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Preparation of alkyl α- and β-D-glucopyranosides, thermotropic properties and X-ray analysis☆

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Abstract

Monohydrates of heptyl to decyl α-D-glucopyranosides as obtained from product mixtures of the Fischer glucosylation were crystallized from water at the Krafft point. The results of the single-crystal X-ray analysis of anhydrous α anomers and their monohydrates provide for a better understanding of crystal formation and stability of their hydrates. The preparation of alkyl β-D-glucopyranosides—without concomitant formation of α anomers as by-products—has been described. The thermotropic properties have been investigated for the α compounds and their monohydrates, and for the β-D-glucopyranosides. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Alkyl D-glucosides have recently attracted attention as surfactants with special properties desirable to customers. They are used e.g., in cosmetic products, as food emulsifiers, textile lubricants, drug carriers and as solubilizing agents for membrane proteins [1–5]. One remarkable advantage is their biodegradability [2,3].

The first preparation of alkyl glucosides as anomeric mixtures was described more than one hundred years ago by Emil Fischer [6]. This procedure provided mainly alkyl α-D-glucopyranosides [7–9]. The classical method for the directed preparation of alkyl β-D-glucopyranosides is a multistep procedure developed by Koenigs and Knorr [10]. A valuable modification of the classical Koenigs–Knorr reaction was described by Kunz and Harreus [11]. It is shown in this paper that this method is best suited for the preparation of alkyl β-D-glucopyranosides.

Alkyl glucosides form micelles in water above their critical micellar concentration (CMC) [8,12,13]. The solubility of surfactants—as a function of temperature—is characterized by the Krafft point (minimal temperature where the surfactants form micelles). Below that temperature, the surfactant precipitates from solution because its solubility becomes lower than the CMC [14]. The Krafft points of alkyl glucosides are higher for α anomers (considerably above room temperature) than for the corresponding β anomers (≤ 0 °C). Consequently, it should be possible to separate, by crystallization, from water an

☆ Dedicated to Professor Dr H. Gerlach.

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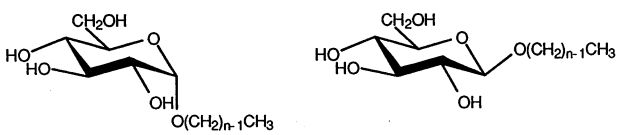
excess of the sparingly soluble α anomers from mixtures of anomers at temperatures between their Krafft points [15].

We have systematically explored this economically superior approach to the separation of certain α anomers from aqueous solutions. It was found that these surfactants form well-defined hydrates, a fact that seems to have eluded most investigators in this field. Until now, only Barrall and co-workers [16] have made a general remark, pointing out the importance of water in the crystallization process, and Dorset and Rosenbusch [17] used such a method for the crystallization of octyl α-D-glucopyranoside without being aware that they possibly obtained a hydrate. It is assumed that the preferred crystallization of alkyl α-D-glucopyranosides originates from optimal crystal packing, i.e., when a maximum number of hydrogen bonds are present [9,17,18].

Traditionally, organic solvents have been used for crystallization of alkyl glucopyranosides [8,19]. This paper describes the preparation and some properties of compounds **1a–g** and **2a–g** and some monohydrates of the former.



Alkyl α-D-glucopyranosides **1a-g** | Alky β-D-glucopyranosides **2a-g**

	1a 2a	1b 2b	1c 2c	1d 2d	1e 2e	1f 2f	1g 2g
n	6	7	8	9	10	12	14

2. Results and discussion

Alkyl α-D-glucopyranosides and monohydrates.—Alkyl α-D-glucopyranosides were prepared according to the procedure of Fischer [6]. In this one-step synthesis, a 5% solution of D-glucose in dioxane was used for the reaction with the respective alcohol. Sulfuric or *p*-toluenesulfonic acid monohydrate was used as catalyst. The formation of undesired oligosaccharides and their alkyl glycosides was reduced by using up to a 12-fold molar amount of the alcohol, the excess of which was removed by subsequent distillation. By-products were removed (after neutralization and evaporation of solvent) by filtration through the 20-fold amount of silica gel. Thus, alkyl α/β-D-glucopyranosides were obtained in a ratio up to 7:3 [7] in about 70% yield. For separation of the major components and their purification, water was used as solvent. Monohydrates of α anomers $\mathbf{1b}_{aq}$ to $\mathbf{1e}_{aq}$ were isolated in yields of up to 34% when an aqueous solution (5–10%) was cooled from about 70 to 4 °C (i.e., below the Krafft point) (see Table 1). The supernatants which contain all of the β anomers were found to be about 1:1 mixtures of α and β compounds.

The mixtures of anomers **1a**/**2a**, **1f**/**2f** and **1g**/**2g** were separated by conventional crystallization from organic solvents to get the sparingly soluble α compounds as pure anhydrous substances. The argument is, that the Krafft point of **1a** is too low for crystallization from water. Those of the α/β anomers **1f**/**2f** and

Table 1
Physicochemical properties of alkyl α-D-glucopyranoside monohydrates $\mathbf{1b}_{aq}$–$\mathbf{1e}_{aq}$

Entry	$[\alpha]_D^{20}$, MeOH	Water, %		Elemental analysis				Krafft points [a](°C)
		(KF-Titration)		Calcd		Found		
		Calcd	Found	% C	% H	% C	% H	
$\mathbf{1b}_{aq}$ $C_{13}H_{28}O_7$	+117.0° (*c* 1.00)	6.09	6.10	52.69	9.52	52.71	9.55	34
$\mathbf{1c}_{aq}$ $C_{14}H_{30}O_7$	+120.0° (*c* 0.93)	5.81	5.70	54.18	9.74	53.82	9.68	40[b]
$\mathbf{1d}_{aq}$ $C_{15}H_{32}O_7$	+107.8° (*c* 1.00)	5.56	5.67	55.54	9.94	55.40	9.78	43
$\mathbf{1e}_{aq}$ $C_{16}H_{34}O_7$	+104.0° (*c* 1.07)	5.33	5.33	56.78	10.13	56.61	10.03	43[c]

[a] Krafft points were determined by heating a mixture of surfactant and water in a probe tube (see Materials and General Methods). The solution temperature corresponds to the Krafft point of the surfactant [14]. The Krafft point of **1a** is ≤5 °C.
[b] 40 °C [18].
[c] Krafft points for **2e**: 22.5 °C, **1f**: 53 °C, **2f**: 37.5 °C [21].

Table 2
Transition points of alkyl α-D-glucopyranoside monohydrates **1b**$_{aq}$–**1e**$_{aq}$ and anhydrous alkyl α-D-glucopyranosides **1b**–**1e**[a]

Entry[b]	(tp)[c] cp[d] (°C)	(mp)[e] cp[d] (°C)	(mp) cp[Lit] (°C)
1b$_{aq}$ ($n=7$)	(48.8–51.6) 95.1[f]		(51.4) 97.9[g]
1b ($n=7$)		(53.7–55.3) 99.9[h]	(52–54)[i]
1c$_{aq}$ ($n=8$)	(57.3–57.8) 117.5[f]		(54.9) 120.1[g]
1c ($n=8$)		(73.0–74.4) 117.4[h]	(73) 117[j]
1d$_{aq}$ ($n=9$)	(59.0–59.2) 130.0[f]		(57.0) 128.0[g]
1d ($n=9$)		(67.5–68.6) 126.2[h]	(69–70)[i]
1e$_{aq}$ ($n=10$)	(66.2–67.6) 135.2[f]		(70.3) 134.2[g]
1e ($n=10$)		(77.0–77.2) 138.3[h]	(76) 138[k]

[a] Determined between crossed polarizers.
[b] n: alkyl-chain length.
[c] tp: loss of H_2O, proved by thermogravimetry.
[d] cp: clearing point (anisotropic ⇒ isotropic liquid).
[e] mp: melting point (solid ⇒ anisotropic liquid).
[f] Water.
[g] Unknown origin (see text), DSC [16].
[h] Lyophilized.
[i] From EtOAc [19].
[j] From EtOAc (DSC) [9].
[k] Unknown origin [18].

1g/**2g** are too close for a convenient separation from water (see Table 1).

With the exception of **1c**$_{aq}$, the isolated alkyl α-D-glucopyranoside monohydrates **1b**$_{aq}$ and **1d**$_{aq}$ to **1e**$_{aq}$ have not previously been described. Storage in a desiccator over KOH for several days or lyophilization transformed the hydrates into the anhydrous compounds **1b** to **1e**; for physical properties see Tables 1 and 2.

To isolate also β anomers and residual α anomers from the supernatants, we chromatographed them on the 50 to 75-fold amount of silica gel (9:1 EtOAc–EtOH). The alkyl β-D-glucopyranosides are less polar and eluted first (R_f about 0.40), followed by the more polar α anomers (R_f about 0.35). The enriched fractions typically still contained some of the undesired anomers. These were successfully removed by crystallization from water or an organic solvent to recover about an additional 10% of mostly pure α and β anomers. The use of anion-exchange resin for separation of the α/β glucopyranosides is also described [20]. We chromatographed successfully a mixture of **1b**/**2b** on Dowex 1×2 (OH^--form) with water. Contrary to the separation on silica gel, the α anomer **1b** eluted first, followed by the β anomer **2b**.

Representative for the synthesis, separation, and isolation, the preparation of decyl α-D-glucopyranoside monohydrate (**1e**$_{aq}$) according to Fischer with the β anomer **2e** as by-product has been described in detail.

Alkyl β-D-glucopyranosides.—For the directed synthesis of anomerically pure alkyl β-D-glucopyranosides, we adapted the well-known Koenigs–Knorr synthesis as modified by Kunz and Harreus [11]. Briefly, we reacted tetrapivaloyl α-D-glucosyl bromide [11] in diethyl ether with the appropriate alcohol in the presence of molecular sieves and silver carbonate to obtain the peracylated glucosides. After chromatographic purification on silica gel, pivaloyl moieties were removed by NaOMe-catalyzed transesterification with methanol. Treatment of the resulting mixture with ion-exchange resin in water or methanol, followed by lyophilization (water) or distillation (methanol), yielded the anomerically pure β-D-glucopyranosides **2a**, **2e** to **2g** in up to 75% yield based on the acylated glucosyl bromide (see Table 3). By this procedure, we avoided the traditional final purification of alkyl β-D-glucopyranosides on silica gel with polar eluent [9,12].

Representative for the synthesis of alkyl β-D-glucopyranosides according to the modified Koenigs–Knorr procedure, the preparation of hexyl β-D-glucopyranoside (**2a**) including the characterization of the tetrapivaloyl intermediate has been described in detail.

Thermotropic properties and single-crystal X-ray structure analysis of alkyl α-D-glucopyranosides.—Alkyl α/β-D-glucopyranosides exhibit phase transitions first to liquid crystals (mp, melting point) upon heating before they melt to isotropic liquids (cp, clearing point)

[16,20,24–26]. Our study of transition points and X-ray analyses of some alkyl α-D-glucosides and their monohydrates may elicit insights into their thermotropic properties. These observations may add some knowledge to the formation of liquid crystals of these substances. Both the spontaneous loss of crystal water of the monohydrates $\mathbf{1b}_{aq}$ to $\mathbf{1e}_{aq}$ and the loss upon heating have been monitored and interpreted. The melting points of the hydrates are lower compared to those of the anhydrous substances [26]. Focher and co-workers [9] found a lower temperature for the gel–liquid crystal transition of hydrated octyl α-D-glucopyranoside (stored at 90% relative humidity) relative to the anhydrous compound.

The transition points of the thermotropic substances **1b** to **1e** and their monohydrates $\mathbf{1b}_{aq}$ to $\mathbf{1e}_{aq}$ have been observed between crossed polarizers in open test tubes and examined side by side. The hydrates $\mathbf{1b}_{aq}$ to $\mathbf{1e}_{aq}$ have distinctively lower transitions points (loss of crystal water, proved by thermogravimetry) in relation to the melting points of the anhydrous substances **1b** to **1e**, whereas the clearing points do not differ substantially (see Table 2). Barrall and co-workers [16] published transition points of alkyl α-D-glucopyranosides confirming those of the monohydrates $\mathbf{1b}_{aq}$ to $\mathbf{1e}_{aq}$ that we observed, but detailed preparation conditions are not described.

According to previous reports [27], the transition to the liquid crystal phase of the alkyl α-D-glucopyranosides is accompanied by a partial melting of the hydrophobic part of the crystal structure.

The hydrocarbon chains are densely packed in the anhydrous compounds. The incorporation of a water molecule increases the bonding energy between the sugar groups. Due to sterical hindrance the hydrocarbon chains lose their optimal packing and become somewhat crossed. This effect reduces the lattice energy of the hydrocarbon chains and explains the low stability of the monohydrates (loss of water).

Structure descriptions

Hexyl α-D-glucopyranoside (**1a**). The anhydrous hexyl α-D-glucopyranoside (**1a**) crystallizes in the same space group ($P2_1$) as the other known anhydrous compounds **1c**, **e** [27–29] (see Figs. 1–3). The unit cell parameters are comparable to those of the anhydrous octyl and the decyl compound **1c**, **e**. In contrast to the hydrates, the 2_1 screw axes point parallel to the plane built by the hydrocarbons, which is also in analogy with the known anhydrous α anomers. This structural feature

Table 3
Physicochemical properties of alkyl β-D-glucopyranosides **2a–2g**

Entry[a]	mp (°C)		$[\alpha]_D^{20}$, MeOH (or as mentioned)		R_f (9:1 EtOAc–EtOH)
	Found	Lit	Found	Lit	
2a ($n=6$)	(88.1) 89.0 [b]	88–91[c]	−33.4° (*c* 1.02)	−33.7° [c]	0.36
2b ($n=7$)	(74.5–74.9) 78.3[d]	74–77[e]	−32.3° (*c* 1.13)	−34.2° (H_2O)[e]	0.37
2c ($n=8$)	(77–83) 99–101[f,g]	65–99[c]	−24.2° (*c* 1.32)[g]	−30.3° [c]	0.38
2d ($n=9$)	(66.2)118.7–119.0[b,h]	65–118[c]	−25.8° (*c* 1.06)[h]	−28.8° [c]	0.39
2e ($n=10$)	(65–70) 130[f]	75–130[c]	−25.4° (*c* 1.15)	−27.8° [c]	0.40
2f ($n=12$)	(73–75) 135[f]	77–137[c]	−24.1° (*c* 1.06)	−24.7° [c]	0.41
2g ($n=14$)	(64.8)147.1[f]	82.0–147.5[i]	−23.9° (*c* 1.02)		0.43

[a] *n*: Alkyl-chain length.
[b] From EtOAc–Et_2O (1:1).
[c] From EtOAc [22].
[d] Lyophilized.
[e] From EtOH [23].
[f] From acetone.
[g] Containing 5% of **1c**.
[h] Containing 5% of **1d**.
[i] DSC [1].

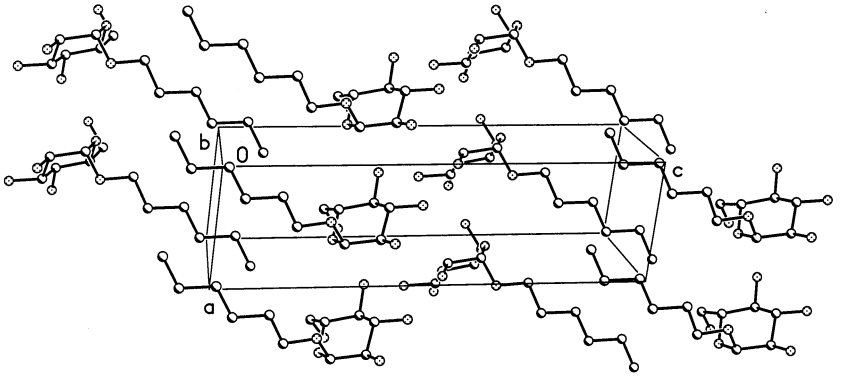


Fig. 1. Packing plot of hexyl α-D-glucopyranoside (**1a**), perspective view along the *b*-axis.

is in agreement with the findings concerning the formation of liquid crystal phases by alkyl α-D-glucopyranosides. To our knowledge, the hexyl α-D-glucopyranoside is the first compound in the series of alkyl α-D-glucopyranosides showing liquid crystal behavior. Analogously to the other anhydrous glucopyranosides, the hydrogen bridging bonds at the hydrophilic end of the molecule form a three-dimensional network without any water:

O-6 – H-6A···O-4 – H-4A···O-3 – H-3A···O-2 – H-2A···O-6 –

*Heptyl α-D-glucopyranoside monohydrate (**1b**$_{aq}$).* The structure of heptyl α-D-glucopyranoside monohydrate (**1b**$_{aq}$) consists of alternating regions of polar and non-polar groups in analogy to the octyl monohydrate 1c$_{aq}$ [28,29] (see Figs. 4 and 5). This arrangement of the molecules constitutes close packing of fully extended alkyl chains between hydrogen-bonded layers of glucopyranoside rings. Inspecting the unit cells of the heptyl- and the octyl-monohydrates **1b**$_{aq}$ and **1c**$_{aq}$ reveals great similarity concerning the orientation of the molecules relative to the cell axes and the metric except for the monoclinic β-angle. The difference in the β-angles can be explained by the shorter alkyl-chains in the heptyl compound. Schematically, pressure against opposite corners of the unit cell will have the same effect as shortening the alkyl-chains. The water molecule plays a decisive role in building the hydrogen bond scheme at the glucopyranoside rings. The hydrogen bond arrangement is

$> O_W$…H-6A – O-6…H-4A – O-4…H-3A – O-3…H_W – O_W – H_W…O-2 – H-2A.

As in other known hydrates of this type (e.g., octyl α-D-glucopyranoside hemihydrate and the monohydrate **1c**$_{aq}$ [28,29]), the 2_1 screw axes of **1b**$_{aq}$ point perpendicularly to the plane built by the alkyl carbons.

By comparing the crystal structures of anhydrous hexyl α-D-glucopyranoside (**1a**) and octyl α-D-glucopyranoside (**1c**) [28,29] with those of the monohydrates **1b**$_{aq}$/**1c**$_{aq}$, the main difference is seen to be in the arrangement of the alkyl chains. Whereas, in all the anhydrous glucopyranosides, the hydrophobic chains lie parallel to one another forming the non-polar layer, in the monohydrates **1b**$_{aq}$ and **1c**$_{aq}$ [28,29] the interwoven chains cross each other. We are now able to state that the crossing angle decreases with increasing chain length, being about 150° in the heptyl compound **1b**$_{aq}$ and about 130° in the octyl compound **1c**$_{aq}$.

3. Experimental

Materials and general methods.—If not otherwise mentioned, the physical constants of the prepared substances and references are given in Tables 1–3. TLC was carried out on Silica Gel 60 F_{254} glass plates (E. Merck); compounds were visualized by concd H_2SO_4/180 °C (≥ 3% β anomer detectable in α anomer). Column chromatography was performed on Silica Gel 60 (E. Merck) and an anion-exchange chromatography on Dowex 1 × 2, OH^--form 200–400 mesh. Melting points and Krafft points were determined with a Büchi 510 apparatus.

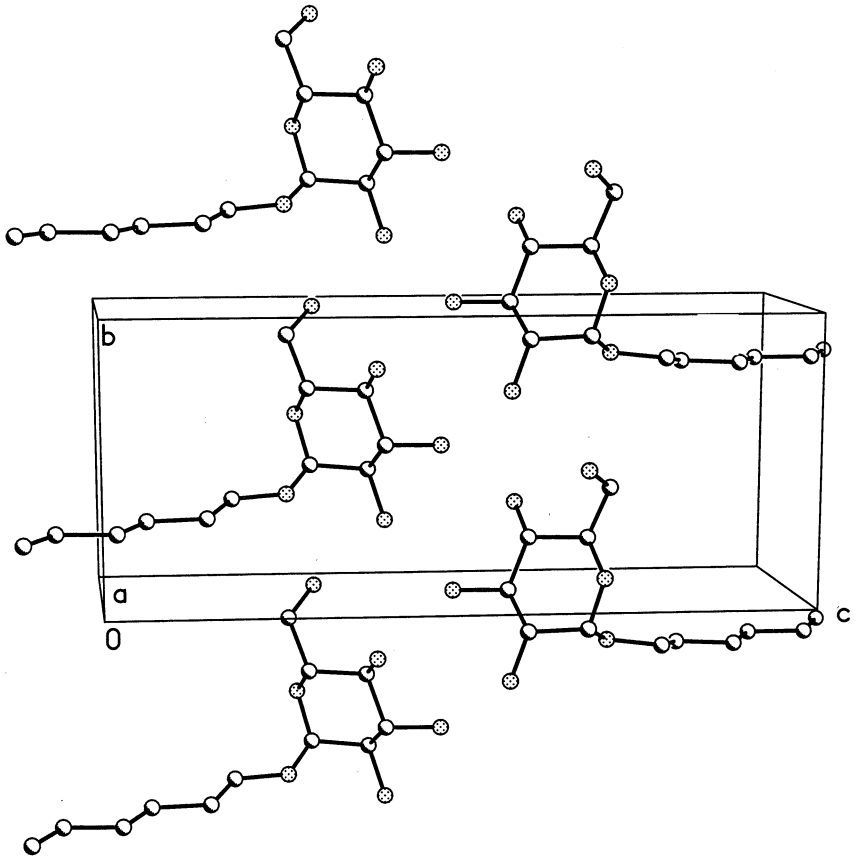


Fig. 2. Packing plot of hexyl α-D-glucopyranoside (**1a**), perspective view along the *a*-axis.

Transition points were estimated with test tubes between crossed polarizers. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Crystal water was determined with a *KF*-coulometer-684 (Metrohm) with voltammetric endpoint determination. For CMC measurements, a Lauda ring tension apparatus (TE 1C) and a Lauda drop volume tension apparatus (TVT 1) were used. IR spectra were recorded on a Paragon 1000 FT IR-spectrometer (Perkin–Elmer) and ^{1}H (270.17 MHz) and ^{13}C (67.94 MHz) NMR spectra on a JEOL JNM-EX 270 instrument in CD_3OD as solvent, if not mentioned otherwise; chemical shifts (δ) measured from the appropriate residual solvent signal are referenced to Me_4Si; quantitative compositions of anomeric mixtures were calculated from the ratio of the H-1-signal integrals (doublets at 4.67 ± 0.10 ppm for the α-D-glucopyranosides and at 4.15 ± 0.20 ppm for β-D-glucopyranosides); ^{13}C signal multiplicities were determined from DEPT spectra. In the case of X-ray analysis reflection intensities were estimated at 296 K on a Siemens P4 diffractometer with graphite-monochromatic Mo K_α radiation (λ 71.073 pm); the intensity of the primary beam was controlled by monitoring three reference reflections every 100 reflections. The structures were solved by direct methods and refined against F by full-matrix least squares using the program package SHELXTL V.4.2 [30,31]. For crystal structure analyses, the positions of the hydrogen atoms were geometrically calculated and refined with fixed U values (0.08 Å^2) applying the riding

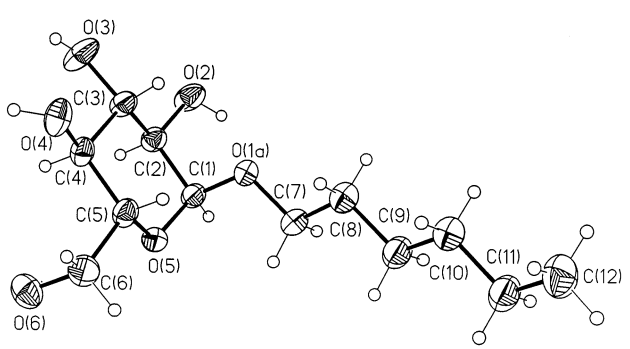


Fig. 3. ORTEP drawing of the molecule of hexyl α-D-glucopyranoside (**1a**).

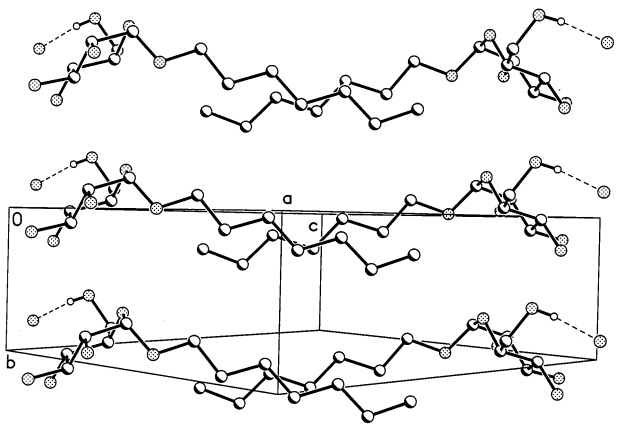


Fig. 4. Packing plot of heptyl α-D-glucopyranoside monohydrate ($\mathbf{1b}_{aq}$), perspective view along [$\bar{1}$01].

model. Elemental analyses were carried out by the Microanalytical Laboratory Ilse Beetz, D-96317 Kronach.

Hexyl α-D-glucopyranoside (**1a**) *and hexyl β-D-glucopyranoside* (**2a**).—D-Glucose (40.4 g, 224 mmol) was reacted with hexanol (275 mL, 226 g, 2.21 mol) in dioxane (800 mL) with *p*-toluenesulfonic acid monohydrate (7.0 g, 37 mmol). After neutralization and evaporation of the solvent, the excess of hexanol was azeotropically distilled with water at 20 Torr. The residue was suspended in water and extracted twice with toluene. The aqueous layer was lyophilized and filtered on silica gel (9:1 EtOAc–EtOH): 40.05 g (68%) of **1a**/**2a** (67:33). The product was recrystallized twice from EtOAc to yield 12.84 g (22%) of anomerically pure hexyl α-D-glucopyranoside (**1a**) as colorless small crystals: mp (58.6) 67.0 °C, lit 70 °C [8]; $[\alpha]_D^{20} + 132.4°$ (*c* 0.99, MeOH), lit + 132.1° (MeOH) [8]; R_f 0.33; ^{1}H NMR: δ 4.67 (d, 1 H, *J* 3.6 Hz, H-1$_{glc}$); ^{13}C NMR: δ 100.06 (d, C-1$_{glc}$); CMC: 0.136 M, lit 0.20 M [8]. From supernatants (28.2 g), following chromatography (9:1 EtOAc–EtOH) and recrystallization, an additional 3.99 g (7%, EtOAc) of **1a** and 5.1 g (9%, 1:1 EtOAc–Et_2O) of hexyl β-D-glucopyranoside (**2a**) were isolated.

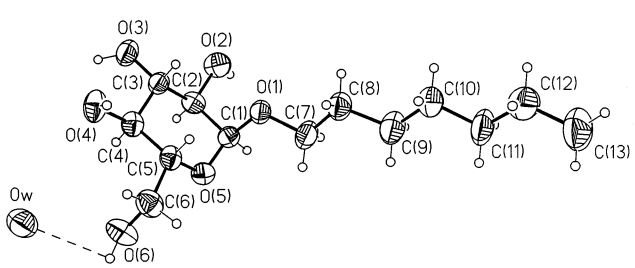


Fig. 5. ORTEP drawing of the molecule of heptyl α-D-glucopyranoside monohydrate ($\mathbf{1b}_{aq}$).

Determination of the crystal structure of hexyl α-D-glucopyranoside (**1a**). The crystal of $C_{12}H_{24}O_6$ (264.32) suitable for X-ray analysis was a colorless platelet of size 0.60 × 0.30 × 0.15 mm. The compound crystallized monoclinically in the space group $P2_1$ with the lattice parameters $a = 511.5(2)$, $b = 758.9(2)$, $c = 1779.5(4)$ pm, $\beta = 96.11(3)°$, $V = 686.8(4) \times 10^6$ pm^3, and $Z = 2$. D_x is 1.278 g cm^{-3}. 3727 Reflections in the range 3–55° (2 Theta) were collected, 3157 were independent, and 3040 were assigned to be observed [$F_o \geq 2\sigma(F_o)$]. The refinement of 164 parameters with anisotropic displacement coefficients for all non-hydrogen atoms converged at $R/wR = 0.058/0.059$ [$w^{-1} = \sigma^2(F_o)$]. The positions of the hydrogen atoms connected to oxygen could be located by successive Fourier syntheses; those which are connected to carbon were calculated geometrically. The max/min residual electron density was 0.42/–0.24 e Å^{-3}.

Heptyl α-D-glucopyranoside monohydrate ($\mathbf{1b}_{aq}$) *and heptyl β-D-glucopyranoside* (**2b**).—D-Glucose (40.0 g, 222 mmol) was reacted with heptanol (373 mL, 307 g, 2.64 mol) in dioxane (800 mL) and 96% H_2SO_4 (2.0 mL, 3.7 g, 37 mmol). The mixture was subsequently neutralized and concentrated in vacuum. The residue was filtered through silica gel (9:1 EtOAc–EtOH): 42.2 g (68%) of **1b/2b** (68:32). The mixture was recrystallized twice from water to give 6.88 g (10%) heptyl α-D-glucopyranoside monohydrate ($\mathbf{1b}_{aq}$) as colorless crude needles. ^{1}H NMR: δ 4.71 (d, 1 H, *J* 3.6 Hz, H-1$_{glc}$); ^{13}C NMR: δ 100.06 (d, C-1$_{glc}$). From supernatants (29.05 g), after chromatography (9:1 EtOAc–EtOH) and recrystallization, 5.33 g (8%, H_2O) of $\mathbf{1b}_{aq}$ and 10.0 g of heptyl α/β-D-glucopyranosides (**1b/2b**, 7:93; 1:1 EtOAc–Et_2O) were isolated as oily products.

For analysis of **2b**, 605 mg (**1b/2b**, 62:38) was separated on Dowex 1 × 2 (170 g) with H_2O as eluent to give 210 mg of pure heptyl β-D-glucopyranoside **2b** as a white powder after lyophilization. ^{1}H NMR: δ 4.14 (d, 1 H,

J 7.9 Hz, H-1_{glc}); ^{13}C NMR: δ 104.37 (d, C-1_{glc}).

*Determination of crystal structure of heptyl α-D-glucopyranoside monohydrate (**1b**$_{aq}$).* The crystal of $C_{13}H_{26}O_6 \cdot H_2O$ (296.36) suitable for X-ray analysis was a colorless needle of dimensions $0.60 \times 0.20 \times 0.07$ mm. The compound crystallized monoclinically in the space group C_2 with the lattice parameters $a =$ 1830.4(4), $b = 497.1(2)$, $c = 1962.0(4)$ pm, $\beta =$ 115.11(3)°, $V = 1616.4(8) \times 10^6$ pm^3, and $Z = 4$. 2460 Reflections in the 2 Theta range 3–55° were measured, 2267 were independent, and 1740 were assigned to be observed [$F_o \geq 3\sigma(F_o)$]. The refinement of 182 parameters with anisotropic temperature factors for all non-hydrogen atoms converged at $R/wR =$ 0.061/0.052 [$w^{-1} = \sigma^2(F_o)$]. The positions of the hydrogen atoms had been calculated geometrically. The max/min residual electron density was 0.34/−0.30 e Å^{-3}.

*Octyl α-D-glucopyranoside monohydrate (**1c**$_{aq}$) and octyl β-D-glucopyranoside* (**2c**).—D-Glucose (20.0 g, 111 mmol) was reacted with octanol (172 mL, 142 g, 1.09 mol) in dioxane (400 mL) containing 96% H_2SO_4 (1.0 mL, 1.8 g, 18 mmol), followed by neutralization and evaporation of volatile compounds. The residue was filtered through silica gel (9:1 EtOAc–EtOH): 21.88 g (67%) of **1c/2c** (7:3). The mixture was recrystallized twice from water to yield 8.99 g (26%) of octyl α-D-glucopyranoside monohydrate (**1c**$_{aq}$) as colorless small needles. ^{1}H NMR: δ 4.68 (d, 1 H, *J* 3.6 Hz, H-1_{glc}); ^{13}C NMR: δ 100.07 (d, C-1_{glc}). The supernatants (9.70 g), after chromatography (9:1 EtOAc–EtOH) and recrystallization, gave additional 1.30 g (4%, H_2O) of **1c**$_{aq}$ and 2.20 g (7%, acetone) of octyl β-D-glucopyranoside (**2c**), containing 5% **1c**, as a white powder. ^{1}H NMR: δ 4.17 (d, 1 H, *J* 7.3 Hz, H-1_{glc}); ^{13}C NMR: δ 104.31 (d, C-1_{glc}).

*Nonyl α-D-glucopyranoside monohydrate (**1d**$_{aq}$) and nonyl β-D-glucopyranoside* (**2d**).—D-Glucose (40.1 g, 223 mmol) was reacted with nonanol (376 mL, 311 g, 2.16 mol) in dioxane (800 mL) and *p*-toluene sulfonic acid monohydrate (7.0 g, 37 mmol), followed by neutralization and evaporation of volatile compounds. The residue was filtered through silica gel (9:1 EtOAc–EtOH): 40.67 g (60%) of **1d**/**2d** (62:38). The product was recrystallized twice from water to yield 12.5 g (17%) of nonyl α-D-glucopyranoside monohydrate (**1d**$_{aq}$) as colorless small needles. ^{1}H NMR: δ 4.75 (d, 1 H, *J* 3.8 Hz, H-1_{glc}); ^{13}C NMR: δ 100.00 (d, C-1_{glc}). From supernatants (27.9 g), after chromatography (9:1 EtOAc–EtOH) and recrystallization was isolated: 5.7 g (8%, H_2O) **1d**$_{aq}$ and 4.04 g (6%, 1:1 EtOAc–Et_2O) nonyl β-D-glucopyranoside (**2d**) as a white powder, containing 5% of **1d**. ^{1}H NMR: δ 4.16 (d, 1 H, *J* 7.3 Hz, H-1_{glc}); ^{13}C NMR: δ 104.38 (d, C-1_{glc}).

*Decyl α-D-glucopyranoside monohydrate (**1e**$_{aq}$) and decyl β-D-glucopyranoside* (**2e**).—A vol of 96% H_2SO_4 (1.0 mL, 1.8 g, 18 mmol) was added to decanol (252 mL, 209 g, 1.32 mol) in dioxane (400 mL). After raising the temperature to 80 °C, D-glucose (20.0 g, 111 mmol) was added. The mixture was stirred for 6 h at 90 °C and then evaporated in vacuum to about 3/4 of the original volume. After heating for another 6 h, 2 M KOH (22 mL) was added (pH 7.5 of the aq phase) and the volatile components were evaporated first at 15 Torr followed by distillation at 0.01 Torr. The residue (38 g) was filtered on 800 g silica gel (9:1 EtOAc–EtOH). The resulting mixture of **1e**/**2e** (24.9 g, 70%, 7:3) was recrystallized from a 5% solution in H_2O. The precipitate was collected from the supernatant by centrifugation (30 min, 9000 U) and dissolved in hot water. After lyophilization, a mixture of 14.3 g of **1e/2e** (9:1) was obtained. Additional recrystallization from a 5% solution in water provided 12.6 g (34%) decyl α-D-glucopyranoside monohydrate (**1e**$_{aq}$) as small colorless needles, containing $\leq 3\%$ β anomer. Further recrystallization for analysis as described above provided the anomerically pure compound. ^{1}H NMR: δ 4.66 (d, 1 H, *J* 3.6 Hz, H-1_{glc}); ^{13}C NMR: δ 100.07 (d, C-1_{glc}).

The aq supernatants were lyophilized (12.2 g, **1e**/**2e** about 1:1) and chromatographed on 950 g of silica gel (9:1 EtOAc–EtOH); (a), (b) and (c) were obtained:

(a) 2.1 g of crude decyl α-D-glucopyranoside (α/β anomer 85:15). After recrystallization from water, another 1.6 g (4%) of pure decyl α-D-glucopyranoside monohydrate (**1e**$_{aq}$) was obtained.

(b) 3.5 g of crude decyl β-D-glucopyranoside (α/β anomer 5:95). This mixture was recrystallized from 8 mL of acetone yielding 2.2 g (6%) of pure decyl β-D-glucopyranoside (**2e**).

(c) 4.4 g (12%) of anomer mixture of **1e**/**2e**, about 1:1.

Dodecyl α-D-glucopyranoside (**1f**) *and dodecyl β-D-glucopyranoside* (**2f**).—D-Glucose (10.0 g, 56 mmol) was reacted with dodecanol (123 g, 0.66 mol) and dioxane (200 mL) containing 96% H_2SO_4 (0.5 mL, 0.9 g, 9 mmol), followed by neutralization and evaporation of volatile compounds. The residue was filtered through silica gel (9:1 EtOAc–EtOH): 12.32 g (63%) **1f**/**2f** (68:32). The α anomer was separated by crystallization from EtOAc yielding 5.26 g (27%) of dodecyl α-D-glucopyranoside (**1f**) as colorless small platelets: mp (76.8) 143.0–144.0 °C, lit 140–141 °C [9]; $[\alpha]_D^{20}$ + 101.0° (*c* 1.72, MeOH), lit + 99.6° (*c* 1, MeOH) [9]; R_f 0.39; ^{1}H NMR: δ 4.66 (d, 1 H, J 3.6 Hz, H-1_{glc}); ^{13}C NMR: δ 100.07 (d, C-1_{glc}). The supernatants (7.27 g), after chromatography and recrystallization yielded additional 1.00 g (5%, EtOAc) of pure **1f** and 1.90 g (10%, acetone) of pure dodecyl β-D-glucopyranoside (**2f**) as a white powder.

Tetradecyl α-D-glucopyranoside (**1g**) *and tetradecyl β-D-glucopyranoside* (**2g**).—D-Glucose (12.6 g, 70 mmol) was reacted with tetradecanol (168.9 g, 0.79 mol) and *p*-toluene sulfonic acid monohydrate (2.20 g, 11.6 mmol) in dioxane (360 mL) for 6 h and after concentration in vacuum (20 Torr) for an additional 18 h. Following neutralization and evaporation of volatile compounds (0.001 Torr), the residue was filtered on silica gel (9:1 EtOAc–EtOH): 14.2 g (54%) of **1g**/**2g**, (56:44). Recrystallization from 1:1 EtOAc–EtOH yielded 2.93 g (11%) tetradecyl α-D-glucopyranoside (**1g**) as a white powder, containing ≤ 2% β anomer: mp (81–84) 144.0 °C; $[\alpha]_D^{20}$ + 93.0° (*c* 1.00, MeOH); R_f 0.40; ^{1}H NMR: δ 4.65 (d, 1 H, J 3.6 Hz, H-1_{glc}); ^{13}C NMR: δ 100.00 (d, C-1_{glc}). Anal. Calcd for $C_{20}H_{40}O_6$: C, 63.80; H, 10.71. Found: C, 63.76; H, 10.54.

From supernatants (6.98 g), after chromatography (9:1 EtOAc–EtOH) and recrystallization, was obtained 0.54 g (2%, 1:1 EtOAc–EtOH) of **1g** and 1.35 g (5%, from acetone) of tetradecyl β-D-glucopyranoside (**2g**), containing ≤ 5% **1g** as a white powder.

Hexyl 2,3,4,6-tetra-O-pivaloyl-β-D-glucopyranoside and hexyl β-D-glucopyranoside (**2a**).—To 360 mL of anhydrous Et_2O were added: 27.0 g (47 mmol) 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide [11], 6.2 mL (5.1 g, 50 mmol) hexanol, 16.7 g (60.6 mmol) Ag_2CO_3, and 75 g of fine powdered molecular sieve (4 Å). The mixture was stirred at room temperature for 24 h, filtered and concentrated. The residue (35.3 g) was chromatographed on 1 kg silica gel (19:1 cyclohexane–EtOAc) to yield 23.07 g (80%) of hexyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside as a white powder: mp 74.3–75.0 °C; $[\alpha]_D^{23}$ −8.69° (*c* 0.84, MeOH); R_f 0.38; IR (KBr): ν 1745 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3 H, J 7.0 Hz, H-6_{alk}), 1.09, 1.13, 1.13, 1.20 (4 s, 36 H, CMe_3), 1.20–1.35 (6 H, H-3_{alk} to H-5_{alk}), 1.43–1.60 (2 H, H-2_{alk}), 3.42 (dt, 1 H, $J_{1a,1b}$ 9.4, $J_{1a,2}$ 6.9 Hz, H-$1a_{alk}$), 3.69 (ddd, 1 H, $J_{5,6a}$ 1.7, $J_{5,6b}$ 6.0, $J_{5,4}$ 9.5 Hz, H-5_{glc}), 3.80 (dt, 1 H, $J_{1b,2}$ 6.6 Hz, H-$1b_{alk}$), 4.03 (dd, $J_{6b,6a}$ 12.0, 1 H, H-$6b_{glc}$), 4.19 (dd, 1 H, H-$6a_{glc}$), 4.33 (d, 1 H, $J_{1,2}$ 7.9, H-1_{glc}), 4.98 (dd, 1 H, $J_{2,3}$ 9.5, H-2_{glc}), 5.07 (t, 1 H, $J_{4,3}$ = 9.5 Hz, H-4_{glc}), 5.29 (t, 1 H, H-3_{glc}); ^{13}C NMR ($CDCl_3$): δ 14.1 (q, C-6_{alk}), 22.6, 25.7, 31.6 (3 t, C-3_{alk} to C-5_{alk}), 29.5 (t, C-2_{alk}), 27.11, 27.14, 27.16, 27.21 (4 q, C(CH_3)$_3$), 38.76, 38.76, 38.81, 38.92 (4 s, CMe_3), 62.2 (t, C-6_{glc}), 68.3 (d, C-4_{glc}), 70.0 (t, C-1_{alk}), 71.3 (d, C-2_{glc}), 72.3, 72.4 (2 d, C-3_{glc}, C-5_{glc}), 101.1 (d, C-1_{glc}), 176.48, 176.53, 177.3, 178.1 (4 s, C=O). Anal. Calcd for $C_{32}H_{56}O_{10}$: C, 63.97; H, 9.40. Found: C, 63.98; H, 9.49.

The above prepared hexyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside (22.7 g, 37 mmol) was dissolved in 335 mL anhyd MeOH containing 70 mmol NaOMe and kept at room temperature for 24 h. After addition of 100 mL toluene, the solvent was evaporated and the residue (15.8 g) was dissolved in 250 mL MeOH. The solution was stirred with ion-exchange resin (20 g, Amberlyst 15) at room temperature for 60 min, and then filtered. The filtrate was concentrated in vacuum. The residue (8.89 g) was recrystallized from 1:1 EtOAc–Et_2O yielding 7.72 g hexyl β-D-glucopyranoside (**2a**) (79% in the de-acy-

lation step) as a white powder; ^{1}H NMR: δ 4.15 (d, 1 H, J 7.3 Hz, H-1_{glc}); ^{13}C NMR: δ 104.40 (d, C-1_{glc}); CMC: 0.190 M.

Decyl β-D-glucopyranoside (**2e**).—Reaction of decanol (3.40 g, 21.5 mmol) with 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide [11] (12.4 g, 21.4 mmol) in Et_2O (120 mL) in the presence of Ag_2CO_3 (7.45 g, 27 mmol) and molecular sieve yielded after silica gel chromatography (9:1 cyclohexane–EtOAc) 12.7 g (89%) of decyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside as an oily product: R_f 0.62; IR (CCl_4): ν 1745 cm^{-1} (C=O). Transesterification of the acylated decyl β-D-glucopyranoside (12.1 g, 18.1 mmol) with $NaOCH_3$/MeOH and subsequent reaction with ion-exchange resin (Amberlyst 15) in water gave, after lyophilization and recrystallization from acetone, 4.20 g decyl β-D-glucopyranoside (**2f**) (72% in the de-acylation step) as a white powder. ^{1}H NMR: δ 4.14 (d, 1 H, J 7.6 Hz, H-1_{glc}); ^{13}C NMR: δ 104.32 (d, C-1_{glc}).

Dodecyl β-D-glucopyranoside (**2f**).—Reaction of dodecanol (5.98 g, 32.1 mmol) with 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide [11] (15.0 g, 25.9 mmol) in Et_2O (150 mL) in the presence of Ag_2CO_3 (9.05 g, 32.8 mmol) and molecular sieve yielded, after chromatography on silica gel (9:1 cyclohexane–EtOAc) 15.02 g (85%) of dodecyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside: mp 44–46 °C; R_f 0.65; IR (KBr): ν 1745 cm^{-1} (C=O). Transesterification and subsequent reaction with ion-exchange resin (Amberlyst 15) in water yielded, after lyophilization and recrystallization from acetone, 6.65 g of dodecyl β-D-glucopyranoside (**2f**) (87% in the de-acylation step) as a white powder. ^{1}H NMR: δ 4.12 (d, 1 H, J 7.6 Hz, H-1_{glc}); ^{13}C NMR: δ 104.37 (d, C-1_{glc}).

Tetradecyl β-D-glucopyranoside (**2g**).—Reaction of tetradecanol (2.78 g, 13.0 mmol), 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide [11] (7.50 g, 13.0 mmol) in Et_2O (100 mL) in the presence of Ag_2CO_3 (4.58 g, 17 mmol) and molecular sieve afforded after chromatography on silica gel (9:1 cyclohexane–EtOAc) 9.16 g (97%) tetradecyl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside: mp 39.8–41.1 °C; R_f 0.65; IR (KBr): ν 1748 cm^{-1} (C=O). Transesterification of the acylated tetradecyl β-D-glucopyranoside (8.55 g, 11.8 mmol) and subsequent reaction with ion-exchange resin (Amberlyst 15) in MeOH yielded, after recrystallization from acetone, 2.38 g of tetradecyl β-D-glucopyranoside (**2g**) (54% in the de-acylation step) as a white powder. ^{1}H NMR: δ 4.14 (d, 1 H, J 7.9 Hz, H-1_{glc}); ^{13}C NMR: δ 104.40 (d, C-1_{glc}). Anal. Calcd $C_{20}H_{40}O_6$: C, 63.80; H, 10.71. Found: C, 63.77; H, 10.51.

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[31] Tables of atomic co-ordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.-fax: +44-1223-336-033; e-mail: deposit@chemcrys.cam.ac.uk on quoting CCDC 115211 for **1b**$_{aq}$ and CCDC 115212 for **1a**.