Amphiphilic Carbohydrate-Based Mesogens, 11 [1]

Synthesis of Mesogenic 1-Alkylthio-1-deoxy-D-galactitols by Glycoside Reduction

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Alkyl-1-thio- α/β -D-galactopyranosides (hexyl-dodecyl, **1a–g**) have been O-diethylborylated and then reduced with tetraethyldiboranes(6) in the presence of 9-methylsulfonyloxy-9-borabicyclo[3.3.1]nonane (MSBBN) catalyst to give 1-alkylthio-1-deoxy-D-galactitols **3a–g** after deprotection. **3** exhibit the smectic A liquid crystalline phase on melting.

Amphiphilic carbohydrate derivatives merit study for a number of reasons. They have, for example, proved useful for the solubilization and crystallization of membrane proteins [2] and they can also have interesting, as yet poorly understood biological functions: Racemic 1-O-*n*-pentyl-glycerol can permeate the blood-brain barrier [3], and the longer chain 3-O-alkyl-D-glucoses exhibit high inhibitory activity toward tumor cell growth [4]. 2-O- [5a] and 3-O-alkyl-L-ascorbic acids [5b] have been shown to be free radical quenchers which display interesting physiological activities. It is now well established that certain amphiphilic carbohydrates can form liquid crystals, and over the past decade these have attracted increasing attention [6].

Our interest in amphiphilic carbohydrates has been centred on the synthesis of chemically and thermally stable mesogens having O, S or CH₂ linkages between the polar alditol head group and the lipophilic alkyl chain [1]. After the first report on the synthesis of a homologous series of mesogenic 1-alkylthio-1-deoxy-D-mannitols [7a], the series of 3-alkylthio-1,2-propanediols [7b] and 1-alkylthio-1-deoxy-D-glucitols [7c] have also been described. Below we extend this list of thioether alditol amphiphiles by describing the prepa-

ration of hexyl to dodecyl 1-alkylthio-1-deoxy-D-galactitols.

Results and Discussion

It has been reported that, in general, 1,2-*trans*-1-thioglycosides can be prepared by reaction of 1,2-*trans* per-O-acetates with thiols in chloroform in the presence of 4–5 equivalents of F₃B–OEt₂ at room temperature [8]. In the case of 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose a mixture containing about 70% of the alkyl-1-thio- α -D-glucopyranosides together with 30% of the β -D-glucopyranosides was obtained [7c, 9].

Because of this, it did not surprise us to find that the condensation of 1,2,3,4,6-penta-O-acetyl- β -D-galactopyranoside with hexanethiol to dodecylthiol in the presence of F₃B–OEt₂ yielded product mixtures containing *circa* 65% alkyl-1-thio- α -D-galactopyranosides and 35% of the corresponding β -D-glycosides. As mentioned previously [7c] for the preparation of alkyl-1-thio- α,β -D-glucopyranosides, the reported procedure can be improved in several ways: Firstly, the amount of F₃B–OEt₂ can be reduced to two equivalents, and secondly the reaction times can be shortened to about 30 min by carrying out the reaction in small volumes of refluxing chloroform.

Deacetylation to give the crude alkyl-1-thio- α,β -D-galactopyranosides **1a–g** was achieved by standard Zemléen saponification using methanolic

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Scheme 1. Reaction scheme.

sodium methoxide. **1a–g** were then converted into alkyl-2,3,4,6-tetra-O-diethylboryl-1-thio- α,β -D-galactopyranosides **2a–g** on reaction with activated triethylborane in heptane.

The quantitative glycoside reductions of **2a–g** were realized by reacting them with tetraethyl-diborane in the presence of 0.1 equivalent of MSBBN (9-BBN mesylate) at 120 °C for *ca.* 7 h. As the course of the reactions were not monitored, it is likely that shorter reaction times might suffice. The reaction mixtures were concentrated *in vacuo* and the residues deboronated to give pure 1-alkylthio-1-deoxy-D-galactitols **3a–g** in yields of 65–83% (see Table II).

This approach to the preparation of 1-alkylthio-1-deoxy-D-galactitols by regioselective hydro-boration of the endocyclic acetal bond is an im-

provement of the procedures reported previously [10].

The amphiphilic **3a–g** display unusual solubility behaviour. They are either insoluble in or dissolve and precipitate out quickly from the following solvents: water, methanol, ethanol, DMSO, pyridine, Et₂O, toluene, pentane and acetone. Usually the shorter chain members in a series of amphiphiles are more soluble in polar solvents whereas an increase in chain length is accompanied by increasing solubility in apolar solvents.

In order to characterize **3a–g** by NMR spectroscopy, samples were first converted to the penta-O-acetyl derivatives by reaction with acetic anhydride in pyridine. The D-galactitol moiety adopts a planar zigzag conformation as evidenced by the characteristic threo couplings $J_{2,3} = J_{4,5} = 1.6$ Hz and the typical erythro coupling von $J_{3,4} = 10$ Hz.

The melting points of **3a–g** are fairly high and cover a very narrow range from 148 to 154 °C (*cf.* Table I and Fig. 1). The phase transition temperatures, as determined by polarizing microscopy, are in good agreement with the values found by differential scanning calorimetry (DSC). Of the amphiphiles **3a–g**, only 1-hexylthio-1-deoxy-D-galactitol **3a** melts to form an isotropic melt. However, on cooling by ~3 °C, mesophase formation occurs as indicated by the appearance of bâtonnets. All the higher homologues are enantiotropic mesogens which melt to give the smectic A mesophase. Polarizing microscopy allows the characteristic textures of this phase to be observed [12]. Typically, the bâtonnets which form at the clearing point on cooling the isotropic melt, coalesce to give the focal-conic texture. Large, essentially homeotropic, areas are also observed together with oily streaks.

Com- pound	<i>n</i> ^b	Crystal–crystal transition [°C] ^c	M.p. [°C]	ΔH [kJ mol ⁻¹]	C.p. [°C]	ΔH [kJ mol ⁻¹]	Stable mesophase range [°C]
3a	6	92.3 (7.8)	154.1	57.4	151.4 ^d	3.2 ^d	– ^c
3b	7	83.5 (4.8)	152.1	55.4	167.4	2.6	~15
3c	8	104.4 (4.7)	149.0	60.2	177.4	2.6	~28
3d	9	108.7 (2.4)	152.0	59.6	186.1	2.4	~34
3e	10	56.6 (0.9), 107.6 (5.2)	148.0	57.5	185.5	2.7	~38
3f	11	52.4 (1.1), 113.4 (7.1)	148.9	57.9	192.5	1.8	~44
3g	12	122.2 (4.6)	148.8	59.7	190	1.5	~41

Table I. Transition temperatures and enthalpies of the phase transition of **3a–g**.

^a Determined with a DuPont 1090 calorimeter. Heating rates 10 °C min⁻¹; ^b number of carbon atoms in the alkyl chain; ^c enthalpies (kJ mol⁻¹) in brackets; ^d values found on cooling the isotropic melt; ^e monotropic mesophase.

Table II. Yields, optical rotations, analytical and mass spectrometric data for the 1-alkylthio-1-deoxy-D-galactitols **3a–g**.

Compound	Yield ^a [%]	Formula [mol. mass]	Analyses [%]			$[\alpha]_D^{20}$ (c, CHCl ₃)	Found M ⁺	m/z (% rel. intensity)	
			C calcd (found)	H calcd (found)	S calcd (found)			Base mass	Other characteristic masses
3a	79	C ₁₂ H ₂₆ O ₅ S [282.4]	51.04 (51.08)	9.28 (9.31)	11.35 (10.92)	3.3 (0.6)	<1	43	264(3), 246(4), 233(6), 215(24), 173(17), 147(30), 129(31), 61(74)
3b	83	C ₁₃ H ₂₈ O ₅ S [296.4]	52.68 (51.89)	9.52 (9.73)	10.82 (10.74)	3.7 (0.6)	<1	57	278(3), 260(4), 247(8), 229(31), 187(21), 147(42) 129(42), 61(83)
3c	75	C ₁₄ H ₃₀ O ₅ S [310.4]	54.17 (53.65)	9.74 (9.66)	10.33 (10.47)	4.3 (0.6)	–	73	292(5), 274(8), 243(50), 201(42), 159(77), 147(76), 129(75), 87(69)
3d	65	C ₁₅ H ₃₂ O ₅ S [324.5]	55.52 (55.70)	9.94 (9.90)	9.88 (10.48)	4.1 (0.5)	–	43	306(4), 288(5), 257(39), 215(27), 173(61), 159(39), 147(71), 129(81)
3e	72	C ₁₆ H ₃₄ O ₅ S [338.5]	56.77 (56.70)	10.12 (10.11)	9.47 (9.56)	3.5 (0.7)	–	43	320(3), 302(4), 271(35), 229(22), 187(48), 173(31), 147(64), 129(70)
3f	65	C ₁₇ H ₃₆ O ₅ S [352.5]	57.92 (57.42)	10.29 (10.58)	9.09 (9.17)	3.2 (0.6)	–	43	334(3), 316(4), 285(29), 243(17), 201(41), 187(24), 147(59), 129(62)
3g	71	C ₁₈ H ₃₈ O ₅ S [366.5]	58.98 (58.62)	10.45 (10.50)	8.75 (8.61)	5.1 (0.5)	–	43	348(2), 330(3), 299(32), 257(26), 215(39), 201(25), 147(50), 129(53)

^a Yields of isolated pure products after reducing **2a–g** and subsequent deboronations *cf.* Experimental section;
^b of the 2,3,4,5,6-penta-O-acetyl derivatives.

While the melting points of **3a–e** lie *ca.* 50 °C above those of the 1-alkylthio-1-deoxy-D-glucitols [7c], the clearing points for **3a–d** only lie ~20 °C above those of the corresponding D-glucitol derivatives, and by the time the alkyl chain length has reached decyl, the clearing points only differ by 7 °C. The lower melting points of the glucitol derivatives may be due to the 1,3-syn-interaction between the C² and C⁴ hydroxy groups when the molecule is in a planar extended chain (zigzag) conformation. This destabilization can cause the sickle conformer to become thermodynamically favoured.

There are two essential requirements for the formation of a mesophase by single tailed carbohydrate-based amphiphiles. Firstly, the carbohydrate head group must have sufficient hydroxyl groups which are capable of participating in the build up of a hydrogen-bonded network, and secondly the alkyl chain must be sufficiently long (usually ≥ C₆) for effective chain interdigitation to occur. The initially proposed model [13] for the

molecular arrangement in the smectic A_d bilayers consists of a central region of hydrogen-bonded carbohydrate moieties with exterior hydrocarbon chains (Model I). A new model has recently been presented [14], in which the opposite arrangement is found, *i.e.* the interdigitated alkyl chains form the central region of the smectic bilayers and the hydrogen-bonded carbohydrate head groups are on the outside (Model II). This arrangement is essentially the same as that found in the fluid lamellar (L_α) lyotropic phase [15], albeit without water being present. Furthermore, in the L_α phase alkyl chain overlap does not occur.

The thickness of the layers in the crystal and of the smectic bilayers of 1-heptylthio- and nonylthio-1-deoxy-D-galactitols **3b** and **3d** have been determined by small-angle X-ray scattering measurements.

For **3b** the d-spacing in the mesophase has been found to be 26.4 Å, which is *ca.* 1.5 times the molecular length if the molecule adopts a planar zigzag conformation. This value indicates that over-

Table III. Characteristic ^1H and ^{13}C NMR data for **1** and penta-O-acetyl-**3**.

Compound	C-1	C-2	C-3	C-4	C-5	C-6	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H ($J_{3,4}$)	4-H ($J_{4,5}$)	5-H ($J_{5,6a}$)	6a-H ($J_{6a,6b}$)	6b-H ($J_{5,6b}$)
α - 1 ^a	85.4	67.9	70.5	68.6	71.5	60.5	5.06 (5.5)						
β - 1 ^a	85.7	69.9	74.8	68.3	79.0	60.6	4.01 (8.7)						
3 -OAc ^b	33.9	68.4 ^c	68.3 ^c	67.7 ^c	67.5 ^c	62.0	2.35 (6.8)	4.95 (1.6)	5.27 (10.0)	5.17 (1.6)	5.14 (4.6)	4.13 (-11.6)	3.68 (7.5)

^a In D_6 -DMSO; ^b in CDCl_3 ; ^c assignments may be interchanged. Fig. 1. Comparison of the phase-transition temperatures of 1-Alkylthio-1-deoxy-D-galactitols **3** and -D-glucitols.

lapping bilayers are present in the smectic phase. The same applies to **3d** which has a layer spacing of 29.0 Å.

This increase in the bilayer spacing of 2.6 Å in the smectic phase on going from **3b** to **3d** corresponds to the length of an extended ethylene group and points to interdigitation of the alkyl chains in the central region of the smectic bilayer. An increase of *ca.* 5 Å would be expected for model I as alkyl chain extension would occur on

Table IV. Layer spacing for **3b** and **3d** in the crystalline and in the liquid-crystalline phase.

Mesogen	<i>n</i>	Layer spacing, <i>d</i> (Å)	
		Crystal	Mesophase
3b	7	35.2	26.4
3d	9	39.8	29.0
Δd^a		4.6	2.6

^a Difference in bilayer spacing between homologues **3b** and **3d**.

both sides of the central bilayer region [14]. In the crystalline state, the layer spacing of **3b** and **3d** is 35.2 and 39.8 Å, respectively. These values correspond to approximately twice the length of the respective molecules. The increase in the layer spacing in the crystal of 4.6 Å on going from **3b** to **3d** suggests that a model I type arrangement might exist. In the usual model I arrangement the individual sugar molecules overlap with the alkyl chains alternately pointing to the left and right of the central region.

A variety of other factors in favour of model II has also been accumulated [14]. For example, the fluid lamellar phase of Aerosol OT (sodium bis-2-ethylhexyl sulfosuccinate) in water and the smectic A phase of decyl β-D-glucopyranoside were found to be fully miscible [16]. Investigations with dodecyl maltoside and water showed that up to 42 wt.% of water is incorporated into the layers before the hexagonal lyotropic phase is formed [17]. Interesting work by H. A. van Doren *et al.* [14] showed that when water is added to crystals of heptyl-1-thio-α-D-glucopyranoside at room temperature, neither dissolution nor water penetration into the crystals is observed. On heating the sample dissolution occurs, without lyotropic mesophase formation. In contrast to this, when

Fig. 2. Schematic drawings of the possible molecular arrangements of the bilayers in the crystalline state and in the mesophase, depicted for **3b**.

water is added to the supercooled smectic A_d phase of the same amphiphile, penetration occurs readily at room temperature giving rise to cubic and hexagonal lyophases. The ease of water penetration is readily understood if one considers the carbohydrate head groups to be on the outside of the smectic bimolecular layer. The water insolubility of the smectogens presented here prevented similar experiments from being carried out.

Experimental

All experiments were carried out in dry deoxygenated solvents under an atmosphere of argon. – MS: Finnigan MAT CH5. – ^1H and ^{13}C NMR: Bruker AC 200. – DSC: DuPont 1090 calorimeter. – Optical rotations: Perkin-Elmer 241. – C,H,S analyses were performed by Dornis and Kolbe, Mülheim an der Ruhr.

Starting compounds

Penta-O-acetyl- β -D-galactopyranoside was prepared from D-galactose with acetic anhydride in the presence of sodium acetate [18]. The 1-alkane-

thiols and $\text{F}_3\text{B}-\text{OEt}_2$ (Aldrich) were vacuum-distilled prior to use. Triethylborane [19], ethyldiboranes(6) [20] and MSBBN [21] were prepared according to the references cited. Triethylborane containing 1 mol.% of diethylborylpivalate (so-called “activated triethylborane”) was used for the O-diethylborylations [22].

General procedures

Alkyl-1-thio- α,β -D-galactopyranosides **1a–g**:

The thiol (8.5 mmol) was added to the penta-O-acetyl- β -D-galactopyranoside (7.7 mmol) in chloroform (5 ml) and then $\text{F}_3\text{B}-\text{OEt}_2$ (15 mmol) was added to the stirred solution. The mixture was heated under reflux for 30 min and after cooling to ca. 20 °C a saturated sodium bicarbonate solution (35 ml) was carefully added in portions to destroy the catalyst. The mixture was transferred to a separating funnel and the flask washed with water (~5 ml). The combined aqueous phase was washed twice with diethyl ether (20 ml) and the chloroform/ether extract was shaken with water (20 ml) before drying over sodium sulfate. Finally the

solvents were removed *in vacuo* to give brown, viscous acetylated glycosides in quantitative yields.

The deacetylations were achieved by adding methanol (10 ml) and sodium methoxide (spatula tip) and stirring at r.t. until TLC (eluent: diethyl ether/hexane 1:1) showed no more starting material. **1a–g** were obtained in quantitative yield on removing the solvent. They were converted to **2a–g** without purification. The anomeric mixtures contained ~65% of the α -D-glycoside and ~35% of the β -D-anomer.

Alkyl-2,3,4,6-tetra-O-diethylboryl-1-thio- α,β -D-galactopyranosides 2a–g: Activated triethylborane (5 ml) was added dropwise to a stirred suspension of **1a–g** (*ca.* 7 mmol) in heptane (15 ml) at 60–70 °C (bath temperature) so that ethane (28 mmol) was evolved at a steady and rapid rate. Insoluble material was filtered off and the solu-

tions were then concentrated *in vacuo* ($0.1\text{--}10^{-3}$ Torr) to leave **2a–g** as orange-coloured residues in *ca.* 90% yield.

1-Alkylthio-1-deoxy-D-galactitols 3a–g: Ethyl-diboranes(6) with hydride contents of 10–15% H^- (about 10 mmol) and MSBBN (about 0.6 mmol) were added to **2** (about 6 mmol), and the stirred mixture was heated under reflux (bath temperature *ca.* 120 °C) for 7 h. The mixture was concentrated *in vacuo* (10^{-3} Torr) and the residue treated with methanol (10 ml) and pyridine (0.5 ml) and concentrated *in vacuo*. 1,2-Ethanediol (five times 3 ml portions) was added and distilled off *in vacuo* (10^{-3} Torr) before adding ethanol (20 ml) and concentrating the mixture *in vacuo*. Pure **3a–g** were isolated as white solids in yields of 65–83% (*cf.* Table II) by addition of diethyl ether (20 ml), filtration and drying.

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