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Alkyl-imidazolium glycosides: non-ionic—cationic hybrid surfactants from renewable resources

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ABSTRACT

A series of surfactants combining carbohydrate and imidazolium head groups were prepared and investigated on their assembly behavior. The presence of the imidazolium group dominated the interactions of the surfactants, leading to high CMCs and large molecular surface areas, reflected in curved rather than lamellar surfactant assemblies. The carbohydrate, on the other hand, stabilized molecular assemblies slightly and reduced the surface tension of surfactant solutions considerably. A comparative emulsion study discourages the use of pure alkyl imidazolium glycosides owing to reduced assembly stabilities compared with APGs. However, the surfactants are believed to have potential as component in carbohydrate based surfactant mixtures.

1. Introduction

Over the last decades sugar based surfactants[1–7] have gained both scientific and economic interest owing to increasing concerns in biocompatibility[8] and sustainable resources.[9,10] Application fields include emulsifiers[11,12], detergents[2] as well as medical delivery systems.[13,14] Most investigations focus on non-ionic surfactants, which utilize the polyhydroxy-character of carbohydrates as hydrophilic surfactant antipode. While non-ionic surfactants provide advantages with respect to an enhanced assembly stability, e.g. towards pH-changes or electrolytes,[15] this insensitivity restricts the application of certain formulation methods, which utilize medium induced phase changes, like the pH-mediated transition of fatty acid micelles into liposomes.[16] Unfortunately, carbohydrate surfactants involving ionic charges have not been investigated extensively. Typical examples are anionic alkyl glycuronates, i.e. salts of oxidized glycosides with a carboxylic acid,[17–19] on the one hand, and cationic N-alkylated amino-derivatives of sugars on the other. Chemical instability[20,21] limits the application of glycosylamines[22] and their subsequent ammonium ions,[23] which resemble the potentially most easily accessible sugar based cationic surfactants. Instead acylated products[24,25] and derivatives of the corresponding reduced glycamines, or amino-polyols,[26–28] have gained more interest.

Both cationic and anionic surfactants are principally susceptible for medium triggered assembly changes. However, the presence of a carbohydrate in the surfactant head group should reduce the impact of the latter. Therefore ionic carbohydrate surfactants are expected to exhibit reasonable assembly stability despite their susceptibility for medium-induced changes. This makes them potentially interesting candidates for medical delivery systems. In view of excess negative charges on biological cell membranes[29,30] cationic surfactants are likely mediating better interactions of a carrier with a cellular target; hence they are favored over anionic surfactants. The introduction of a positive charge, referring to an amino- or ammonium group, on a carbohydrate can be achieved in various ways. Constraints, however, arise from economic considerations. While glycamines provide the most direct access, the resulting open chain structure does not match nature-typical carbohydrate patterns. This has implications on molecular interactions based on the hydrogen bonding network in sugar-based surfactant assemblies and potentially affects the bio-recognition of a drug carrier, thus disfavoring the approach. The preparation of a glycolipid[19] and subsequent introduction of an amino-group,[31,32] on the other hand, requires a multi-step synthesis, which renders it non-economic. In order to reduce the number of required chemical transformations and optimize the production efficiency, an

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approach comprising of glycosylation and subsequent amination was targeted, where the latter not only introduces the cation to the sugar but the hydrophobic domain as well. This approach reflects the previously reported strategy for the synthesis of alkyl triazole glycosides (ATG).[33]

2. Results and discussion

2.1. Synthesis

The surfactants were synthesized in a 3-stage process, involving glycosylation of bromoethanol,[34] its subsequent use for the alkylation[35] of mono-N-alkylated imidazoles[36] and a final deprotection step.[37] The synthetic scheme is displayed in Fig. 1.

Alkyl-imidazolium glycoside surfactants (AIGs) with C_8 (**6a**), C_{12} (**6b**) and C_{16} (**6c**) hydrocarbon chains were obtained in practically identical high yields, as shown in Table 1. This indicates high efficiency and suggests a wide application range for the surfactant synthesis. The overall yield, however, was limited by the carbohydrate precursor **4**,[34] which's preparation was not yield optimized. The use of xylene as solvent instead of the more common toluene[35] enabled a higher reaction temperature and considerably sped up the conversion of **4** into the surfactant precursor **5**. Despite the short reaction time the conversion was not affected by the chain length.

2.2. Physical properties

In order to rationalize the physical behavior of AIGs their surfactant properties were compared with those of the corresponding alkyl glycosides, **7** (resembling APG surfactants), as well as their methyl-imidazolium counterparts, **8**. The structures of the surfactants are displayed in Fig. 2, while their behavior is summarized in Table 2.

Table 1
Synthesis of glycosyl imidazolium surfactants

Compd	Alkyl chain	Yield (basis: **4**)
6a	C_8H_{17}	91%
6b	$C_{12}H_{25}$	91%
6c	$C_{16}H_{33}$	92%

The investigation on Krafft and cloud points indicated no temperature limitations for the use of the surfactants **6**; none of the compound exhibited clouding behavior at high temperature, while all enabled the formation of micelles below room temperature. This behavior is in agreement with the corresponding methyl-imidazolium chlorides,[38] which were referred to in lieu of published data for the corresponding bromides **8**. However, similar behavior of quaternary ammonium surfactants with chloride and bromide ions[40] justifies this reference. In contrast, APG models **8** with alkyl chains above 10 carbon atoms exhibit Krafft points above room temperature, which moreover, increase upon extension of the alkyl chain.[39] The lower Krafft temperatures for **6** indicate increasing water solubility upon introduction of the imidazolium ion. The latter is also reflected in significantly increased CMC values for the surfactants **6** with respect to the APG-analogs **7**.[40,41] However, the water solubility of AIGs remains far below that of the imidazolium surfactants **8**,[42,43] thus proposing dominance of the sugar over the cation with respect to interactions with water. This dominance is mirrored in the surface tension of solutions above the CMC, which resemble those of the APG-models[42,44] rather than the imidazolium surfactants.[44,45] A similar behavior has previously been reported for ester-linked cationic carbohydrate surfactants involving a head group comprising of a sugar and an ammonium salt.[45]

Contact penetration experiments with water, an example is shown in Fig. 3, only indicated the presence of a hexagonal phase for compounds **6**. It was assumed to be the normal H_I phase. The exclusive formation of this phase is in contrast to the previous reports on the behavior of alkyl glycosides, for, which a diversity of phases was found in case of the C_8 surfactant **7a**,[46–48] while only lamellar lyotropic phases were reported for the higher homolog **7b**.[49] In order to understand the different lyotropic phase behavior of **6** and **7**, the molecular surface area of compound **6b** was determined based on the slope for the concentration depending region of the surface tension plot displayed in Fig. 4.

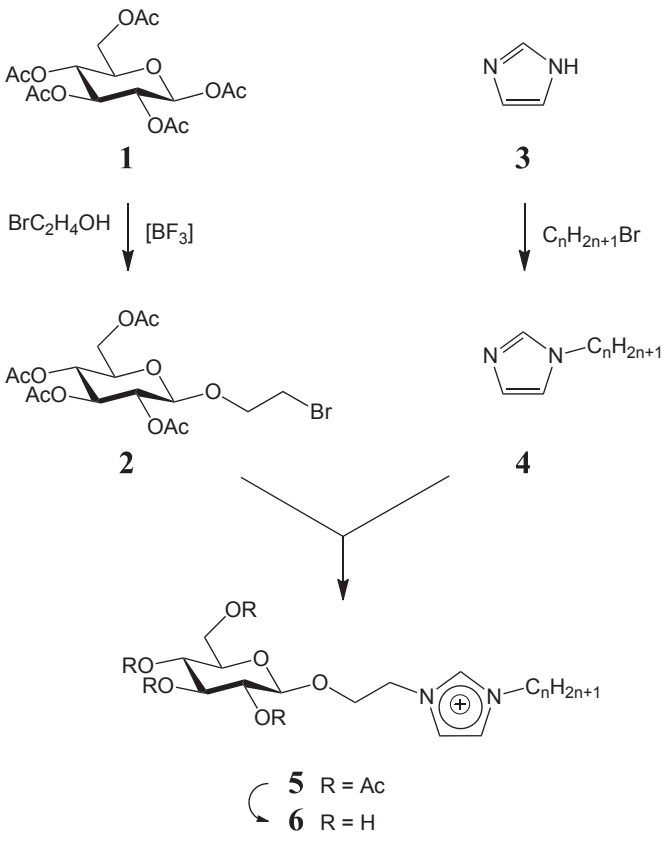

Fig. 1. Synthetic scheme for glycosyl imidazolium surfactants.

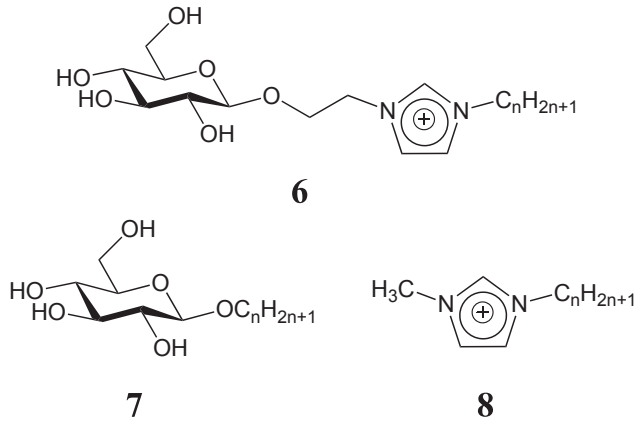

Fig. 2. Structure comparison of surfactants.