension. Increasing the surfactant concentration one finally reaches a concentration (critical micelle concentration, cmc) at which surfactants start to form spherical or ellipsoid agglomerates which are called micelles (*cf.* Fig. 1).

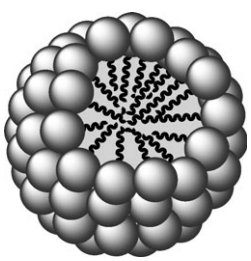


Fig. 1 Schematic drawing of a micelle. The amphiphilic molecules are symbolised by a sphere representing the hydrophilic head group and a wavy line representing the lipophilic part.

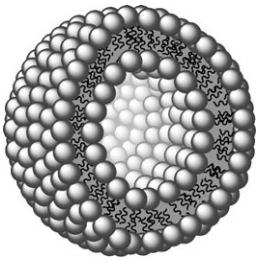


Fig. 2 Schematic drawing of a unilamellar vesicle. The membrane consists of a double layer of amphiphilic molecules. The hollow inside is filled with the solvent and effectively sheltered from the surrounding media.

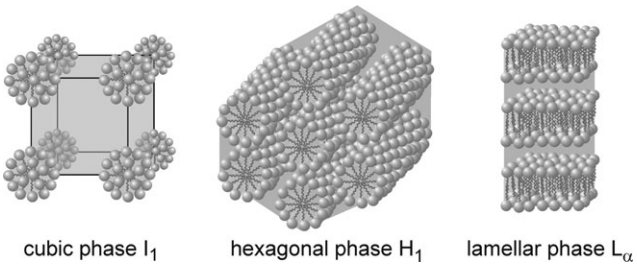


Fig. 3 Three different structures of lyotropic liquid crystalline phases. The cubic phase I_1 consists of spherical micelles (left); the building blocks of the hexagonal phase H_1 are cylindrical micelles (middle); and the lamellar phase L_α consists of stacked surfactant bilayers (right). Examples of inverse structures and nematic phases are not given. In binary water–surfactant systems the structure of the lyotropic liquid crystal can be tuned by the molecular structure of the surfactant, the temperature, and the surfactant concentration.[6]

Under certain conditions surfactants can form vesicles, which consist of surfactant bilayers that are filled and surrounded with the same solvent, usually water (*cf.* Fig. 2). Vesicles are divided into multilamellar vesicles (MLV, many surfactant bilayers surrounding the inner compartment like an onion), large unilamellar vesicles (LUV, interior coated by a single bilayer, mean diameter of more than 100 nm, up to microns), and small unilamellar vesicles (SUV, mean diameter of about 15–50 nm, up to 100 nm). The specific type and mean diameter of vesicles are very much dependent on the preparation procedure, the composition, and the concentration of the surfactant or surfactant mixture, the temperature, the sonication time, power and volume, or the extrusion filters, pressure *etc*.

2.2 Lyotropic liquid crystals

Generally speaking, lyotropic liquid crystals are formed by dissolving surfactants in suitable solvents in clearly defined concentration and temperature ranges. As the concentrations are far beyond the cmc it is now the micelles that self-organise, thus forming a supramolecular structure. The nature and structure of the resulting lyotropic liquid crystal depend, not only on the surfactant concentration and the temperature, but also on the molecular structure. Lyotropic liquid crystals are usually denoted by a capital letter, namely by I (discontinuous cubic), H (hexagonal), V (bicontinuous cubic), and L (lamellar).[4,5] Furthermore, lyotropic liquid crystals are divided into normal (subscript 1 or I) or inverse (subscript 2 or II) subtypes, indicating whether the surfactant monolayer is curved towards the apolar (normal) or the polar (inverse) sub-phase. A Greek letter as subscript denotes the state of the alkyl chains (α: liquid-like, β: ordered gel-like). A selection of some well-known lyotropic liquid crystals is shown in Fig. 3.

2.3 Microemulsions

Another type of supramolecular organisation called microemulsions might occur in ternary systems composed of oil, water, and surfactant. Microemulsions are thermodynamically stable phases that form spontaneously under well-defined conditions. The surfactants adsorb at the interface between the oil and the water sub-phase, thus forming a protective layer. Since surfactants may decrease the interfacial tension between water and oil down to 10^{-4} mN m^{-1} the thermal energy kT is sufficient to mix the otherwise immiscible phases.

The simplest structures formed in microemulsions are oil-in-water or water-in-oil droplets as depicted in Fig. 4. However, more complex structures such as cylindrical aggregates or bicontinuous sponge-like structures are also formed.

3 Special applications of surfactants

The above-mentioned abilities of molecular self-organisation, in combination with the selective affinities of the antagonistic molecular parts of surfactants, lead to various highly specialised, interesting applications far beyond the everyday utilisation of surfactants in detergents. Some examples will be given in the following.

3.1 Supramolecular structures as templates for nanomaterials

Lyotropic liquid crystals are used as templates for the formation of nano- or mesoporous materials which may be applied in catalysis, adsorption, membrane and separation technologies. For example, the hydrophilic sub-phase of the lyotropic

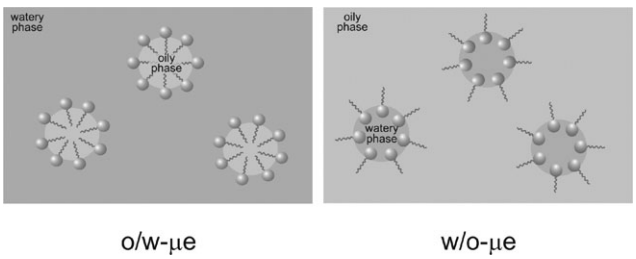


Fig. 4 Two different structures of microemulsions. The oil-in-water droplet microemulsion (o/w-μe, left) consists of oil droplets dispersed in an aqueous phase, while in the inverse water-in-oil microemulsion (w/o-μe, right) water droplets are the dispersed phase. In both cases the formation of the microemulsion is mediated by a surfactant which suitably covers the interface between both immiscible liquids. The droplet diameter is around 5–10 nm. A further swelling of the droplets with oil and water, respectively, leads to a change of the structure, *i.e.* to the formation of cylindrical and/or bicontinuous supramolecular structures. Examples of the latter are not given here. In ternary water–oil–surfactant systems the structure of the microemulsion can be tuned by the molecular structure of the surfactant, the temperature, and the composition.[7]

liquid crystal can consist of polymerisable—often inorganic—components so that the resulting polymer resembles a cast of the liquid crystalline structure. With this technique the topology and the domain sizes of the resulting porous material can be tailored by choosing and modifying the templating phase. Typical pore sizes are in the range of 1.5 to 10 nm. The most prominent example of such an application is the production of the mesoporous material MCM-41 using a hexagonal lyotropic liquid crystalline phase (H_1).[8,9]

However, it is not only lyotropic liquid crystals that are used as templates for new materials; microemulsions can also serve this purpose (reviewed in ref. 10). For example, the synthesis of nanoparticles *via* water-in-oil microemulsions is a widely used method (reviewed in ref. 11). For that purpose two microemulsions of equal structure are mixed, one of which contains a metal salt and the other a reducing agent. With this technique nanoparticles as small as 5 nm in diameter and of a very narrow size distribution can be obtained. Last but not least, microemulsions can be used as reaction media, *e.g.* as ''nanoreactors'', in which reactions between water-soluble and water-insoluble components can be carried out.[12]

3.2 Protein crystallisation

Another outstanding field of application of specialised surfactants is in the crystallisation of integral membrane proteins. In this case the surfactant is used to solubilise an integral protein from a biological membrane by covering its hydrophobic surfaces. Besides, the ''membrane-mimicking'' aggregation of the surfactant at the hydrophobic parts of the protein also stabilises the natural and functional state of the protein to a certain extent. Given a suitable size and uniformity of the resulting protein–surfactant complexes these may—under appropriate conditions—crystallise in an ordered lattice suitable for high-resolution structure determinations (*cf.* Fig. 5). The exact assembly of the resulting complex, *i.e.* how surfactants cover the lipophilic parts of the protein, is assumed to be either micellar[13] or monolayer-like.[14]

However, the solubilisation procedure puts a heavy strain on the membrane protein because the surfactant cannot entirely replace a natural bilayer. Surfactants with a high cmc would be desirable for protein crystallisation since their high monomer concentration in solution and usually smaller micelles simplify the removal of excess surfactant by dialysis, which is frequently necessary during the crystallisation process. Unfortunately the high cmc is connected to a low affinity of these surfactants with the protein, which, in turn, implies that the resulting complexes are dynamic and fluctuating, sometimes exposing the hydrophobic parts of the protein to the aqueous phase. This may lead to a destabilisation of the membrane protein and possibly to a rearrangement of its structure (denaturation).[15] To prevent this, often low cmc surfactants are required, better mimicking the natural bilayer and thus helping to keep the protein in an active form. Beyond this, the native biological membrane exerts a lateral pressure on the integral protein which is largely reduced during the surfactant-induced solubilisation which again possibly leads to denaturation.[16]

In summary, the crystallisation of membrane proteins is still exceedingly challenging and demands sophisticated procedures and profound knowledge. A compilation of practical hints and further literature can be found in the references.[15,17–19]

The surfactants used in the classical ''micellar'' type of membrane protein crystallisation are almost exclusively single-chained surfactants with an uncharged or zwitterionic hydrophilic head group. The length of their alkyl chain usually lies between heptyl and dodecyl, *i.e.* 7–12 carbon atoms long. Some of the most common surfactants used for such purposes and containing a natural substructure are octyl-β-D-glucopyranoside (**1**) or decanoyl-*N*-methylglucamide (**2**), depicted in Fig. 6. Often the surfactants are used in mixtures with amphiphilic

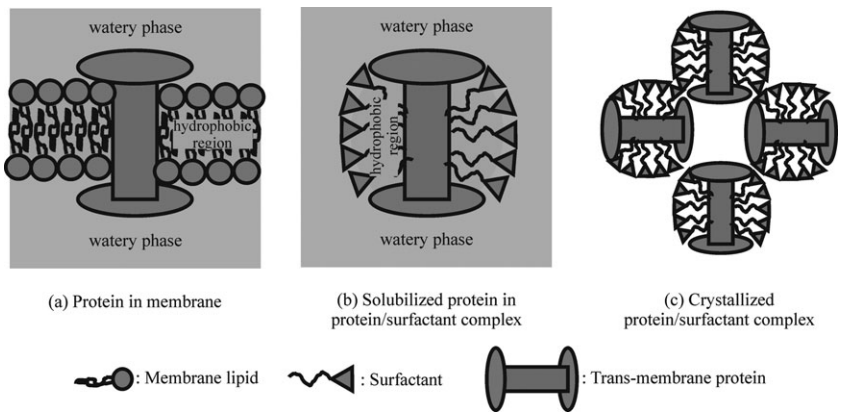


Fig. 5 Membrane proteins are fixed in cellular membranes mostly because of their amphiphilic nature. Hydrophilic parts of the protein reach into the aqueous cytosol or interstice while their nonpolar membrane-spanning part resides in the lipophilic inner part of the membrane bilayer (a). Such proteins are notoriously hard to crystallise. A breakthrough in the crystallisation procedure was the solubilisation of membrane proteins by surfactants in protein–surfactant complexes (b). The scheme shown here is merely intended to illustrate the solubilisation principle; the possible structures of protein–surfactant complexes are discussed in the literature.[13,14] The protein–surfactant complex may also protect the overall structure of the protein, preserving its functional conformation, though it has to be mentioned that this is not always the case and denaturation may occur. Given a suitable size and shape, these protein–surfactant complexes might be precipitated in three-dimensional ordered crystals, suitable for high-resolution structure determination (c).

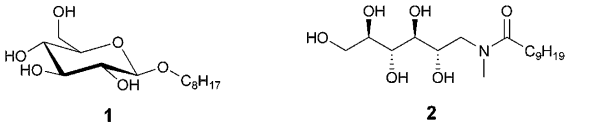


Fig. 6 Structures of two single-tailed surfactants often used for membrane protein crystallisation, both containing natural building blocks as the hydrophilic head group.

additives, like *e.g.* heptanetriol, in order to fine-tune their self-assembly properties. Such additives are called co-surfactants.

One of the most prominent examples of a successful crystallisation of a membrane protein is the crystallisation of bacteriorhodopsin with the help of octyl-β-D-glucopyranoside (**1**).[20] Two years later[21] the photosynthetic reaction center of the bacterium *Rhodopseudomonas viridis* was crystallised and its structure was resolved, for which H. Michel, J. Deisenhofer, and R. Huber, received the Nobel Prize in Chemistry in 1988.[22] However, the method still has its drawbacks and two important developments circumvent some of the problems which often occur during classical micellar crystallisation: the lipidic cubic phase crystallisation[23] and the bicelle crystallisation.[24] Both methods often employ double-tailed, lipid-like surfactants and make ample use of their supramolecular aggregation properties and phase behaviour.

3.3 Transfection

Another biochemical use of specialised surfactants is their application in transfection, *i.e.* the transport of genetic material through biological membranes into eukaryotic cells.[25] This technique is particularly important for potential gene therapy purposes or in biotechnology. A variety of methods to achieve transfection are known, *e.g.*[26] the use of viruses or liposomes. Of course, each approach has its particular advantages and disadvantages. The use of viruses is the most efficient method in terms of successful gene expression[27] and furthermore often allows specific tissue targeting. The main disadvantages of this technique are the limited size of the transferable genetic material, the remaining possibility of an immunological response to the residual virus capsid and the labour-intensive production and safety aspects.[28] From this point of view it is clearly desirable to develop non-viral vectors which avoid these problems. The employment of surfactants, in the form of unilamellar or multilamellar liposomes, as carriers for the genetic material is one such possibility and known as lipofection.[28–38] (Note that also surfactant-based but non-liposomal transfection reagents are known and commercially promoted.)

The advantages of lipofection are the absence of any viral components and thus a significantly lower danger of immunological responses, a high viable payload of genetic material and a comparatively effortless procedure.[28] Furthermore, in contrast to some virus-based methods, lipofection hardly leads to the integration of the genetic material into the cell genome, which thus cannot replicate, recombine or lead to tumorigenic mutations. Conversely, the missing integration of the genetic material into the host DNA may also be seen as deficiency for some curative purposes. A difficult but exceedingly important and ongoing topic of the research on liposomal gene or drug delivery is tissue targeting, *i.e.*, the pre-programming of the liposomes in order to consign the load to specific types of cells.[39]

The mechanism of lipofection is quite complex and still not entirely understood in detail. However, certain steps are decisive and must be performed by the gene carrier so that, in the case of liposomes, the applied surfactants play a crucial role. Initially, the dissolved genetic material has to be compacted by complexation and its negative charge, originating from the phosphate groups of the DNA/RNA backbone, must be (over-)compensated. The resulting complex of the genetic material with the liposome (lipoplex) stabilises the nucleic acid against degradation and promotes the interaction with the negatively-charged cell membrane, eventually leading to the incorporation of the lipoplex into the cell.[40] Shortly after the endocytosis has been completed, at the right time, the genetic material must be released into the cytoplasm before the endosome can be transported to the lysosomal machinery of the cell which otherwise would lead to the destruction of the genetic material.

Cationic surfactants, occasionally in combination with neutral surfactants, can accomplish these demands and various surfactant mixtures are commercially available as transfection reagents. However, cationic surfactants occasionally turned out to be toxic and thus a large number of new surfactants is steadily being synthesised and investigated, with a view to reducing toxicity, to further optimising transfection efficiency, to elucidating further mechanistic details or to overcoming the remaining drawbacks of lipofection. A number of structurally different surfactants have been developed, most of them containing one or more ammonium functions as cationic groups, among them dimethyldioctadecylammonium bromide (DDAB) or decamethonium bromide (DMB). A modern and highly interesting transfection efficient class of surfactants are the so-called gemini-surfactants,[36,41–46] the principal composition of which is depicted in Fig. 7 together with some typical sample structures, **3** and **4**.

The design of gemini-surfactants takes the specific demands of transfection into account. The respective substructures of the surfactants should be similar to natural metabolites in order to decrease toxic effects while the distance between the cationic centres should resemble the distance of their negative counterparts in DNA ($n \approx 6$ in **3** and **4**). The amine functions can be protonated at distinct pH according their specific pK_a

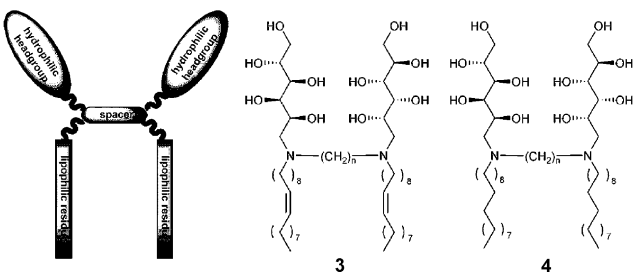


Fig. 7 Principal design of a gemini-surfactant and two exemplary structures, **3** and **4**.[43,45] The surfactant **3** is about six-fold more transfection active than its saturated analogue **4**.

values. Ideally, the first amine function is protonated before or during the complexation of the DNA/RNA, generating the necessary positive counter-charge. A further decrease of the pH, *e.g.* inside the cell, partly protonates the second amine function and possibly changes the type of phase from condensed lamellar (L_α) in the lipoplex to an inverted hexagonal (H_2) phase, which promotes the release of the genetic freight.[45,46] A comparison of **3** with its approximately six times less active saturated analogue **4** shows that the double bonds in the lipophilic residues of **3** are important. Probably this structural feature reduces the intercalation of the lipophilic side chains of **3** in the membrane (L_α phase) of the lipoplex, facilitating the aforementioned phase transition from L_α to H_2.[46]

4 Surfactants containing a natural structural motive

As can be seen from these examples of specialised surfactant applications, the most important features of surfactants are doubtlessly related to their supramolecular abilities in solution. It has to be kept in mind, however, that these properties do not only depend on the hydrophilic but also on the hydrophobic part of the surfactant. It is a delicate balance between the hydrophilic and the hydrophobic parts of the molecule that determines the final properties. This is not to be seen as a drawback but rather as an advantage as it allows us to "design" properties *via* the molecular structure of the surfactant. The detailed in-depth understanding of the relevant interactions and of the processes and dynamics associated with surfactant–solvent systems is thus of utmost scientific and technological importance. Our work is dedicated to the fundamental research on the principles of self-organisation of surfactants, including the development and synthesis of new such materials. As the previously outlined examples show, surfactants containing substructures similar to natural compounds are of high interest. Not only because they can perform highly specialised functions; they also can be synthesised from renewable materials and are, for the most part, environmentally friendly. Since nature offers an overwhelming variety of different structures appropriate for designing new surfactants and numerous groups are working in this field with considerable results under manifold aspects it is beyond the scope of such a short review to give a comprehensive overview. In the following we will therefore concentrate on surfactants containing some selected structural motifs of natural compounds which from our point of view are of special interest and thus form the focus of our work. However, additional reviews on related topics are given in the references.[3,5,47–50] In the following we will first report on surfactants for which the head groups are made of a natural compound (Section 4.1). In the second part, surfactants will be described which contain a hydrophobic tail possessing a natural archetype (Section 4.2).

4.1 Surfactants containing a natural hydrophilic head group

The hydrophilic head group of a surfactant can be synthesised from fossil fuels or from renewable raw materials. An example of the former group is poly(ethylene glycol), while examples of the latter are carbohydrates and amino acids. Surfactants that contain one or more amino acids as hydrophilic parts have most of the desirable properties which today's research interest is focused on. Mostly they are biodegradable, biocompatible, renewable and easily accessible. Furthermore, such molecules are able to mimic natural amphiphilic structures and therefore used in the food, pharmacy and cosmetic industry sectors. Moreover, some amino acid-based surfactants have been found to be effective against viruses, bacteria and even tumors. Lately, they have also been used in medicinal applications like gene transfer or as antiviral drugs.[50]

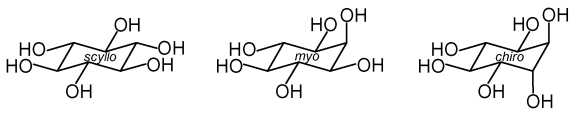
Carbohydrates are one of the most prominent classes of natural hydrophilic head groups. Currently nonionic sugar surfactants are produced in Germany at a rate of approximately 35 000 tonnes per year.[51] Alkylpolyglucosides and *N*-alkylglucamides are mainly used as surfactants in new detergents and as saccharose fatty-acid esters in cosmetic products. Compared with other nonionic surfactants like poly(ethylene glycol) alkyl ethers, the sugar-based surfactants are often superior in their physicochemical properties.[2,52,53] Generally speaking, they are relatively insensitive to temperature changes and to water hardness. Physiologically, they are mostly nontoxic and skin-compatible.[2,54–58] Their widespread use for the extraction and purification of membrane proteins, which plays a major role in the determination of protein structures and functions, is reasonable due to their reduced protein denaturing properties in comparison to conventional surfactants.[59]

An alternative to the classical sugar-based surfactants are inositols. Inositols also belong to the group of carbohydrates since they have the same molecular formula $C_6H_{12}O_6$ as conventional hexoses, but a different constitution. In a way, they present the homocyclic carbon analogue of pyranoses, which is why they are sometimes also called "C-sugars". The structural formulas of *scyllo*- (**5**), *myo*- (**6**) and *chiro*-inositol (**7**) are shown in Fig. 8 as representative examples of this cyclitol class, which in total consists of 8 diastereomers.

All 8 diastereomeric inositols are renewable primary natural products. But especially, *myo*-inositol (**6**) is a cheap and easily accessible compound, as it can be extracted from wheat pods.

Furthermore, naturally occurring inositol lipids like **8** (Fig. 9), are "*one of the most remarkable burgeoning stories in cell biology over the last 20 years* [...] *and, even more so, the number of their functions*".[61] For example, phosphatidyl inositols like **8** have been identified as essential regulators of nuclear functions, cytoskeletal dynamics, cell signalling and membrane trafficking.[62–68] As they possess an amphiphilic structure, one can consider them as naturally occurring surfactants.

The polyol structure of inositol makes it as suitable as conventional sugars to serve as a hydrophilic head group in surfactants. Thus, suitable inositol derivatives can be expected to have properties which are very similar to those of sugar-



5 **6** **7**

Fig. 8 *scyllo*- (**5**), *myo*- (**6**) and *chiro*-inositol (**7**), as representative examples of inositols. The ring positions are numbered according to the IUPAC naming rules of cyclitols.[60]

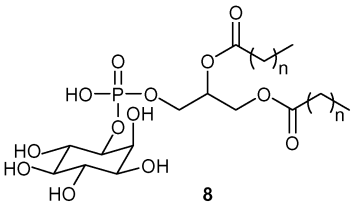


Fig. 9 Structure of a phosphatidyl inositol lipid **8**, a class of naturally occurring and important phospholipids with *myo*-inositol as a hydrophilic head group.

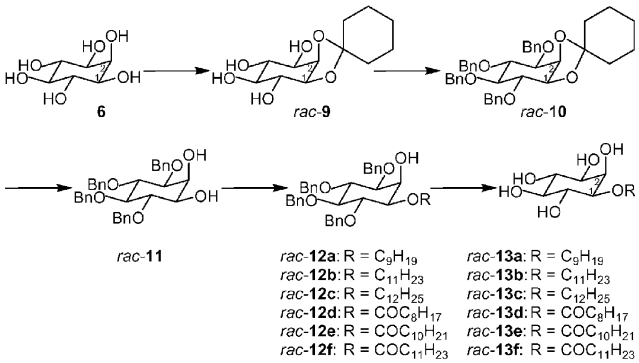
based ones. However, in contrast to the latter, inositol cannot undergo mutarotation or ring opening reactions, not even at very low pH-values, because an anomeric center is lacking. Thus inositol-based surfactants are more stable than the respective sugar surfactants, but, due to their structural similarity, they should be as biodegradable as other carbohydrates. To our knowledge, there is only one publication about the solution properties of synthetically derived inositol-based surfactants.[69] Although the respective publication is solely available in Korean, it appears that the described monoesters have been isolated and investigated only as a mixture of all possible regioisomers.

Different inositol ethers and esters with various aliphatic side chains have already been synthesised and their thermomesomorphism, *i.e.* their ability to form thermotropic liquid crystals, has been studied.[70] Apart from these synthetic approaches the 1-*O*-(17-methylstearyl) ester of inositol has been isolated as a natural compound from the seeds of *Asphodelus tenuifolius* Cav.[71] Due to the limited number of available data on inositol-based surfactants we decided not only to synthesise or re-synthesise a number of regio- and stereochemically defined inositol ethers and esters, but also to investigate their surface activities in greater detail with respect to structure–property relations.

4.1.1 Synthesis of *myo*-inositol monoethers and -esters. The well-established protecting group chemistry[72–77] of *myo*-inositol (**6**) mainly consists of selective acetalisation, etherification, esterification and the respective deprotection reactions. The main factor for the synthetic differentiation of the dissimilar ring positions in **6** is the axial hydroxyl function at the 2-position. Firstly, this leads to the formation of *cis*-annealed 6-ring/5-ring acetals like in *rac*-**9**, which are energetically favoured over the respective *trans*-annealed structures; secondly, the axial or equatorial hydroxyl functions *e.g.* in **11** can be distinguished by their accessibility and reactivity.

Subsequent application of such protecting group strategies allows one to specifically address and modify the different ring positions in inositols. The synthesis of 1-*O*-substituted inositol surfactants is outlined by way of an example in Scheme 1.[70]

With similar synthetic strategies all the other ring positions of the inositol can be selectively substituted, too.[70] However, performing reactions outside the symmetry plane of *myo*-inositol (**6**), *i.e.* at the 1-, 3-, 4- or 6-position, breaks the C_s symmetry and thus leads to chiral products. So far we have done the syntheses shown in Scheme 1 in a racemic manner. However, we are currently following the respective stereoselective pathway by employing enantiomerically pure camphor instead of cyclohexanone in the acetalisation reaction, with subsequent resolution of the resulting diastereomers. This will lead to stereochemically defined *myo*-inositol ethers and esters **13**, the properties of which we will compare with their respective racemates, since the possibly different crystal lattices and intermolecular interactions of the enantiopure compounds and the racemate may influence their solubility and self-assembly properties. The same holds for the enantiomers and their potential biological activities.



Scheme 1 Synthesis of 1-*O*-substituted *myo*-inositol surfactants **13**. All the depicted reactions lead to racemic products (indicated as *rac*), since the C_s-symmetry of *myo*-inositol is broken in the first reaction step. However, performing the same sequence with enantiomerically pure camphor instead of cyclohexanone in the first step allows the resolution of the resulting diastereomers and hence the stereoselective synthesis of **13**.

Using the same strategy for "single point connections" to the inositol ring we will also synthesise and investigate some inositol glycerolipids of type **14** shown in Fig. 10.

In conclusion, numerous possibilities exist to synthesise new inositol-based surfactants. As a starting point, we synthesised a variety of monoethers and monoesters like *rac*-**13a**–*rac*-**13f** shown in Scheme 1 above. Within the framework of an EC-funded Research Training Network, the properties of these new surfactants are, and will continue to be, studied. Although this article does not deal with these properties, the surface tension isotherm of 1-*O*-dodecanoyl-*myo*-inositol (*rac*-**13f**) is given in the appendix to demonstrate that inositol-based surfactants are indeed surface active. Having countless synthetic possibilities will allow us to "design" new surfactants and thus to "design" properties. In other words, the wide variety of accessible structures will allow us to study structure–property relations in the broadest sense of the word.

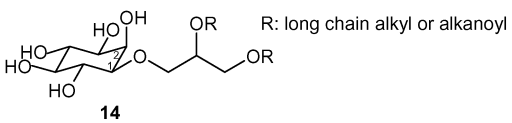
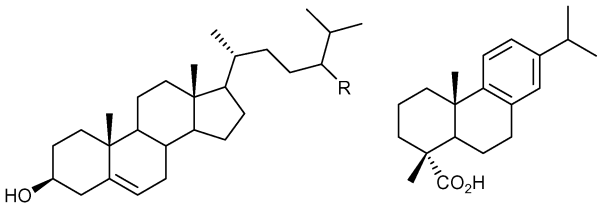


Fig. 10 Structure of an inositol glycerol lipid. In contrast to the phosphatidyl inositol lipids **8** shown in Fig. 9 the structure of **14** shown here lacks the phosphate ester link between the inositol head group and the glycerol residue. If at all, inositol derivatives of this type have only rarely been synthesised or investigated yet.[78]



15a Cholesterol (R = H)
15b β-Sitosterol (R = C_2H_5)

16

Fig. 11 Cholesterol (**15a**), β-sitosterol (**15b**) and dehydroabietic acid (**16**) are structurally demanding examples of polycyclic organic moieties, which are used as hydrophobic tails in some surfactants.

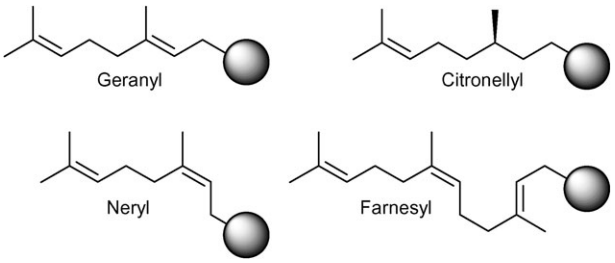


Fig. 12 Selection of surfactants possessing a terpene-based lipophilic chain. The beads symbolise hydrophilic head groups.

4.2 Surfactants containing a natural hydrophobic tail

There are a lot of effective surfactants that contain a hydrophobic tail made of natural compounds. These hydrophobic parts can be saturated or unsaturated, linear or branched, or they may even contain cyclic units. The main source for the hydrophobic tail is either saturated or unsaturated fatty acids. In the majority of cases natural fatty acids have an even number of carbon atoms because they are polyketides, which means that they are built up biologically by the respective synthase protein from acetate units in the form of acetyl-CoA. Industrially, fatty acids are obtained by ester hydrolysis of fats or oils. Thus, a wide range of different hydrocarbon chains can be obtained in a cheap and easy way. Linking these fatty acids or their reduced derivatives, like *e.g.* fatty alcohols, to the hydrophilic head groups *via* esterification, etherification, amination or amidation, one obtains the desired surfactant. Another kind of naturally derived hydrocarbon used as the hydrophobic part in surfactants are sterol derivatives, *e.g.* cholesterol (**15a**) or β-sitosterol (**15b**) depicted in Fig. 11. This is due both to the availability of a large number of structurally different sterols and to their rather planar annulated structure, which is thought to induce good packing at interfaces.[79] It has to be mentioned that the employment of steroids as substructures in surfactants may cause environmental problems, *e.g.* in soil water, since they generally are highly bioactive compounds.

Another annulated system that is applied as the hydrophobic chain in surfactants is dehydroabietic acid (**16**).[23,80] This chiral tricyclic system is an easily obtainable component of tall oil, a by-product of the pulping process and thus a cheap natural raw material.[2,49] Since this octahydro-phenanthrencarboxylic acid can be attained in enantiomerically pure form, it may also induce chirality, *e.g.* in mesogenic phases. These hydrophobic tails are commonly used in exploratory and commercial applications, with a wide range of different hydrophilic (anionic, cationic or nonionic, inorganic or organic) head groups.

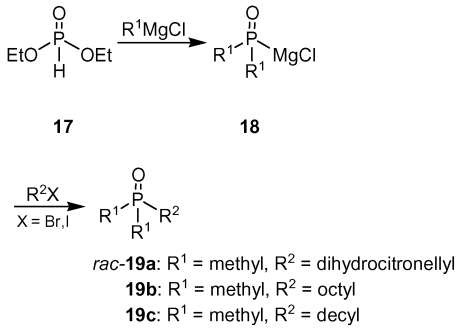
Last but not least, terpenes can be used as hydrophobic tails of surfactants, a concept that has hardly been pursued yet. Terpenes and the closely related terpenoids[81] are classes of organic, mostly natural, compounds occurring naturally in animals and plants. Known for quite some time already, these classes of natural compounds are named after the first known source, turpentine, which is also the reason for the unusual nomenclature of terpenes.[82] Generally, terpenes appear in a wide variety of structures, *e.g.* as chains or rings, or in a combination of both. Furthermore, they commonly appear functionalised by hydroxyl groups, ethers, esters, glycosides, aldehydes, ketones or by carboxyl groups. Technically, terpenes are most often extracted from the essential oils of plants. Some of the most famous examples of terpenes are menthol, camphor, and retinol. The high potential of using terpenes as co-surfactants to tune the properties of microemulsions was first discussed 8 years ago.[83] The aim was to formulate microemulsions that are based entirely on renewable materials. Unfortunately, this route was not pursued further. Our approach, however, is not to use terpenes as co-surfactants, but to use the hydrocarbon skeleton of terpenes as the hydrophobic part of new surfactants. Possible structures are given in Fig. 12.

Although some publications exist where (mostly) apolar terpenes were mixed with surfactants, to our knowledge, there are, to date, only very few publications dealing with surfactants for which the hydrophobic part consists of a terpene substructure.[84–87] This is quite surprising as such compounds are expected to be highly interesting, not only from a physicochemical point of view, but also for potential pharmaceutical, biomedical or biochemical applications.

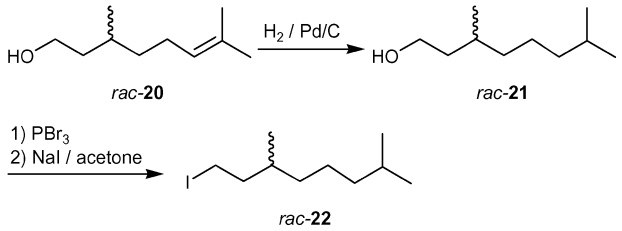
4.2.1 Synthesis of terpene-based phosphine oxides. As a starting point for the syntheses of terpene-based surfactants we decided to use a well-known and straightforward approach. The synthesis of choice was that of tertiary phosphine oxides of type **19** (see Scheme 2).[88]

To avoid any confusion we have to mention that a tertiary phosphine oxide becomes a surfactant if two of the three substituents are short alkyl chains such as methyl or ethyl, while the third substituent is a long alkyl chain or large apolar ring system. For example, dimethyl alkyl phosphine oxides with linear alkyl chains ranging from 9 to 14 carbon atoms are classic surfactants and their surface properties have been studied in detail.[89–92]

Obviously, these surfactants are of great interest from a scientific point of view. However, they have never been produced on a large scale, although there are some patents[93] dating from the 1960s which describe unbranched alkyl phosphine oxides. This is quite surprising as tertiary phosphine oxides mostly have a low toxicity and should be biodegradable. Moreover, phosphine oxide surfactants are chemically quite resistant, pH- and temperature-stable.[94] It is because of these properties that applications can be thought of in which



Scheme 2 General synthesis of tertiary phosphine oxides **19** with different lipophilic residues.[88] To obtain surface active phosphine oxides, R^1 should be small, *e.g.* methyl or ethyl, while R^2 is a large apolar alkyl, terpenyl or steroidyl group. The surface tension isotherms of *rac*-**19a**, **19b** and **19c** are given in the appendix.



Scheme 3 Short synthetic sequence to 1-iodo-3,7-dimethyloctane *rac*-**22** (dihydrocitronellyl iodide).

the use of the traditional two classes of nonionic surfactants, *i.e.* alkyl polyglycol ethers C_iE_j and alkyl polyglycosides C_nG_m, is impossible or at least difficult.[95]

For example, the properties of both phosphine oxide and C_iE_j surfactants (*cf.* Fig. 13) are strongly temperature dependent.[7,96] However, while C_iE_j surfactants degrade at high temperatures, the respective phosphine oxides are stable. In the case of C_nG_m surfactants we are faced with the problem of ring opening reactions at extreme pH-values, while phosphine oxide surfactants are pH-stable. Last but not least, the synthesis and purification of C_iE_j and C_nG_m surfactants is much more time-consuming compared to phosphine oxide surfactants. The fact that phosphine oxides of different hydrophobic chains are easily accessible is one of the main reasons why we are interested in these surfactants. Again, as was the case with the inositol-based surfactants, from a synthetic point of view it will be relatively easy to design surfactants with specific properties. For example, phosphine oxide surfactants can be designed such that they can be used for the formation of highly efficient microemulsions. It is well known from ternary water–oil–nonionic alkyl polyglycol ether (C_iE_j) microemulsions that an increase in efficiency is always accompanied by the unwanted formation of a lamellar (L_α) phase.[96–98] It is also well known that branches in the lipophilic side chains of surfactants suppress the (most often undesired) formation of lyotropic liquid crystalline phases. Thus the hydrophobic chain of the phosphine oxide needs to be designed such that highly efficient microemulsions are formed and lyotropic liquid crystal phases are suppressed simultaneously. We believe that the terpene structures shown in Fig. 12 are potential candidates that meet these requirements.

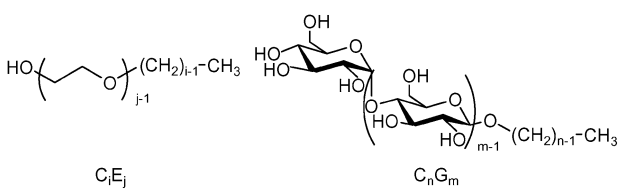


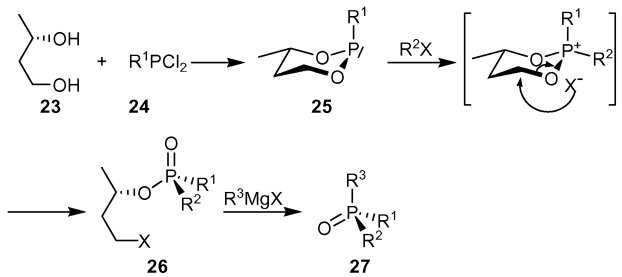
Fig. 13 General structures of the nonionic surfactants alkyl polyglycol ethers C_iE_j and alkyl polyglycosides C_nG_m.[95]

In a first tentative investigation we decided to employ racemic citronellol (*rac*-**20**). In order to prevent possible synthetic problems with its double bond we hydrogenated *rac*-**20** first to yield dihydrocitronellol *rac*-**21**, before we replaced the hydroxyl function by bromine and the latter again by iodine in a Finkelstein reaction (*cf.* Scheme 3).

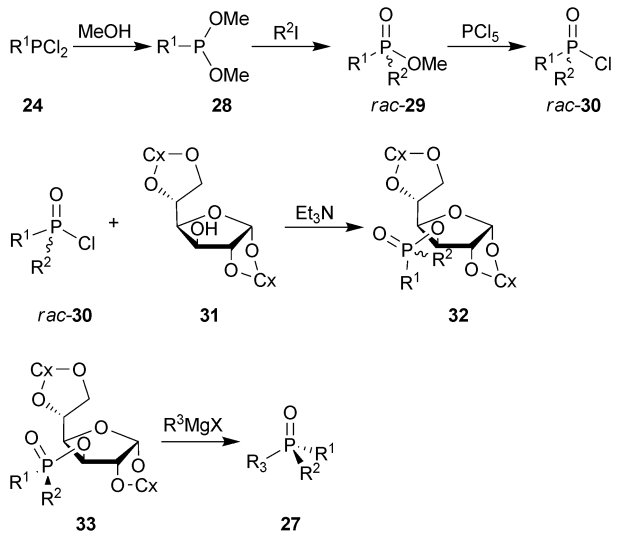
The resulting branched alkyl halide *rac*-**22** served as R^2X (R^1 = Me) in a synthesis as shown in Scheme 2, yielding the respective dihydrocitronellyldimethylphosphine oxide (*rac*-**19a**, dihydrocitronellyl DMPO), of which the surface tension isotherm is given in the appendix and compared with the corresponding values of octyldimethylphosphine oxide[99] (**19b**, C_8DMPO) and decyldimethylphosphine oxide (**19c**).

A possible reaction sequence leading to P-chiral tertiary phosphine oxides is shown in Scheme 4.[100] A chiral template, 3-(*S*)-butane-1,3-diol (**23**), is reacted with an alkyl or aryl dichlorophosphine **24**, to yield the phosphonite **25**. After separation of the resulting diastereomeric mixture (the second stereocenter, generated by the reaction, is the phosphorus atom)—which could be performed by distillation[100] in the case of R^1 = phenyl—the phosphonite **25** is reacted with an alkyl halide (*e.g.* R^2X = ethyl iodide) in a Michaelis–Arbuzov reaction, under retention of the stereochemistry at the phosphorus centre, to introduce the second alkyl substituent. In the next step, the third residue is introduced by a Grignard reaction (*e.g.* with R^3MgX = methylmagnesium chloride) at the phosphorus atom, proceeding under inversion of configuration.

Another published reaction sequence[101] which we will employ uses 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (**31**) as chiral auxiliary, forming diastereomeric phosphinate esters **32** which could be separated by column chromatography (*cf.* Scheme 5). A subsequent Grignard reaction would again, under inversion of configuration, yield the desired chiral tertiary phosphine oxide **27** in an enantioselective manner.



Scheme 4 Reaction sequence leading to P-chiral phosphine oxides by employing a chiral 1,3-diol as chiral template.[100] The ring opening occurs in a stereocontrolled Michaelis–Arbuzov reaction.



Scheme 5 Reaction sequence leading to enantiomerically pure tertiary phosphine oxides.[101] Resolution of the diastereomeric mixture **32** can be achieved by chromatography to yield *e.g.* **33**, which can be converted to the desired P-chiral phosphine oxides of type **27**.[101] Cx: cyclohexylidene.

In conclusion, phosphine oxide surfactants like **19** or **27**, with tailored hydrophobic chains, do not command adequate attention, which motivated us to develop synthetic routes for terpene-based phosphine oxides. As was the case with the inositol-based surfactants, numerous possibilities exist to synthesise terpene-based surfactants. The surfactants we have synthesised so far are monoterpene derivatives, carrying citronellyl or dihydrocitronellyl as the lipophilic chain R^2, combined with methyl or ethyl residues R^1 (*cf.* Scheme 2), respectively. As the surface activity and efficiency of surfactants with an octyl chain as the hydrophobic part (the monoterpene has to be regarded as an octyl chain with two branches rather than as a decyl chain) are known to be rather low, the synthesis of sesquiterpene derivatives is under way. As "proof of concept", the surface tension isotherm of the racemic dihydrocitronellyldimethylphosphine oxide was measured. The results are shown and discussed in the appendix. Once we have a pool of terpene-based surfactants their surface activity properties will be studied in detail.

5 Future of the field

In this perspective we have presented an overview of surfactants containing structural motifs which are derived from natural compounds. Two new promising classes of nonionic surfactants, namely inositol-based surfactants and phosphine oxides with a terpene-based hydrophobic chain, have been introduced and some respective syntheses have been discussed. From a synthetic point of view, we believe that the future of this field will be characterised by two synthetic challenges. Firstly, the synthesis of maltose-like diinositol units as hydrophilic head groups is strongly desirable, a possible amphiphile of this type is **34**, shown in Fig. 14.

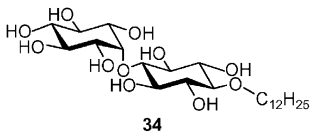


Fig. 14 Structure of one possible diinositol surfactant of which the head group is structurally comparable to maltose.

What is well known from the study of the corresponding alkyl glycosides is that the water solubility of glucosides, and hence their use as surfactants, is rather limited, while the maltosides show typical surfactant behaviour. A similar trend is expected for the inositol-based surfactants. First surface tension results indeed demonstrate that the properties of inositol- and glucose-based surfactants are comparable. It is because of this observation that we also expect similar properties of diinositol- and maltose-based surfactants. Moreover, as most of the data available deal with properties of maltosides, a surfactant with a diinositol head group would facilitate the comparison of these two carbohydrate surfactants. Secondly, the synthesis of surfactants derived entirely from natural compounds is another major aim. A surfactant with a terpene as the hydrophobic and an inositol as the hydrophilic part is a possible example. With regard to the countless possibilities for both the terpene-chemistry and the inositol-chemistry, creativity knows no bounds.

As regards possible applications, the future in this field will lie in intensive studies of the physicochemical behaviour, *i.e.* surface activity, adsorption at liquid and solid surfaces, phase behaviour *etc.* of inositol- and terpene-based surfactants. Although these properties have been studied for numerous surfactants, we are still far from being able to predict the properties of new surfactants. An example of how complex the adsorption process can be is the adsorption of two different nonionic surfactants on silica. At first sight, one does not expect a big difference as both surfactants are uncharged, *i.e.* that the interactions between the silica surface and the nonionic surfactants cannot differ very much. In fact, quite the opposite was observed. While the nonionic surfactant hexaethylene glycol monododecyl ether ($C_{12}E_6$) adsorbs strongly on silica, the respective dodecyl maltoside (β-$C_{12}G_2$) does not adsorb at all.[102] This is surprising and still not understood. To what extent inositol- and terpene-based surfactants adsorb on silica is only one of the numerous questions that need to be studied before one can discuss potential applications of these new surfactants.

Appendix

As "proof of concept" the surface tensions σ of two classes of newly synthesised surfactants were measured as a function of the surfactant concentration c and compared with those of typical surfactants. The resulting σ–c curves are given in Fig. 16 and the corresponding molecular structures are shown in Fig. 15.

1-Dodecanoyl-*myo*-inositol

For the sake of comparison we plotted the measured σ–c curve of 1-dodecanoyl-*myo*-inositol (*rac*-**13f**) together with those of the corresponding sugar surfactants, namely β-dodecylmaltoside (β-$C_{12}G_2$) and β-dodecylglucoside (β-$C_{12}G_1$). As can be

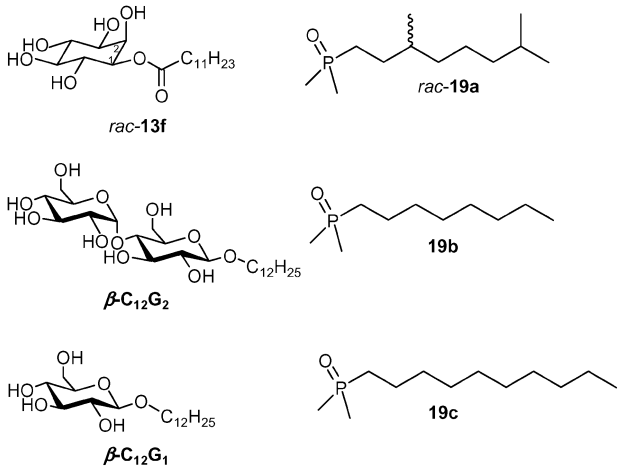


Fig. 15 Left: Molecular structures of 1-dodecanoyl-*myo*-inositol (*rac*-**13f**), β-dodecylmaltoside (β-$C_{12}G_2$), and β-dodecylglucoside (β-$C_{12}G_1$). Right: Molecular structures of the racemic dihydrocitronellyldimethylphosphine oxide (dihydrocitronellyl DMPO, *rac*-**19a**), octyldimethylphosphine oxide (C_8DMPO, **19b**), and decyldimethylphosphine oxide (C_{10}DMPO, **19c**). The corresponding surface tensions are shown in Fig. 16.

seen in Fig. 16, the slope of the C_{12} *myo*-ester isotherm is similar to the one of β-$C_{12}G_1$ rather than to the one of β-$C_{12}G_2$, which, in turn, would lead to areas per head group similar to β-$C_{12}G_1$. This is exactly what one would expect looking at the molecular structure of these two surfactants (see Fig. 15). However, for a quantitative comparison, a detailed analysis of the adsorption properties needs to be carried out which will be presented in a forthcoming paper. One important difference, however, needs to be mentioned. The aqueous solution of *rac*-**13f** went turbid at concentrations higher than 6×10^{-5} M. Thus the cmc could not be determined. It is exactly because of this very low solubility of 1-dodecanoyl-*myo*-inositol (*rac*-**13f**) that we are working on feasible routes to synthesise the maltoside-analogon, *i.e.* a surfactant with a diinositol head group. This approach is justified by the observations made for the sugar-based surfactants, namely that the solubility increases significantly if the glucoside unit is replaced by a maltoside unit.[103] We expect this trend also to be seen in the case of inositol-based surfactants.

Dihydrocitronellyldimethylphosphine oxide

The σ–c curve of one of the new terpene-based surfactants is very similar to those of the corresponding-dimethylphosphine oxides with linear alkyl chains. This is not surprising, as only the alkyl chain was changed, while in the case of the inositol-based surfactants the head group was changed, which, in turn, is expected to have a higher impact on the general properties. In Fig. 16 the σ–c curve of the racemate dihydrocitronellyldimethylphosphine oxide (dihydrocitronellyl DMPO, *rac*-**19a**) is compared with those of C_8DMPO (**19b**) and C_{10}DMPO (**19c**), respectively. Looking at Fig. 15 one sees easily the similarities of these surfactants from a structural point of view: the terpene-based alkyl chain consists of a linear octyl chain branched with two methyl groups, which leads to a total of 10 carbon atoms. Thus the hydrophobicity of this chain—and thus the surface activity of the surfactant—is expected to be between the two linear analoga. As is seen in Fig. 16 this is indeed the case. In a forthcoming paper the adsorption properties (surface concentration, surface area, and cmcs) of terpene-based phosphine oxides will be compared quantitatively with their linear counterparts. What is of importance in the present context is the fact that the σ–c curve of dihydrocitronellyl DMPO (*rac*-**19a**) was measured only up to 0.02 mol l^{-1} simply because the amount of synthesised surfactant was not enough and not because of an insolubility as was the case with *rac*-**13f**.

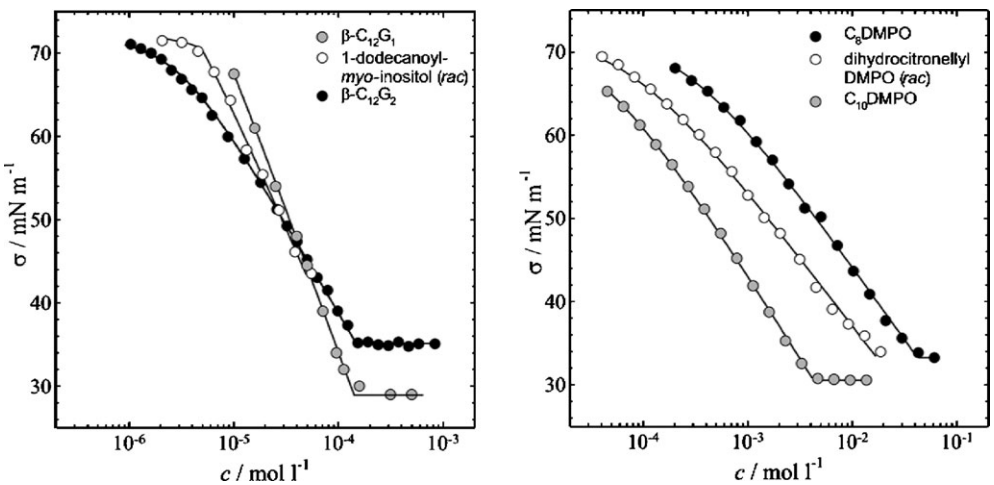


Fig. 16 Left: Surface tensions of 1-dodecanoyl-*myo*-inositol (*rac*-**13f**), β-dodecylmaltoside (β-$C_{12}G_2$), and β-dodecylglucoside (β-$C_{12}G_1$). All data were fitted with the Frumkin adsorption model. The data for β-$C_{12}G_1$ are taken from ref. 104 while those of β-$C_{12}G_2$ are unpublished results of the authors. Note that the data of Wydro and Paluch[104] indicate that the β-$C_{12}G_1$ was not pure. Right: Surface tensions of the racemic dihydrocitronellyldimethylphosphine oxide (dihydrocitronellyl DMPO, *rac*-**19a**), octyldimethylphosphine oxide (C_8DMPO, **19b**), and decyldimethylphosphine oxide (C_{10}DMPO, **19c**). All data were fitted with the Langmuir adsorption model and are unpublished results of the authors.

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