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ORIGINAL CONTRIBUTION

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Synthesis and gel formation of amphiphilic semicarbazones containing saccharide units

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Abstract The synthesis of 4-alkyl-semicarbazones derived from reducing sugars and semicarbazides is presented as a convenient route for the preparation of amphiphilic saccharides. This semicarbazone route allows to employ a large variety of reducing sugars as hydrophilic building block for saccharide tensides. The preparation of two series of amphiphiles based on D-maltose with non-methylated and mono-N-methylated semicarbazone units is described. The *n*-alkyl chains were varied from *n*-octyl to *n*-hexadecyl. Various maltotriose derivatives have also been prepared. Critical micelle concentration (CMC) as well as critical gel concentration of the derivatives were studied in dependence of the *n*-alkyl chain length. Both values decreased with increasing length of the *n*-alkyl chain. Self-organization of the gels was studied by transmission electron microscopy of freeze-fractured samples. Due to the supramolecular organization of the amphiphiles, the gels consisted of twisted rope-like molecular assemblies with the same helical twist sense. The helical pitch depended on the hydrophilic/lipophilic balance. In contrast to gels of *n*-alkylgluconamides, the gels were formed in dilute aqueous solution and exhibited striking longevity without additional stabilization by surfactants. In the solid, the amphiphiles exhibited thermotropic transitions to partially disordered mesophases.

Key words Saccharide-based amphiphiles – 4-alkyl-semicarbazones – gelation of saccharide-amphiphiles – self-organization – supramolecular organization

Introduction

Amphiphiles consisting of mono- or oligosaccharide units as hydrophilic carbohydrate head groups and long lipophilic *n*-alkyl chains are compounds with unusual properties [1, 2]. Such amphiphiles, also designated "sugar-lipid hybrids" constitute nonionic surfactants, which can be employed as emulsifying agents and detergents [3]. The main advantages of such detergents are their often low toxicity and the fact that they are derived from renewable resources. Some of these compounds, such as *n*-alkanoyl-N-methyl glucamides are applied for the solubilization and extraction of proteins [4].

Recently, the self-organization behavior of saccharide-based amphiphiles in dilute as well as semidilute solution and upon crystallization has been investigated intensely with respect to the chirality of the head groups and the length of the *n*-alkyl chains [1, 2, 5–8]. Based on the supramolecular organization [1, 2, 9], use as new, biomimetic membrane materials has been suggested [8]. Saccharide based amphiphiles may be viewed as model compounds for glycolipides [10].

The preparation of saccharide based amphiphiles is often tedious due to the polyfunctionality of the starting saccharides, which leads to an inseparable mixture of products with various degrees of substitution [11]. Different strategies have been developed to overcome the problems encountered with the synthesis of monofunctional saccharide derivatives. Protecting groups can be employed to avoid multisubstitution [12]. An alternative is the selective introduction of new functionalities, such as amino functions or lactones into the sugar molecule for subsequent modification [8, 13, 14].

Our present work was aimed at a versatile synthetic route to oligosaccharide based amphiphiles in which the hydrophilic and the hydrophobic part of the molecule can be varied independently *without* the use of protecting groups. Our approach is based upon semicarbazone sugar derivatives and allows to employ a large variety of different mono- and oligosaccharides as hydrophilic building blocks. Semicarbazones have long been known as stable derivatives of aldehydes and ketones [15] and are easily accessible via the respective *n*-alkylamines or acyl chlorides. In this paper we report the synthesis of semicarbazone amphiphiles*) based on maltose and malto-oligomers with various *n*-alkyl chains. Furthermore, first results on surface behavior, aggregation and gelation in solution as well as supramolecular organization of the gels are presented.

Experimental part

General

All materials employed were of reagent grade (p.a.) and used as received. Solvents were dried following the usual procedures.

All reactions were followed by thin-layer chromatography on silica gel plates 60 F 254 (Merck), using either cyclohexane/ethylacetate 3/1 (carbamates and semicarbazides) or methanol/trichloromethane/aqueous NH_3 2/2/1 (semicarbazone synthesis) as eluent. *Melting points* were determined with a Leitz Ortholux microscope and a Mettler hot stage FP 80/82 and are uncorrected. ^{1}H-NMR *spectra* were obtained on a Bruker AMR 300 spectrometer at 300 MHz with usual standards in D_2O, $CDCl_3$, dimethylsulfoxide-d_6 or methanol-d_4. *Elemental analyses* were carried out with a Perkin Elmer 240 C Elementar Analyzer. *Surface tensions* were measured in double distilled water with a Krüss Digital Tensiometer K 10 T at 20 °C, employing the Wilhelmy-plate method, after 30 min. *Polarizing microscopy* (crossed polarizers) was employed to study the thermotropic liquid crystalline behavior (Leitz Ortholux Pol BK II, Mettler hot stage FP 80/82).

Light scattering was carried out on a home-modified sofica static light scattering apparatus operated at 632.8 nm.

Transmission electron microscopy (TEM) was carried out using a *Zeiss CEM* 902, 80 kV. Clear solutions of the tensides in the range of 1–3% were obtained by heating to 80 °C in distilled water. The samples for TEM-analysis were prepared according to the method described by Pfannemüller and Welte [8] for alkylgluconamides.

For *freeze-etching*, a freshly cleaved mica rectangle was dipped into the hot solution and kept at room temperature for a few seconds. Then a mica plate was placed on top. The sandwich consisting of two mica plates with the gel layer enclosed was instantaneously frozen by dipping into liquid propane cooled by liquid nitrogen. This sample was used for fracturing. For etching, the fractured gel was kept in a Balzers BAF 301 freeze-fracturing device at −100 °C while a metal surface held at −150 °C, functioning as a trap, was positioned 1 cm above the sample for 20 s. Immediately after that, the surface was shadowed with Pt/C and covered by an additional layer of carbon. The replica on the carbon film was floated off, adsorbed on a carbon coated grid and studied directly by TEM.

Synthetic procedures

Phenyl N-octylcarbamate 1a [16]

12.6 ml (0.10 mol) of phenyl chloroformate were added dropwise at 0 °C to a well-stirred solution of 16.5 ml (0.10 mol) octylamine in 1 l of anhydrous ether. During the second period of addition, a solution of 4 g (0.10 mol) of sodium hydroxide in 100 ml distilled water was added simultaneously. The mixture was stirred vigorously for 1 h at 0 °C and for 1 h at 20 °C after the addition. The organic layer was washed with 250 ml 2 M hydrochloric acid and water and finally dried over $MgSO_4$. Evaporation of the solvent yielded 24.6 g (99%) phenyl N-octylcarbamate *1a* as a colorless solid; m.p. 38–40 °C.

The carbamates *1b–1f* were prepared following the same procedure as *1a*; *Phenyl N-nonylcarbamate 1b*: Yield

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*) For reasons of simplicity and based on the traditional designation, the amphiphiles are generally termed "semicarbazones" throughout the text, although ^{13}C-NMR spectra indicated that the saccharide groups are present in the cyclic form; thus no C=N bond is present.

95 %, m.p. 41–43 °C; *Phenyl N-decylcarbamate 1c*: Yield 97%, m.p. 44–46 °C; *Phenyl N-undecylcarbamate 1d*: Yield 90%, m.p. 52–54 °C; *Phenyl N-dodecylcarbamate 1e*: Yield 98%, m.p. 55–57 °C; *Phenyl N-hexadecylcarbamate 1f*: Yield 100%, m.p. 64–66 °C.

4-Octyl semicarbazide 2a [17]

A solution of 12.5 g (50 mmol) *1a* in 100 ml ethanol was treated with 2.5 ml (50 mmol) $N_2H_4{*}H_2O$ and catalytic amounts of 4-dimethylaminopyridine. The mixture was refluxed for 7 h, the solvent evaporated to dryness and the product recrystallized from ethylacetate. Yield: 6.8 g (73%) *2a* as white crystals, m.p. 68–70 °C.

The synthesis of the semicarbazides *2b–2f* followed the same procedure as employed for *2a*;

4-Nonyl semicarbazide 2b: Yield 54%, m.p. 72–75 °C; *4-Decylsemicarbazide 2c*: Yield 70%, m.p. 83–85 °C; *4-Undecyl semicarbazide 2d*: Yield 51%, m.p. 86–88 °C; *4-Dodecyl semicarbazide 2e*: Yield 59%, m.p. 86–87 °C; *4-Hexadecyl semicarbazide 2f*: Yield 63%, m.p. 98–100 °C;

4-Octyl semicarbazone of D(+)-maltose 3a [18]

A solution of 4.8 g (25 mmol) *2a* and 9.2 g (25 mmol) D-(+)-maltose monohydrate in 75 ml hot methanol containing one drop of glacial acetic acid was refluxed for 4 h and then evaporated to dryness. The oily viscous residue was treated with ether and the ether-insoluble material was collected and dried; yield 13 g *3a* (98%) as a nearly colorless powder, m.p. 117–120 °C. The only impurity found by thin-layer chromatography was a small trace of unreacted maltose (< 1%).

^{1}H-NMR (D_2O): $\delta = 5.37$ (CH–N), 4.5–3.2 (m, CH–O, CH–N), 1.51 ($N\text{–}CH_2\text{–}C\underline{H}_2$), 1.31 ($(CH_2)_5$), 0.88 ($CH_3$)

Elemental analysis ($C_{21}H_{41}N_3O_{11}$, 511.56 g/mol)

found	C	48.27	H	8.03	N	8.06
cal.	C	49.30	H	8.08	N	8.21

The semicarbazones *3b–3f*, *4e* and *f* were prepared in the same manner as *3a*.

4-Nonyl semicarbazone 3b

Yield 95%, m.p. 122–125 °C

^{1}H-NMR (D_2O): $\delta = 5.37$ (CH–N), 4.5–3.2 (m, CH–O, CH–N), 1.51 ($N\text{–}CH_2\text{–}C\underline{H}_2$), 1.31 ($(CH_2)_6$), 0.88 ($CH_3$)

Elemental analysis ($C_{22}H_{43}N_3O_{11}$, 525.58 g/mol)

found	C	48.72	H	8.26	N	7.48
cal.	C	50.27	H	8.25	N	7.99

4-Decyl semicarbazone 3c

Yield 93%, m.p. > 140 °C (decomp., see Table 3)

^{1}H-NMR (D_2O): $\delta = 5.35$ (CH–N), 4.1–3.1 (m, CH–O, CH–N), 1.52 ($N\text{–}CH_2\text{–}C\underline{H}_2$), 1.32 ($(CH_2)_7$), 0.85 ($CH_3$)

Elemental analysis ($C_{23}H_{45}N_3O_{11}$, 539.66 g/mol)

found	C	49.77	H	8.58	N	7.46
cal.	C	51.19	H	8.41	N	7.79

4-Undecyl semicarbazone 3d

Yield 96%, m.p. > 140 °C (decomp.)

^{1}H-NMR (DMSO-d_6): $\delta = 7.35$ (NH), 6.7 (NH), 5.6–4.5 (m, CH–N, OH), 3.7–3.05 (m, CH–O, CH–N), 1.4–1.2 (m, $(CH_2)_9$), 0.85 (CH_3)

Elemental analysis ($C_{24}H_{27}N_3O_{11}$, 553.68 g/mol)

found	C	50.96	H	8.49	N	7.48
cal.	C	52.05	H	8.56	N	7.59

4-Dodecyl semicarbazone 3e

Yield 95%, m.p. > 150 °C (decomp.)

^{1}H-NMR (DMSO-d_6): $\delta = 7.34$ (NH), 6.71 (NH), 5.6 (OH), 5.35 (CH–N), 5.01 (OH), 4.55 (OH), 3.75–2.95 (m, CH–O, CH–N), 1.41–1.20 ($(CH_2)_{10}$), 0.81 (CH_3)

Elemental analysis ($C_{25}H_{49}N_3O_{11}$, 567.66 g/mol)

found	C	50.76	H	8.33	N	6.91
cal.	C	52.89	H	8.70	N	7.40

4-Hexadecyl semicarbazone 3f

Yield 65%, m.p. > 160 °C (decomp.)

^{1}H-NMR (DMSO-d_6): $\delta = 7.15$ (NH), 6.45 (NH), 5.3, 5.1, 4.75, 4.3 (m, OH, CH–N), 3.45–2.7 (m, CH–O, CH–N), 1.2–0.90 ($(CH_2)_{14}$), 0.55 (CH_3)

Elemental analysis ($C_{25}H_{49}N_3O_{11}$, 567.66 g/mol)

found	C	54.69	H	9.38	N	6.56
cal.	C	55.82	H	9.23	N	6.73

4-Dodecyl semicarbazone of D(+)-maltotriose 4e

Yield 92%, m.p. > 160 °C (decomp.)

^{1}H-NMR (DMSO-d_6): $\delta = 7.31$ (NH), 6.71 (NH), 5.6 (m, OH), 5.3 (CH–N), 4.9 (m, OH), 4.55 (m, OH), 3.7–2.95 (m, CH–O, CH–N), 1.41–1.20 ($(CH_2)_{10}$), 0.81 (CH_3)

Elemental analysis ($C_{31}H_{59}N_3O_{16}$, 729.8 g/mol)

found	C	50.60	H	8.11	N	6.06
cal.	C	51.02	H	8.15	N	5.76

4-Hexadecyl semicarbazone of D(+)-maltotriose 4f

Yield 98%, m.p. > 160 °C (decomp.)

^{1}H-NMR (DMSO-d_6): $\delta = 7.29$ (NH), 6.65 (NH), 5.6 (m, OH), 5.3 (CH–N), 5.0 (m, OH), 4.60 (m, OH), 3.7–2.95 (m, CH–O, CH–N), 1.41–1.20 ($(CH_2)_{14}$), 0.85 (CH_3)

Elemental analysis ($C_{35}H_{67}N_3O_{16}$, 785.91 g/mol)

found	C	52.02	H	8.29	N	5.04
cal.	C	53.49	H	8.59	N	5.35

Nonylisocyanate 5a [19]

21 ml (0.1 mol) decylic acid chloride were added to a solution of 30 ml (0.2 mol) trimethylsilyl azide in 250 ml dioxane under nitrogen. The mixture was slowly heated until the evaporation of N_2 commenced (usually reflux). The reaction was monitored by IR spectroscopy by following the decrease of the carbonyl absorption of the acid chloride at 1800 cm^{-1} and the increase of the isocyanate band a 2260 cm^{-1}. Finally, 150 ml of dioxane, trimethylsilylchloride and unreacted trimethylsilylazide were removed by distillation and the resulting solution was used as obtained for the synthesis of semicarbazones.

Undecylisocyanate 5b was prepared according to *5a*.

2-Methyl-N-Nonylsemicarbazide 6a [20]

15.5 ml (0.3 mol) methylhydrazine were slowly added to a cooled solution of 0.1 mol nonylisocyanate. The mixture was stirred for 3 h at room temperature and 30 min at 100 °C, solvent was evaporated and the residue recrystallized from ethylacetate, yield 16.6 g (77%), m.p. 49–51 °C.

2-Methyl-N-Undecylsemicarbazide 6b was prepared in the same manner as *6a*; yield 16.0 g (66%) m.p. 57–59 °C.

2-Methyl-N-Nonylsemicarbazone of D(+)-maltose 7a

A solution of 6 g (25 mmol) *6a*, one drop glacial acetic acid and 9 g (25 mmol) D(+)-maltose monohydrate in 200 ml methanol were refluxed for 5 h. After evaporation of the solvent the amorphous residue was treated with ethylacetate, yield 10.8 g (77%), m.p. 100–101 °C.

^{1}H-NMR (D_2O): $\delta = 5.35$ (m, CH–N), 4.1–3.05 (m, CH–O, CH–N), 1.45 (m, $N{-}CH_2{-}C\underline{H}_2$), 1.3 (m, $(CH_2)_6$), 0.85 (m, CH_3)

Elemental analysis ($C_{23}H_{15}N_3O_{11}$, 539.61 g/mol)

found	C	49.73	H	8.05	N	7.45
calc.	C	51.19	H	8.41	N	7.79

2-Methyl-N-Undecylsemicarbazones 7b and 8b were prepared according to *7a*.

2-Methyl-N-Undecylsemicarbazone 7b

Yield 86%, m.p. 104–109 °C

^{1}H-NMR (D_3COD): $\delta = 5.2$ (m, CH=N), 4.1–3.1 (m, CH–O, CH–N), 1.45 (m, $N{-}CH_2{-}C\underline{H}_2$), 1.3 (m, $CH_2)_8$), 0.9 (m, CH_3)

Elemental analysis ($C_{25}H_{49}N_3O_{11}$, 567.66 g/mol)

found	C	49.28	H	8.09	N	5.88
cal.	C	52.89	H	8.70	N	7.40

2-Methyl-N-Undecylsemicarbazone of D(+)-maltotriose 8b

Yield 57%, m.p. 135–140 °C

^{1}H-NMR (DMSO-d_6): $\delta = 6.95$ (m, NH), 5.6, 5.35, 5.01, 4.55 (m, CH=N, OH), 3.75–2.9 (m, CH–O, CH–N), 1.41–1.20 ($(CH_2)_{10}$), 0 81 (CH_3)

Elemental analysis ($C_{31}H_{59}N_3O_{16}$, 729.8 g/mol)

found	C	47.13	H	7.52	N	4.03
cal.	C	51.02	H	8.15	N	5.76

Results and discussion

Synthesis

Various synthetic methods for the preparation of derivatives of mono- and oligosaccharides with selective functionalization [8, 12, 21, 22] have been reported. Most of these pathways are based on the conversion of the aldehyde function. Aldonolactones, which are prepared by electrolytic oxidation of mono- or oligosaccharides can be converted to carbohydrate-based saccharideamides by reaction with *n*-alkyl-amines [22].

Two synthetic routes for the conversion of reducing sugars were explored. As shown in Fig. 1, *n*-alkyl amines were reacted to the respective activated carbamates *1a–1f*

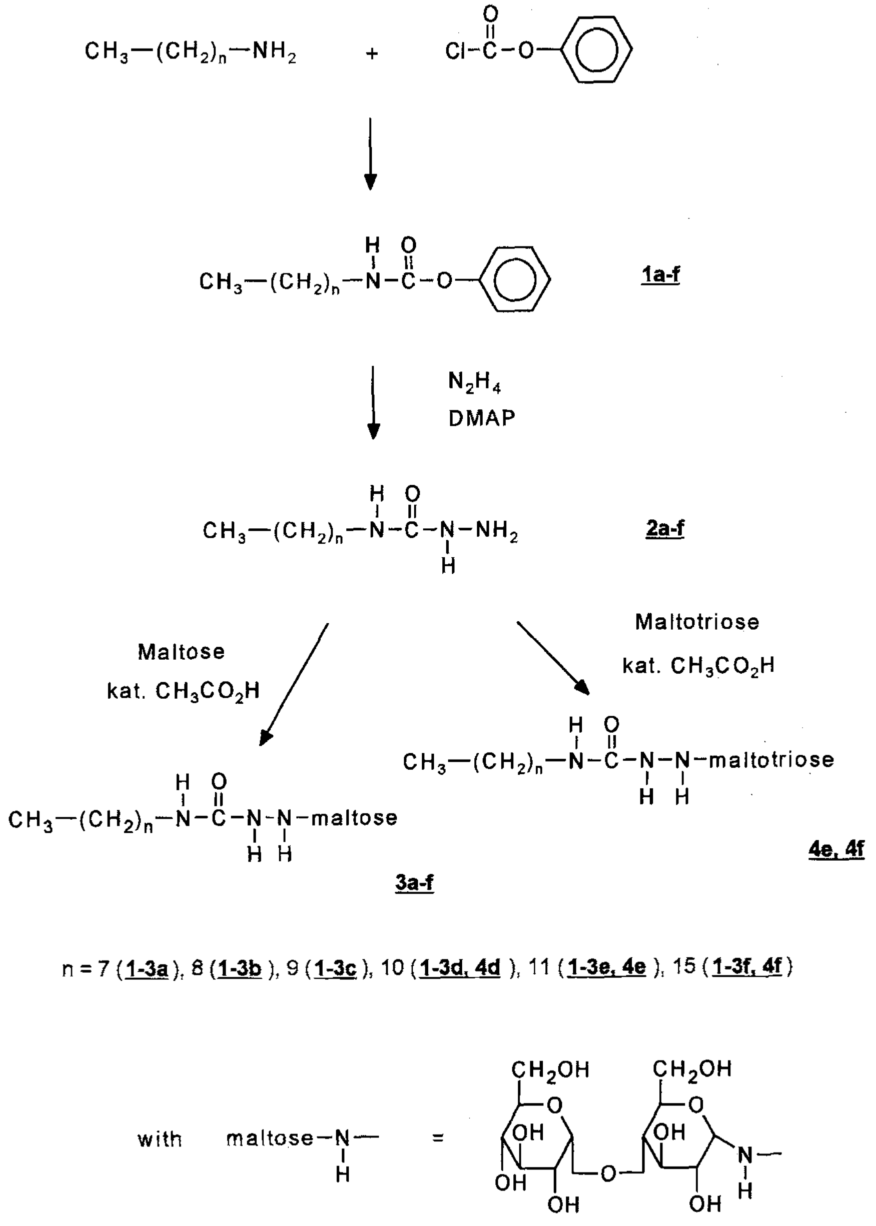


Fig. 1 Synthesis of semicarbazone-based tensides (unsubstituted derivatives)

[16]. Subsequently, hydrazine substituted phenol [17], using 4-dimethylaminopyridine as transesterification activator, was employed. The condensation reaction of the resulting *n*-alkyl semicarbazides *2a–2f* with reducing sugars such as D(+)-maltose or maltotriose [18] led to the corresponding semicarbazones *3a–3f*, *4e* and *4f*, respectively. The compounds synthesized via this route can be viewed as urea derivatives substituted with a hydrophilic and a hydrophobic unit.

The central link between the two different building blocks of the amphiphile plays a crucial role for the organization of sugar based tensides in solution and upon crystallization, due to the formation of hydrogen bonds between the respective units [8, 23]. In order to evaluate the effect of the central urea units on the supramolecular organization, a second series of N-methylated amphiphiles was synthesized using an alternative route (Fig. 2). The acyl chlorides were transformed to the isocyanates *5a, b* by reaction with trimethylsilylazide and Curtius rearrangement [19]. Addition of methylhydrazine [20] and condensation with D(+)-maltose or maltotriose led to the N-methylated semicarbazones *7a, b* and *8b*.

Both synthetic pathways shown in Fig. 1 and Fig. 2, respectively, were comparable with respect to the purity of

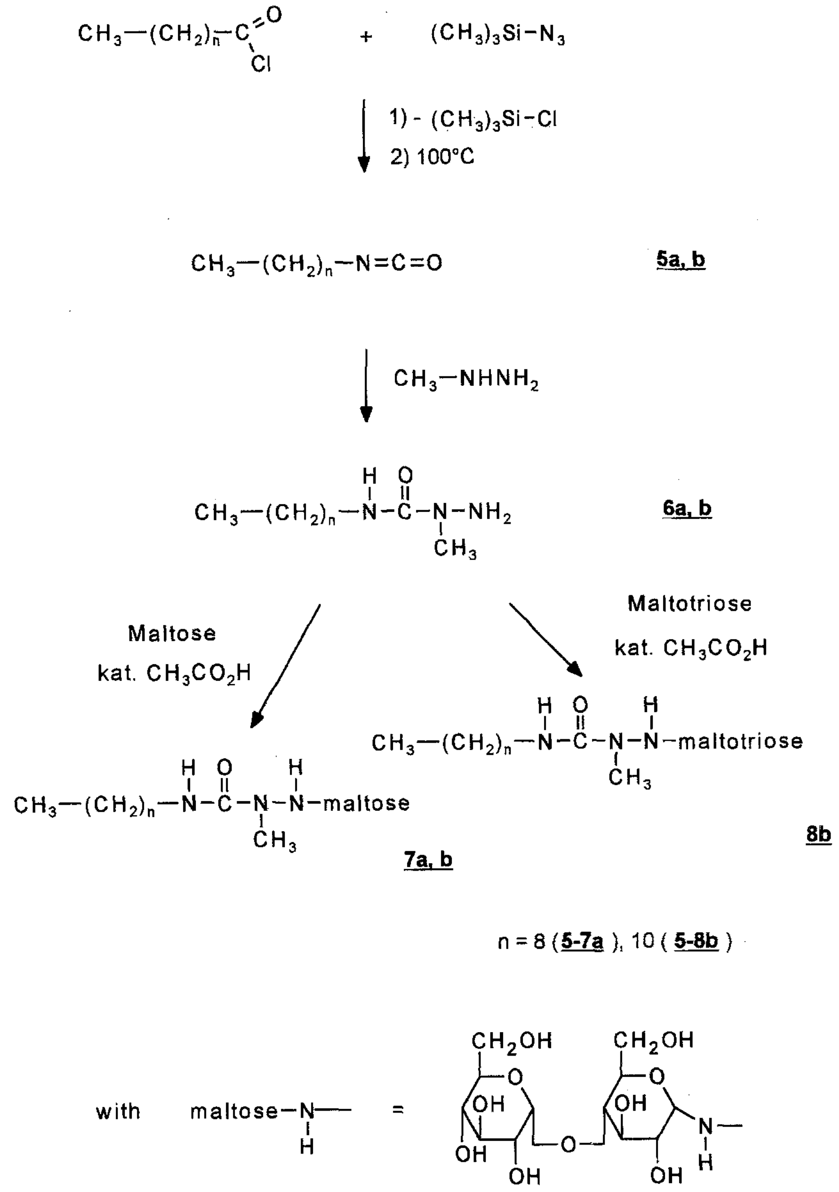


Fig. 2 Preparation of semicarbazone-based tensides (N-methyl-substituted derivatives)

the resulting amphiphiles and afforded overall yields of approximately 60%. The last step was nearly quantitative in all cases with respect to the carbohydrate unit. As a comparison, the oxidative coupling method is known to give yields in the range of 40 to 70% as given in refs. [22, 24] and [25], respectively.

The main advantages of the new synthetic route described in this paper are i) the carbohydrate unit is conveniently introduced in the last step, thus avoiding hydrolysis of the glycosidic linkage and ii) the reaction is specific for aldehyde groups. This excludes the possibility of multisubstitution by reaction of the hydroxyl-moieties.

Solution properties and surface activity

The solution structures of saccharide based amphiphiles, i.e., formation of micelles or other aggregates depend on the interaction of lipophilic and hydrophilic segments as well as interaction with the solvent. Therefore, it has been suggested that the balance between lipophilic and hydrophilic interaction determines the organization in solution [1, 5–8]. In the case of the semicarbazone surfactants described in this paper, an additional, strong effect can be expected from the H-bonding type interaction of the urea-like linkages. The contribution of the different interactions are likely to influence the critical micelle concentration (CMC) of semicarbazone amphiphiles. Therefore, amphiphilic properties were investigated with respect to three parameters: i) the length of the *n*-alkyl chain, ii) the size of the saccharide segment of the tensides, and iii) the structure of the linkage between the segments, which determines the possibility of H-bonding.

With respect to these considerations, various representative D(+)-maltose- and D(+)-maltotriose-based amphiphiles were prepared (Table 1). In the first series of maltose-semicarbazones, the length of the *n*-alkyl chain was varied between $n = 8$ and 12. Additionally, a derivative with $n = 16$ was synthesized. N-methylated maltose based tensides with $n = 9$ and $n = 11$ were prepared according to the second route. Maltotriose based amphiphiles were prepared, with $n = 11, 12$ and 16.

The surface tension and critical micelle concentration (CMC) of the maltose and maltotriose amphiphiles was characterized via surface tension measurements in dilute solutions of the compounds. The Wilhelmy-plate method was employed to determine the surface tension at the air-water interface. The data are summarized in Table 1.

Generally, the CMC-values are similar to those known for other saccharide tensides [26] and nonionic surfactants. For the maltose derivatives *3a*–*3f*, an increasing length of the *n*-alkyl unit led to a decrease of the CMC (see Fig. 3). An extremely low value is found for the *n*-hexadecyl derivative *3f*, as also observed for the respective maltobionamide [22]. This decrease appears to be general for tensides and is due to the "hydrophobic effect": Elongation of the hydrophobic chain leads to an increase of the hydrophobicity of the molecule and a decrease of the molecular solubility. As a result, the equilibrium between micellar aggregates and molecularly dispersed amphiphiles is shifted towards the aggregates.

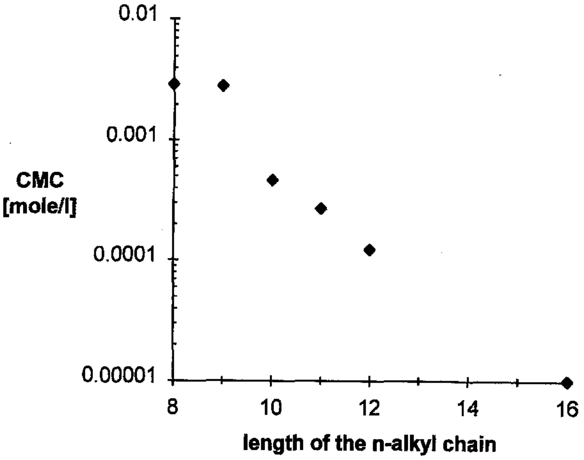
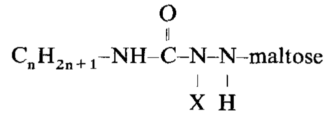


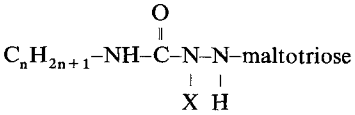
Fig. 3 Dependence of CMC on the length of the *n*-alkyl chain (maltose based tensides)

Molecular surface areas were estimated using the Gibbs adsorption isotherm, which was applied to the slope of the surface tension curve close to the CMC [27]. The molecular surface areas were in the range of 0.3–0.5 nm², which is also typical for other sugar-based tensides [1]. Contrary to the behavior of the maltose-based amphiphiles, the CMC of the maltotriose derivatives exhibited only little dependence on the length of the *n*-alkyl chain, i.e. for the *n*-dodecyl (*4e*) and *n*-hexadecyl derivatives (*4f*) almost identical CMC-values were found. This

Table 1 CMC values of maltose based tensides

Length of alkyl chain *n*	Maltose-based semicarbazones[a]				Maltotriose-based semicarbazones[b]	
	X = H		X = CH_3			
	Sample	CMC[c]	Sample	CMC[c]	Sample	CMC[c]
8	*3a*	0.15 (2.93)				
9	*3b*	0.15 (2.85)	*7a*	0.17 (3.15)		
10	*3c*	0.025 (0.46)				
11	*3d*	0.015 (0.27)	*7b*	0.017 (0.30)	*8b*	0.03 (0.41) X = CH_3
12	*3e*	0.007 (0.12)			*4e*	0.003 (0.041) X = H
16	*3f*	lower than 0.001 (< 0.015)			*4f*	0.003 (0.038) X = H

[a]) 
$C_nH_{2n+1}-NH-\overset{\overset{O}{\|}}{C}-\underset{\underset{X}{|}}{N}-\underset{\underset{H}{|}}{N}-\text{maltose}$

[b]) 
$C_nH_{2n+1}-NH-\overset{\overset{O}{\|}}{C}-\underset{\underset{X}{|}}{N}-\underset{\underset{H}{|}}{N}-\text{maltotriose}$

[c]) in g/100 ml (in brackets mole/l* 10^{-3})

may be attributed to the dominating effect of the large hydrophilic head group in comparison with the small lipophilic chain.

The solubility of the N-methyl-substituted compounds *7a, b* and *8b* was better than for the unsubstituted amphiphiles. N-methyl-substitution, however had no significant effect on the CMC. This is in contrast to gluconamides and related compounds, where a dependence of the CMC on the methyl-substitution is found. In this case the CMC is higher for N-methylated compounds [8], which is explained by reduced intermolecular attractive forces. In the case of semicarbazone amphiphiles, only one of the possible two hydrogens was substituted by a methyl unit. This may account for the small influence on the CMC.

In order to characterize the solution structures of the amphiphiles, static light scattering was attempted. Light scattering of the *n*-decyl maltose derivative *3c*, showed complex behavior. At 40 °C and in the concentration range between 0.03 and 0.3 mg/ml a continuous increase of the size of the aggregates was observed. These aggregates (about 200 nm) were stable until the concentration reached 0.9 mg/ml, then apparently a second aggregation step occurred. In spite of the clear CMC, it appeared difficult to observe well-defined aggregates due to a strong tendency towards gel-formation. Further measurements are in progress at present.

Gelation

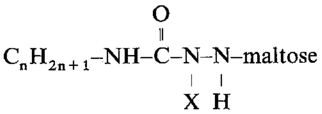
As a consequence of the supramolecular organization, gelation in aqueous solution at concentrations as low as 0.5% is a common phenomenon for saccaride based amphiphiles [1, 23]. Pfannemüller and Welte [8] as well as Fuhrhop and coworkers have characterized the morphology of such gels extensively and have observed a variety of different ribbon-like or rope-like morphologies [5–7], which are determined by the nature of the chiral saccharide headgroup and the length of the *n*-alkyl chain. It is assumed that the fibrillar structure of the aggregates is due to linear hydrogen-bonding of the amphiphiles, whereas the twist of the ribbon like morphologies is due to the chirality of the polar head groups.

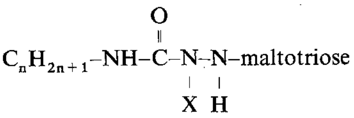
In the case of the non-N-methylated semicarbazone derivatives *3a–3f*, *4a* and *4f*, similar morphologies were observed. The compounds formed gels even at concentrations below 0.125% upon standing at room temperature (see Table 2). In contrast to gels of *n*-alkylgluconamides, which have to be stabilized by surfactants like SDS to obtain long-term stability [7], our gels were mostly clear and stable for prolonged periods of time without additional stabilization. This was especially striking in the case of the *n*-decyl derivative *3c*, which exhibited good stability over a period of several months.

Parallelling the results of the CMC-measurements, tensides with longer *n*-alkyl chains formed gels at lower concentration than amphiphiles with shorter *n*-alkyl substituents (Fig. 4). The generally extremely low concentrations necessary for gel-formation in these systems in comparison to *n*-gluconamides may be explained by additional stabilization by hydrogen bonds of the urea units. The importance of H-bonding of the linking unit between the hydrophilic and the hydrophobic parts of such molecules has been pointed out before by various authors and

Table 2 Minimum tenside concentration for gelation

Length of alkyl chain	Maltose-based semicarbazones[a])				Maltotriose-based semicarbazones[b])	
n	X = H		X = CH_3			
	Sample	min. conc.[c])	Sample	min. conc.[c])	Sample	min. conc.[c])
8	*3a*	> 2.5				
9	*3b*	> 1	*7a*	no gelation up to 10		
10	*3c*	> 0.125				
11	*3d*	> 0.125	*7b*	no gelation up to 10, needle-like crystals	*8b*	no gelation up to 1 (X = CH_3)
12	*3e*	> 0.125			*4e*	> 0.25 (X = H)
16	*3f*	hardly soluble, no gelation			*4f*	> 0.2 (X = H)

[a])

$C_nH_{2n+1}\text{–NH–}\overset{\overset{O}{\|}}{C}\text{–}\underset{X}{N}\text{–}\underset{H}{N}\text{–maltose}$

[b])

$C_nH_{2n+1}\text{–NH–}\overset{\overset{O}{\|}}{C}\text{–}\underset{X}{N}\text{–}\underset{H}{N}\text{–maltotriose}$

[c]) in g/100 ml

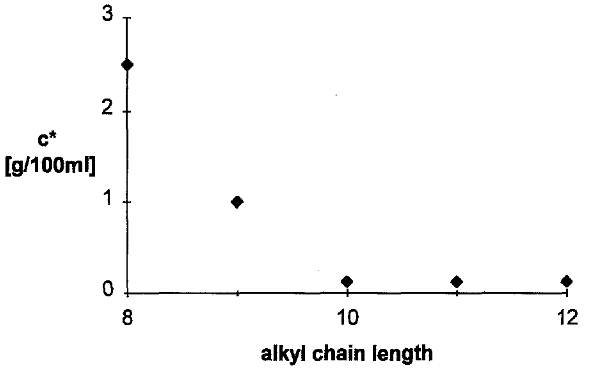


Fig. 4 Correlation between alkyl chain length and c^* = minimum tenside concentration for gelation (maltose-based tensides)

also seems to play a crucial role for the gelation of *n*-octylgluconamide [8].

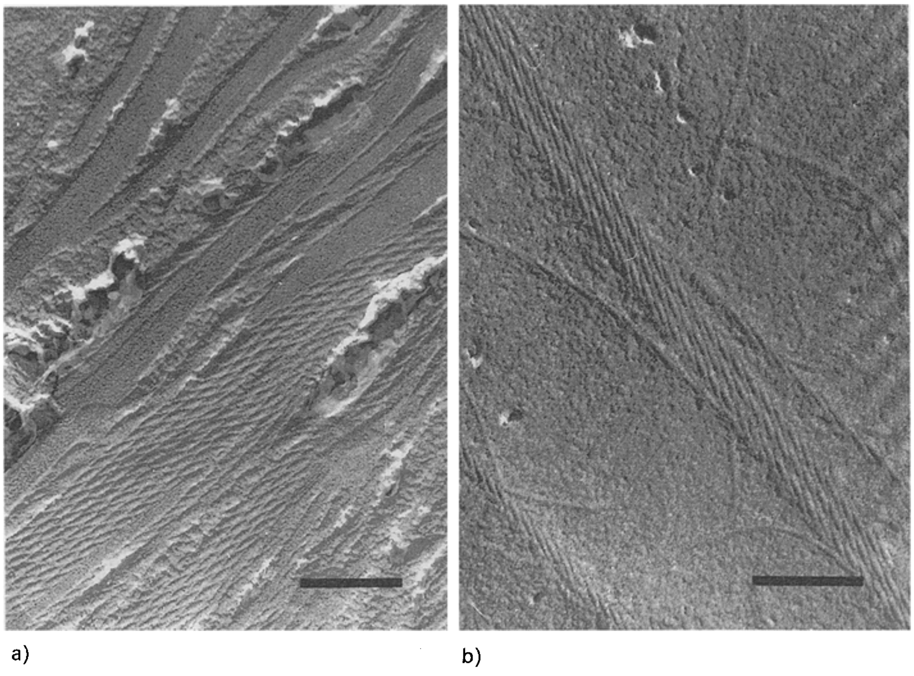
The crucial effect of H-bonding is confirmed by the observation that no gelation occurred for the N-methyl-substituted tensides *7a* and *7b* even at concentrations as high as 10%. This behavior is similar to that observed in N-alkanoyl-N-methyl glucamides, however N-decanoyl-N-methyl glucamide still forms gels at concentrations of 2.5–10% [8]. Obviously, N-methylation impairs formation of hydrogen bonds and reduces intermolecular attractive forces considerably. This evidences the importance of the interaction of the central urea units in the semicarbazone based amphiphiles.

The morphology of the gels is correlated to the molecular structure of the respective tensides, i.e., the size and chirality of the hydrophilic head groups and the hydrophilic/lipophilic balance. Twisted helical fibers are commonly found for gels of *n*-octyl L- and D-gluconamides. This has been explained by the chiral bilayer effect [23], i.e., the formation of twisted bilayer-structures due to the chirality of the polar head group.

In our investigation of the gel-morphology we were mainly interested in the effect of a gradual increase of the length of the lipophilic part of the maltose-based amphiphiles upon the self-organization. Furthermore, a comparison of the supramolecular organization of the novel semicarbazone amphiphiles with the well known gluconamides was attempted. Generally, TEM-images of freeze-fractured gels of D(+)-maltose semicarbazones exhibited ribbon- and ropelike morphologies, which resemble to a certain extent the structures known for other saccharide based amphiphiles [23, 8]. All fibers and ropes showed the same helical twist sense. The twist sense is determined by the chirality of the saccharide head groups, as known for gluconamides [23]. In all cases, at least two structural levels of fiber organization could be distinguished.

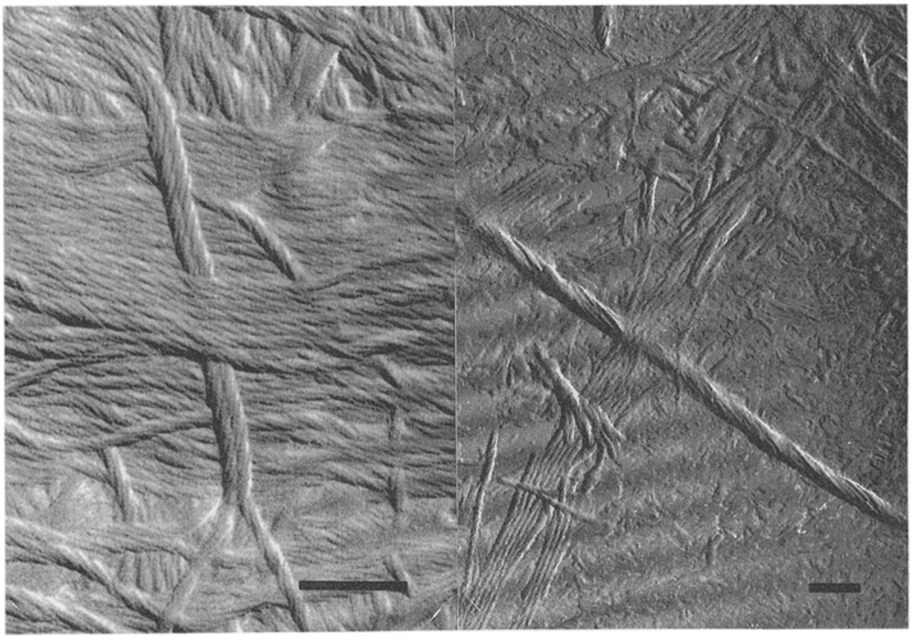
Figures 5a, b depicts the freeze-fracture replica of gels of the *n*-octyl- and the *n*-nonyl maltose semicarbazone, respectively. Both gels are composed of parallel packed, rope-like fibrils. The diameter of the twisted strands is between 20 and 25 nm in both cases, the helical pitch is approximately 40 nm. In the case of the *n*-octyl derivative, a considerable fraction of non-ordered material is discerned. For the *n*-nonyl maltose semicarbazone (Fig. 5b), two

Fig. 5a, b TEM micrographs of the freeze fractured gels of the *n*-octyl maltose derivative *3a* (left) and the *n*-nonyl derivative *3b* (right) scale bar = 200 nm


a)

b)

Fig. 6a, b TEM micrographs of the freeze fractured gels of the n-decyl maltose derivative *3c* scale bar = 200 nm


a) b)

different levels of supramolecular organization can be distinguished. Nanofibrils of 10–15 nm diameter are organized to tightly twisted strands of approximately 25 nm thickness.

Intriguing structures were observed for the n-decyl derivative. Figure 6a shows twisted strands which are approximately 30 nm in diameter. Different structural levels of self-organization can be distinguished in Fig. 6b. Small (25 nm) twisted strands either associate laterally, as in Fig. 6a, or organize into larger, rope-like superstructures (100 nm) with a right-handed twist and a helical pitch of 35 nm. In the images, different levels of ordering from nanofibrils to larger ropes can clearly be discerned. Also, the unwinding of large helical superstructures to smaller, twisted ropes can be seen. Apparently, the hydrophobic/hydrophilic balance of the n-decyl-derivative highly favors the formation of helical aggregates.

The n-undecyl maltose semicarbazone (Fig. 7) forms a network of helical ropes similar to the structures observed for the n-decyl derivative. Twisted strands with a helical pitch of 35 nm and 20–30 nm diameter, consisting of 10–15 nm fibrils are observed, as well as needle-like nanocrystals of 10–15 nm thickness and up to 0.2 μm length. The thickness of the fibrils and crystallites may be correlated to the dimensions estimated for a double bilayer structure (ca. 12 nm).

The n-dodecyl maltose semicarbazone is organized in different superstructures. A variety of ribbon-like morphologies as well as small vesicle-like spherical aggregates (Fig. 8b) of 20–25 nm are found for the n-dodecyl derivative. Rather thick fibers of up to 80 nm in diameter, less twisted than the helical structures found for the semicarbazones with smaller n-alkyl chains are depicted in Fig. 8a. Figure 8b shows spherical aggregates as well as rather flat fibers (diameter 20 nm), which appear to be twisted every

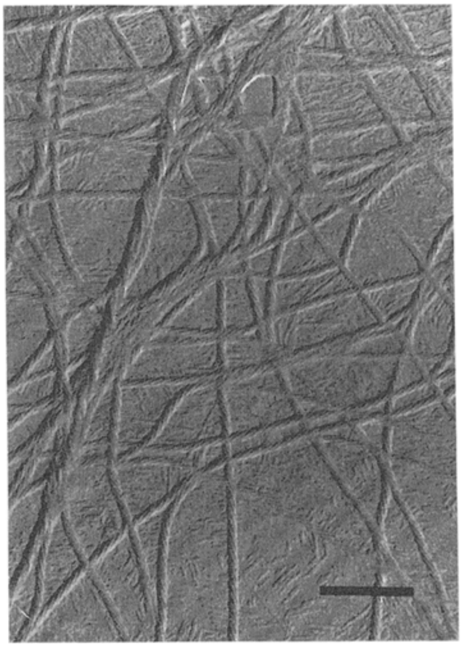


Fig. 7 TEM micrograph of the freeze fractured gel of the n-undecyl maltose derivative *3d* scale bar = 200 nm

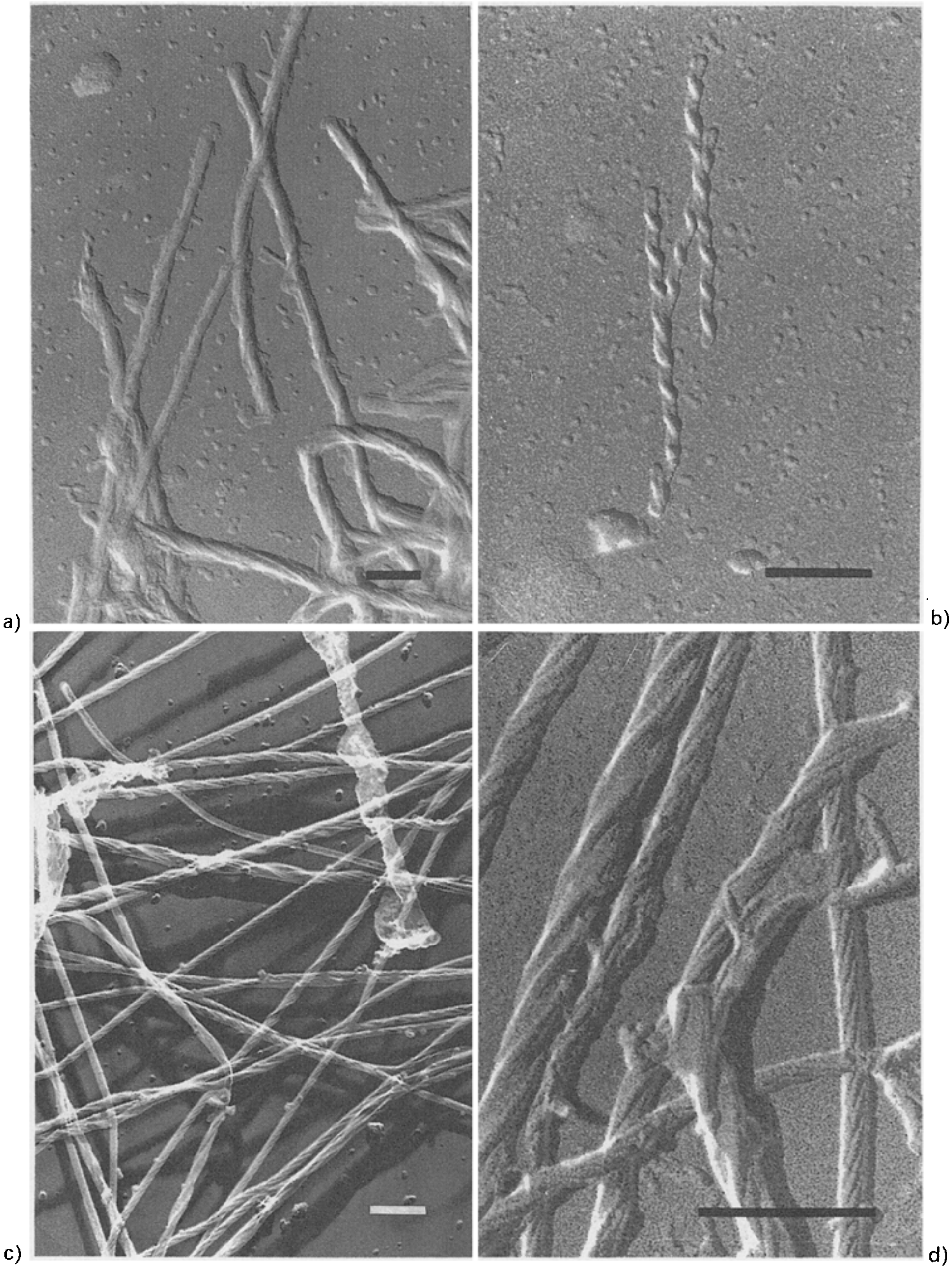


Fig. 8a–d TEM micrographs of the freeze fractured gel of the *n*-dodecyl maltose derivative *3e* scale bar = 200 nm

55 nm. Twisted fibers with rather nonuniform thickness between 25 and 50 nm similar to the morphologies observed for the *n*-decyl and *n*-undecyl derivatives are also present (Fig. 8c and d). Generally, the strands observed for the *n*-dodecyl amphiphile are less twisted than for the semicarbazones with smaller *n*-alkyl chains. This is most likely due to the decreasing effect of the hydrophilic headgroup due to the change of the hydrophilic/hydrophobic balance.

For the *n*-hexadecyl maltose semicarbazone, only a small fraction of the amphiphiles was organized in helical strands (Fig. 9b). The *n*-hexadecyl semicarbazone was considerably less soluble in water than the shorter chain analogs. Mainly network structures without helical ordering (Fig. 9a) were found for this tenside. This mirrors the effect of the long lipophilic chain. Only in some places could helically organized fibrils be discerned (diameter 15 nm, pitch 50 nm).

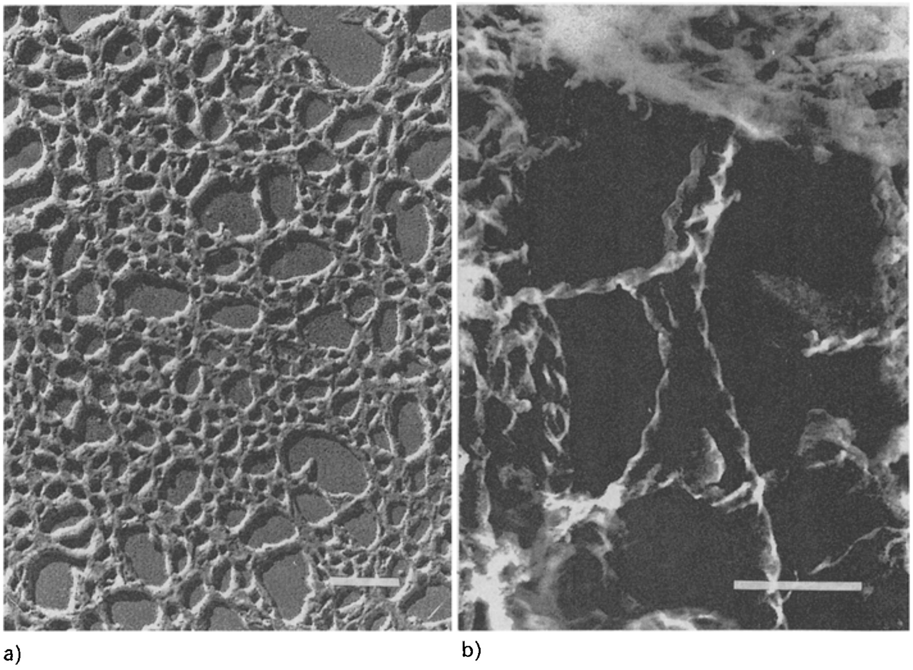


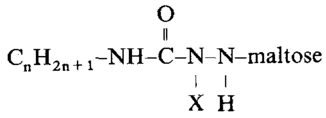
Fig. 9a, b TEM micrographs of the freeze fractured gel of the *n*-hexadecyl maltose derivative *3f* scale bar = 150 nm

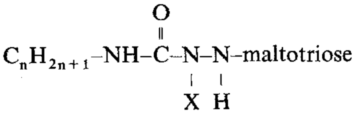
Summarizing the morphological data, it can be concluded that all maltose-semicarbazone amphiphiles form organized supramolecular structures, which can be explained by the chiral bilayer principle [23]. As for gluconamides, hydrogen-bonding constitutes a major prerequisite for the formation of ordered fibrillar structures. The organization of the bilayers in helically twisted strands depends on the length of the lipophilic segment. Apparently, an *n*-alkyl chain length between 10 and 12 represents an optimum for the formation of organized molecular assemblies. This is longer than in gluconamide amphiphiles, where the *n*-octyl chain represents an optimum for self-organization to helical strands [8]. Most probably, this is a consequence of the larger hydrophilic head group of the molecule in the maltose semicarbazones.

An increase of the length of the lipophilic segment leads to a decrease of the twist of the strands, which is most probably due to the diminishing effect of the chirality of

Table 3 Liquid crystalline and melting behavior of amphiphiles

Length of alkyl chain *n*	Maltose-based semicarbazones[a])				Maltotriose-based semicarbazones[b])	
	Sample	X = H	Sample	X = CH_3	Sample	
8	*3a*	m.p. 117–122 °C				
9	*3b*	m.p. 122–125 °C	*7a*	m.p. 100–102 °C		
10	*3c*	LC phase > 132 °C				
11	*3d*	LC phase > 134 °C	*7b*	m.p. 104–109 °C	*8b*	m.p. 135–140 °C (X = CH_3)
12	*3e*	LC phase > 138 °C			*4e*	LC phase > 145 °C (X = H)
16	*3f*	LC phase > 145 °C			*4f*	LC phase > 145 °C (X = H)

[a])

$C_nH_{2n+1}\text{-NH-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}\underset{X}{\underset{|}{N}}\text{-}\underset{H}{\underset{|}{N}}\text{-maltose}$

[b])

$C_nH_{2n+1}\text{-NH-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}\underset{X}{\underset{|}{N}}\text{-}\underset{H}{\underset{|}{N}}\text{-maltotriose}$

the saccharide head group. Also, we have not been able to observe ordered supramolecular assemblies for the maltotriose-derivatives *4e* and *4f* yet, despite gelation. We attribute this to the imbalance of hydrophilic and lipophilic segments.

Thermotropic behavior

Saccharide-based amphiphiles generally show both thermotropic and lyotropic liquid crystalline behavior [28, 21]. For example, *n*-alkyl gluconamides show smectic S_A phases, where the carbohydrate cores overlap to produce a bilayer structure [29]. Due to the similar structure of our tensides, we expected analogous behavior.

In fact, the thermotropic liquid crystalline behavior of the semicarbazone tensides follows the same order as gel formation (see Table 3). N-methyl substituted tensides melt directly to the isotropic phase, unsubstituted derivatives show a thermotropic liquid crystalline phase, when the alkyl chain length reaches a critical length of about 10 carbon atoms. Isotropization could not be observed due to thermal degradation, which occurs to a certain extent already above 100 °C and accelerates above 150 °C. The textures observed so far were unspecific. So far, we have not been able to obtain typical smectic textures as known for example for 1-deoxy-1-(N-methylundecanamido)-D-glucitol [28].

Fig. 10 Micrograph of the texture (crossed polarizer) of the *n*-decyl maltose derivative *3c*, 135 °C

Figure 10 shows an example for the strongly birefrigent textures observed. (*n*-decyl maltose tenside *3c*). Further work on the mesomorphic properties is in progress.

Conclusions

A convenient synthetic route to amphiphiles based on reducing saccharides has been developed, which uses the direct conversion of the aldehyde function with a tailor-made functionality attached to an alkyl chain. The resulting semicarbazones represent an easily accessible class of sugar-based amphiphiles. A wide range of different alkyl segments and hydrophilic head groups can be employed in the synthesis.

Two series of saccharide tenside molecules with central unsubstituted urea-like units and N-methylated urea-like units with different *n*-alkyl chains have been synthesized.

Solution and gel characterization experiments revealed the formation of organized, ribbonlike morphologies with structural variety, depending on the lipophilic unit attached. In some cases, the gels were surprisingly stable over long periods of time, which distinguishes the materials from gels of *n*-alkylgluconamides. Subsequent to gelation, no further crystallization was observed.

The following trends were observed for the series of amphiphiles prepared:

i) CMC and the minimum concentration for gel formation decreased with increasing *n*-alkyl chain length due to the "hydrophobic" effect, in analogy to other tensides.
ii) Gel formation at concentrations lower than 1% is only found for non-N-methylated amphiphiles. Similar to the morphologies observed for gluconamides, we also found twisted rope-like structures as constitutive structures of the tenside gels. Apparently, H-bonding in the urea units plays a dominant role for the stabilization of the supramolecular, ribbon-like aggregates.
iii) Thermotropic LC-phases were only observed for amphiphiles with unsubstituted urea linking units.

Further studies of the spontaneous association of the semicarbazone amphiphiles are in progress. In view of the current vivid interest in the area of organized molecular assemblies [30], we consider saccharide based semicarbazones as a very promising new class of amphiphiles.

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