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Synthesis and surface-active properties of glycosyl carbamates and thioureas

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Abstract

Several amphiphilic glycosyl carbamates, glycosyl thiocarbamates and glycosylthioureas were prepared by addition of the anomeric hydroxyl group of acetylated glycosyl derivatives to alkyl isocyanates, or by reaction of glycosyl isothiocyanates with alcohols or amines. The solubility, critical micelle concentrations and detergent efficiency for the extraction of proteins of these compounds were evaluated and compared.

Keywords: *O*-Glycosyl carbamates; *N*-Glycosyl carbamates; *N*-Glycosyl thiocarbamates; *N*-Glycosylthioureas; Surfactants; Protein extraction

1. Introduction

A general approach to the study of complex biological membranes involves the dissociation, characterisation and re-assembly of membrane components [1]. The most important aspect of this approach is the use of an appropriate detergent (solubilizing agent) to dissociate and extract the intrinsic membrane proteins. Ideally, the detergent should give maximum dissociation of the membrane while preserving the enzymatic, antigenic or other biological activities of the components. It is also desirable that the properties of the solubilizing detergent include the following parameters: (i) electrical neutrality, thus avoiding alteration of the charge properties of the proteins; (ii) a high critical micelle concentration (cmc) to allow rapid removal of the detergent by dialysis; (iii) optical transparency in the UV region to allow spectrophotometric detection of proteins; (iv) a well-defined chemical composition and a high purity to ensure experimental reproducibility; (v) a low cost for industrial application.

Some biological active proteins are retained within the cell and their extraction and purification are difficult. Several methods are used to liberate these intracellular components. Among them, chemical extraction with detergents is of particular interest because it offers improved selectivity. The proteins of the membrane are solubilized to a greater or lesser extent, making the cell permeable to the passage of cytoplasmic proteins.

As we are involved in a program devoted to the preparation of new surfactants, our interest has been turned towards the synthesis and properties of non-ionic glycosidic detergents.

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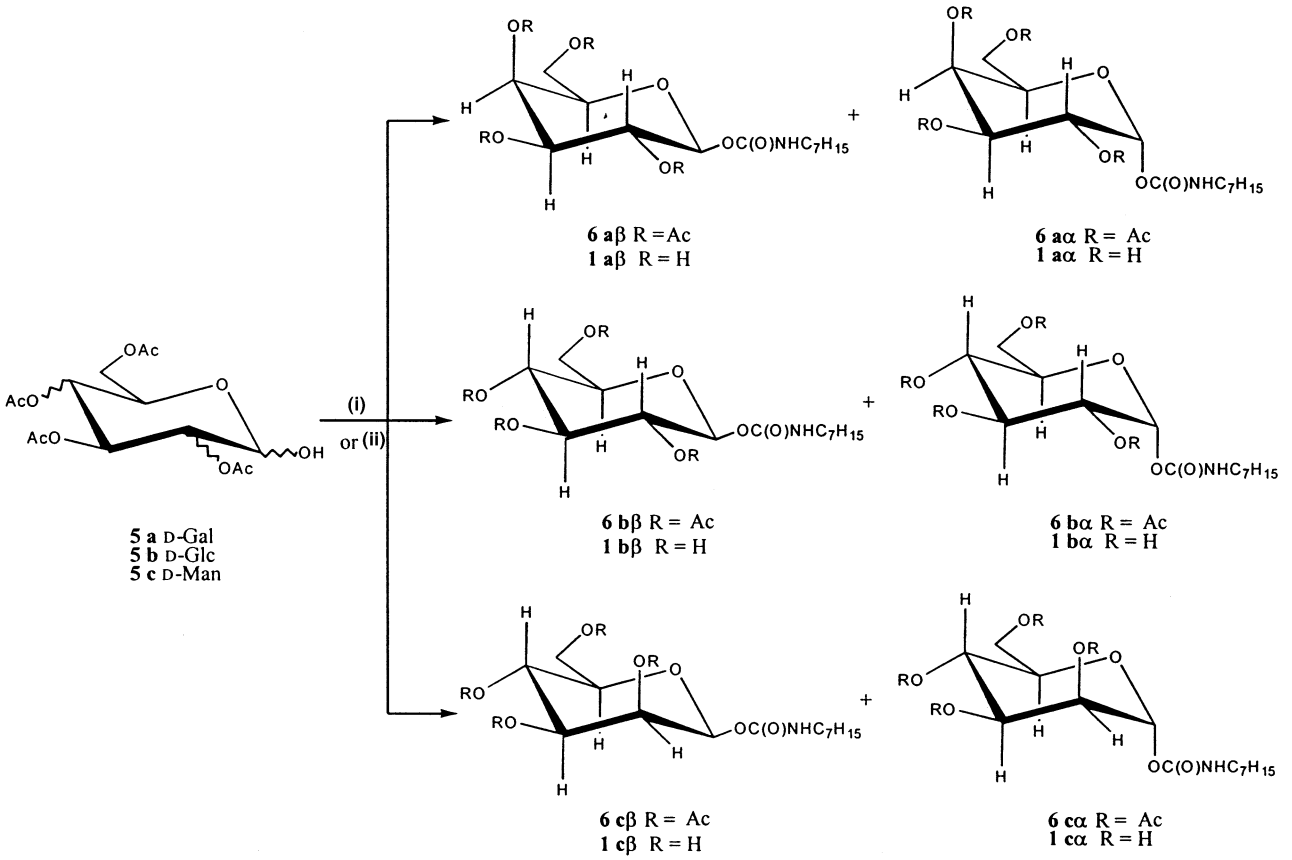


Scheme 1. (i) $C_7H_{15}NCO$, DABCO, toluene, rt, 18 h. (ii) $C_7H_{15}NCO$, Et_3N, CH_3CN, reflux, 8 h.

Expensive alkyl glycosides and thioglycosides are commercially available for membrane studies [2,3]. Methyl 6-*O*-(*N*-heptylcarbamoyl)-α-D-glucopyranoside (HECAMEG) is a good detergent of the cell membrane [4,5]. So we expected that *O*-glycosyl carbamates **1a–c**, *N*-glycosyl carbamates **2a–c**, *N*-glycosyl thiocarbamates **3a–c** and *N*-glycosylthioureas **4a–c**, which offer a structural similarity to octyl(thio)glycosides and to HECAMEG, could exhibit interesting solubilizing and surfactant properties.

In the present study, we report the synthesis of various glycosyl carbamates and thioureas, together with some of their physico-chemical properties.

2. Results and discussion

Synthesis of O-*glycosyl carbamates* **1a–c**.— As already reported, anomeric hydroxyl groups react with isocyanates to give *O*-glycosyl carbamates [6,7]. These reactions usually lead to an anomeric mixture, limiting the scope of these procedures. To overcome this problem, various experimental conditions were tested (solvent, catalyst, temperature) allowing stereoselective synthesis of *O*-glycosyl carbamates (Scheme 1). Among them, the best result, i.e. 100% of β anomer (except for D-mannose, where a 3:1 α/β ratio was found), was obtained when the reaction was carried out in toluene at room temperature (rt) with 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst[1].

Thus, acetylated monosaccharides **5a–c** having an unprotected anomeric hydroxyl group [8] react with alkyl isocyanates to afford β-*O*-glycosyl carbamates **6a–c**, in good yields.

As expected, the influence of the temperature, solvent and catalyst is of importance in controlling the diastereoselectivity of the reaction.

[1] The diastereoselectivity of the reaction will be discussed in further paper.

When the addition was carried out in boiling acetonitrile, in the presence of triethylamine (Et_3N), the α anomer was obtained in good yield and diastereoselectivity (70–80%). The two anomers **6a–c** were purified by flash chromatography (Scheme 1). The *O*-glycosyl carbamates were finally O-deacetylated using the Zemplén procedure to obtain the expected compound **1a–c** in quantitative yields.

The anomeric configuration of the various carbamates was clearly established by NMR spectroscopy. The β anomers of D-glucose and D-galactose show characteristic signals for ^1H (5.6–5.7 ppm, $J_{1,2}$ 7–8 Hz) in agreement with the 1,2-trans relationships between protons. The chemical shifts for the anomeric carbon (92–93 ppm) confirmed the β configuration.

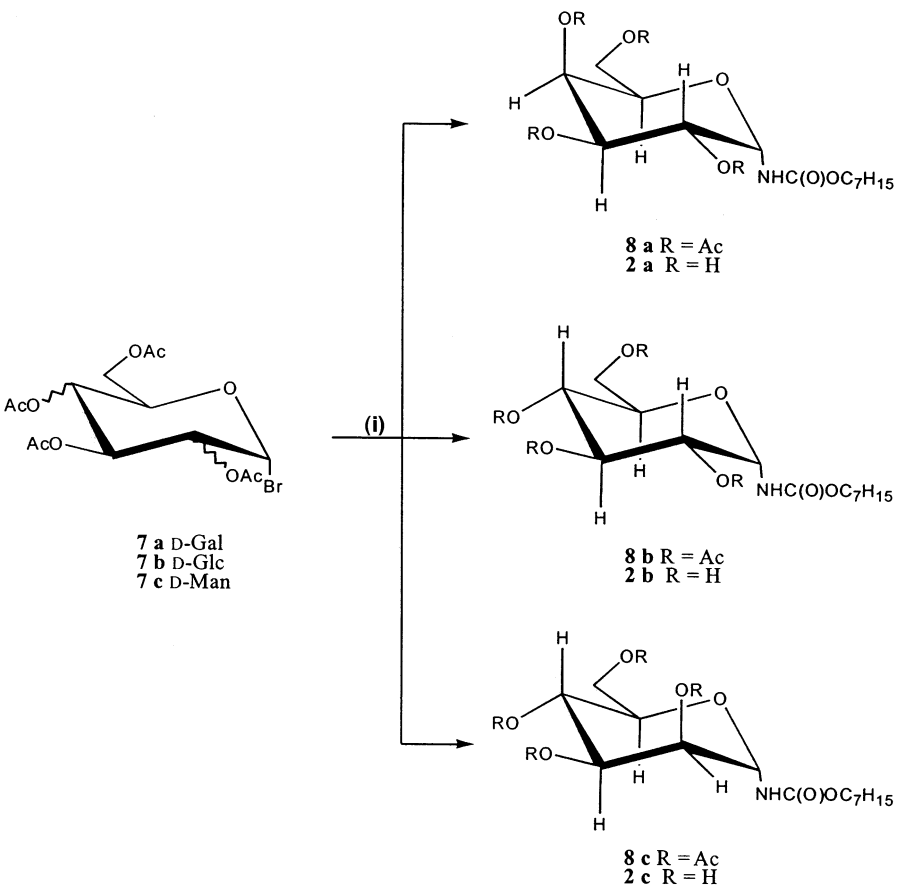
Proton H-1 of α anomers was deshielded (6.2–6.3 ppm) with a $J_{1,2}$ coupling constant characteristic for protons in the *gauche* relative disposition. The anomeric carbons were shielded (89–90 ppm).

The anomeric configuration assignment in D-mannopyranosyl derivatives was supported by $J_{C\text{-}1\text{–}H\text{-}1}$ measurements. The values of $J_{C\text{-}1\text{–}H\text{-}1}$ for the **6cβ** (156 Hz) and for the **6cα** (178 Hz) are in agreement with the axial or equatorial position of the anomeric proton.

The NMR data of acetylated carbamates **6a–c** are reported in Tables 1 and 2.

Synthesis of N-*glycosyl carbamates* **2a-c**.— These carbamates were readily prepared by a 'one-pot reaction' [9] involving acetylated glycosyl bromides, potassium cyanate and *n*-heptanol. The reaction, carried out in toluene with 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst, afforded only the α anomer of the *N*-glycosyl carbamates **8a–c** in good yield (Scheme 2).

The compounds were purified by flash chromatography. The acetylated compounds were deprotected by using the Zemplén procedure to afford amphiphilic molecules **2a–c** in almost quantitative yield.



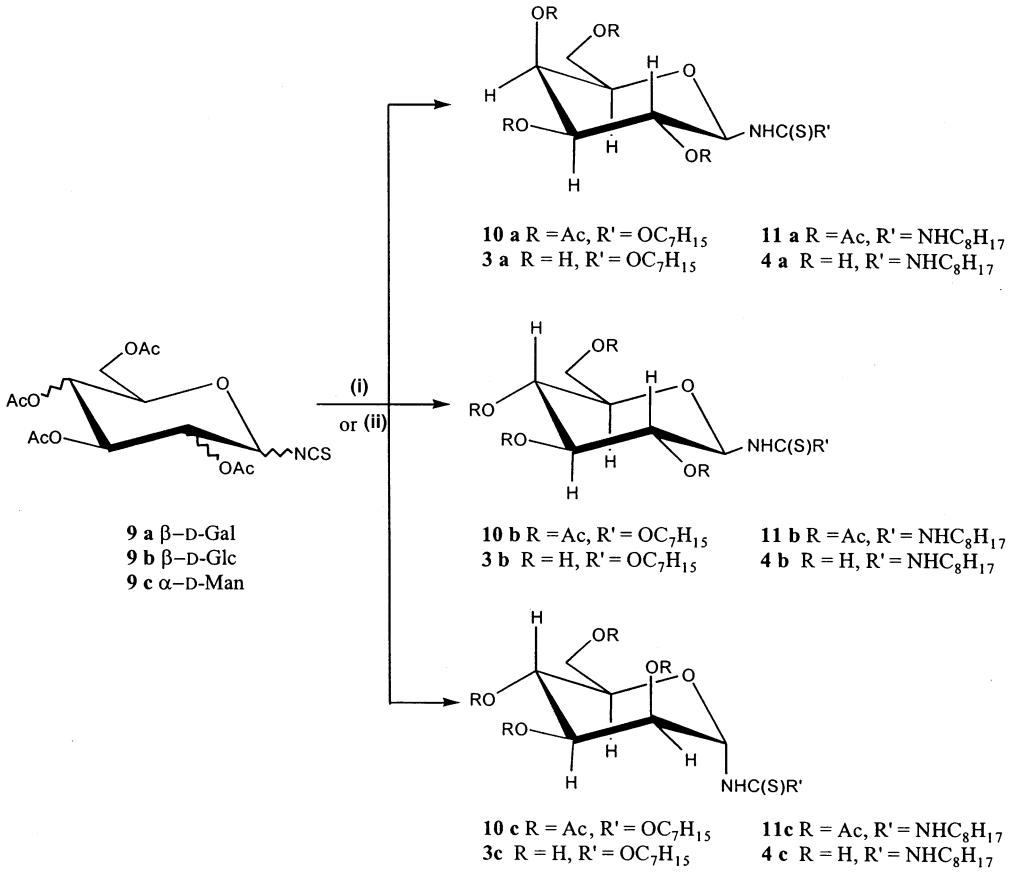
Scheme 2. (i) $C_7H_{15}OH$, KOCN, DMF, rt, 48 h.

Table 1
^{1}H chemical shifts (δ ppm) in $CDCl_3$ for acetylated derivatives **6**, **8**, **10**, **11**

Number	H-1 (J_{1-2})	H-2	H-3	H-4	H-5	H-6	H-6′	NH	NH	$CH_2CH_2(CH_2)_nCH_3$			
6aβ	5.65 (8.32)	5.30	5.07	5.43	4.07–4.18	4.07–4.18	4.07–4.18	4.90	–	3.16–3.20	1.49	1.28	0.87
6aα	6.28 (1.52)	5.31–5.34	5.31–5.34	5.47	4.31	4.08–4.12	4.08–4.12	4.89	–	3.10–3.22	1.51	1.29	0.88
6bβ	5.67 (8.55)	5.06–5.16	5.27	5.06–5.16	3.84	4.32	4.10	5.03	–	3.12–3.21	1.49	1.28	0.89
6bα	6.22 (3.85)	5.07–5.13	5.46	5.07–5.13	4.06–4.10	4.28	4.06–4.10	4.92	–	3.09–3.21	1.47	1.28	0.87
6cβ	6.02 (1.52)	5.27	5.30–5.35	5.30–5.35	4.07–4.10	4.30	4.12	4.98	–	3.12–3.21	1.51	1.25	0.88
6cα	6.08 (1.70)	5.26–5.36	5.26–5.36	5.26–5.36	4.06–4.15	4.29	4.06–4.15	4.90	–	3.10–3.22	1.47	1.28	0.87
8a	5.80 (4.80)	3.96–4.36	5.05	5.44	3.96–4.36	4.12–4.16	4.12–4.16		–	3.46–3.51	1.57	1.30	0.88
8b	5.80 (5.21)	4.46	5.17	4.90	3.91–4.11	4.19–4.21	4.19–4.21	5.49	–	3.91–4.11	1.59	1.29	0.88
8c	5.46 (2.51)	5.15	5.30	4.59	3.68	4.24	4.14		–	3.43–3.51	1.53	1.26	0.88
10a	5.69	5.22–5.36	5.22–5.36	5.46	4.07–4.16	4.38–4.48	4.38–4.48	6.94	–	3.67	1.69	1.29	0.89
10b	5.60	4.96–5.12	5.36	4.96–5.12	4.83–4.89	4.29–4.43	4.13	6.91	–	3.64	1.68	1.29	0.89
10c	5.22–5.36	5.22–5.36	5.22–5.36	5.22–5.36	4.05–4.17	4.36–4.45	4.36–4.45	5.99	–	3.67	1.72	1.29	0.88
11a	5.40	5.22	5.22	6.40	4.00–4.41	4.00–4.41	4.00–4.41	6.65	6.75	3.40	1.60	1.30	0.87
11b	5.37	4.97–5.14	4.97–5.14	4.97–5.14	3.88	4.38	4.10	5.76	6.67	3.51	1.57	1.27	0.88
11c	5.28–5.41	5.28–5.41	5.28–5.41	5.28–5.41	4.12–4.17	4.30	4.12–4.17	6.97	7.37	3.49–3.65	1.61	1.27	0.88

Table 2
^{13}C chemical shifts (δ ppm) in $CDCl_3$ solution of acetylated derivatives **6**, **8**, **10**, **11**

Number	C-1	C-2	C-3	C-4	C-5	C-6	CO or CS	CH_2	CH_2			$(CH_2)_n$			CH_3
6aβ	93.22	67.97	70.92	66.87	71.41	60.96	153.70	41.20	31.78	29.01	29.76	26.86	22.56		14.04
6aα	90.46	68.36	67.56	67.54	66.65	61.33	153.94	41.23	31.74	29.01	28.93	26.69	22.58		14.04
6bβ	92.74	70.31	72.87	67.94	72.44	61.54	153.70	41.88	31.78	29.61	28.87	26.68	22.58		14.20
6bα	89.70	70.10	69.71	68.11	69.34	61.59	153.83	41.23	31.74	29.01	28.93	26.69	22.58		14.04
6cβ	91.25	70.23	68.97	68.65	65.70	62.19	153.07	41.27	31.73	29.91	29.06	26.94	22.59		14.04
6cα	90.46	68.36	67.56	67.54	66.65	61.33	153.94	41.23	31.74	29.01	28.93	26.69	22.58		14.04
8a	97.50	73.92	71.43	66.03	69.08	61.46	153.79	62.66	31.80	29.60	26.09	23.70	22.61		14.08
8b	97.86	68.14	74.09	67.33	70.22	65.27	153.84	63.17	31.72	28.90	25.78	24.74	22.57		14.05
8c	97.39	76.31	71.43	65.63	70.65	62.44	153.81	62.72	31.75	29.48	26.93	24.53	22.59		14.07
10a	83.50	68.31	70.51	67.27	72.45	61.17	171.32	32.82	29.11	28.90	28.40	25.75	22.56		14.04
10b	83.18	70.53	73.68	68.31	73.68	61.68	171.06	31.70	29.11	28.89	28.39	25.76	22.57		14.05
10c	79.57	70.41	68.93	66.61	68.58	62.07	170.99	31.84	29.11	28.90	28.43	25.75	22.57		14.05
11a	83.33	73.60	71.12	68.45	67.55	61.00	180.10	41.97	31.74	29.15	28.75	28.65	26.87	22.60	14.06
11b	82.87	73.01	73.61	68.57	70.87	61.93	180.01	41.97	31.74	29.16	28.70	28.60	26.88	22.59	14.06
11c	81.15	68.65	68.68	66.01	68.58	62.19	180.06	45.81	31.75	29.24	29.16	28.93	26.93	22.61	14.07



Scheme 3. (i) $C_7H_{15}OH$, DABCO, toluene, rt, 8 h. (ii) $C_8H_{17}NH_2$, DABCO, toluene, rt, 8 h.

The structures of intermediates and final products were confirmed by NMR spectroscopy. The chemical shifts of **8a–b** anomeric protons (5.4–5.8 ppm) and the corresponding $J_{1,2}$ coupling constants (4.8–5.2 Hz) agree with the α-D-anomeric configuration. The coupling between the anomeric proton and the NH proton was not observed, the latter appearing as a singlet. The anomeric carbons (97–98 ppm) confirm the α configuration of the anomeric linkage, which is supported by $J_{C\text{-}1\text{–}H\text{-}1}$ measurements (175–181 Hz).

The α anomeric configuration assignment for **8c** was supported by $J_{C\text{-}1\text{–}H\text{-}1}$ measurements (175 Hz). The NMR data of acetylated compounds **8a–c** are summarised in Tables 1 and 2.

Synthesis of N-*glycosyl thiocarbamates* **3a–c**.—The *N*-glycosyl thiocarbamates were obtained by addition of the corresponding readily available glycosyl isothiocyanates (**9a–c**) [10–13] to heptyl alcohol. This reaction was performed in toluene at rt, in the presence of DABCO (Scheme 3). The compounds were purified by flash chromatography.

The β configuration of compounds **10a** and **10b** was clearly established by ^1H NMR spectra, which demonstrates the axial position of H-1 ($J_{1,2}$ 8–9 Hz, δ 5.6 ppm). The single resonance observed for C-1 shows that only one isomer was present and its chemical shift (83 ppm) and $J_{C\text{-}1\text{–}H\text{-}1}$ (157 Hz) are in agreement with the proposed configuration.

The α configuration of compound **10c** was established by the $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constant (177 Hz). The H-1 and C-1 signals are shielded (5 and 79 ppm, respectively).

Compounds **10a–c** were finally O-deacetylated by using the Zemplén procedure to afford the expected compounds **3a-c** in quantitative yields.

NMR data for acetylated derivatives **10a–c** are summarised in Tables 1 and 2.

Synthesis of N-*glycosylthioureas* **4a–c**.—The *N*-glycosylthioureas were obtained by reaction of glycosyl isothiocyanates [10–13]

with octylamine in toluene at rt in the presence of DABCO. Compounds **11a–c** were purified by flash chromatography. The final products **11a–c** were characterised by NMR spectroscopy (Tables 1 and 2). The H-1 signal was observed at 5.4 ppm for **11a** and **11b** [14]. The high value for $J_{1,2}$ (8–9 Hz) was indicative of a β anomeric configuration. The chemical shifts of the anomeric carbon (82–83 ppm) confirmed the β configuration, which was supported by the $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constant (158–160 Hz).

The anomeric α configuration of **11c** was established by comparison with similar products available in the literature [15] and was supported by the $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constant (171 Hz).

These compounds were finally deacetylated to give the expected products (**4a–c**) in quantitative yields. No anomerisation (^{13}C NMR) was observed during the deacetylation in the case of the D-mannopyranosyl derivative [16] and this result was confirmed by $J_{C\text{-}1\text{–}H\text{-}1}$ measurements (172 Hz).

Tensioactive properties.—Water solubility at 20 °C for **1a–c**, **2a–c**, and **3a–c** is low (Table 2) as compared with HECAMEG. The glucosyl derivatives were found to be more soluble than the corresponding galactosyl and mannosyl derivatives.

The α anomers were found to be more soluble than the corresponding β anomers, which probably results from the linear structures of β anomers allowing a more compact arrangement in the solid state and thus a more difficult solubilisation.

The *N*-glycosyl carbamates showed a much higher solubility than that of the corresponding *O*-glycosyl carbamates. The low solubility of the *O*-carbamates could be due to a hydrogen bond between the NH group and O-5. This assumption is in agreement with the IR of **1b** in the solid state. Thus, characteristic absorption bands for **1b** could be assigned as follows: 1705.8 cm^{-1} (amide I), 1592.9 cm^{-1} (amide II, bound C–N) and 1552.4 cm^{-1} (amide II, free C–N). These data are similar to results reported by Boullanger and co-workers [17] for 6-aminocarbonyl derivatives (isomers of HECAMEG). The solubility of *N*-glycosyl thiocarbamates was lower than that of the *O*- and *N*-glycosyl carbamates as expected from the lower electronegativity of the sulfur atom as compared with oxygen. The low solubility in water of the thioureas (<1 g L^{-1}) is probably due to both the presence of the sulfur atom and of a hydrogen bond between the NH group and O-5.

The values of the cmc of compounds **1**, **2**, **3** are listed in Table 3. The cmc of the products is low (3–8 mM) as compared with HECAMEG (19 mM) [17]. For *O*-glycosyl carbamates, the α anomers have a cmc lower than that of the β anomers, which is similar to the results obtained for the α–β maltosides [18]. As shown in Table 3, the cmc depends on the type of linkage between the hydrophobic tail and the sugar head. The *N*-glycosyl carbamates **2a–c** showed a higher cmc (7–8 mM), which reflects the more hydrophilic character of the *N*-glycosylcarbamate linkages compared to the *O*-glycosyl carbamates **1a–c** (3–7 mM) and the *N*-glycosyl thiocarbamates **3a–c** (3–5 mM). The *N*-glycosyl thiocarbamates **3a–c** have cmc values of comparable magnitude to those of *O*-glycosyl carbamates **1a–c**, probably because the *O*-glycosylcarbamate and the *N*-glycosylthiocarbamate linkages possess similar hydrophilic character [17,19].

The solubilizing properties of these products (**1**, **2** and **3**) were assayed on various liver subcellular fractions: cell membrane and nuclei, mitochondria and microsomes [20]. The amount of protein solubilized expressed as a percentage of the weight of freeze-dried tissue is shown in Table 3. The results were compared with those obtained with Triton X100. For compound **1b**, the *O*-glycosyl carbamates exhibited a solubilizing power similar to Triton X100. The α anomer had a solubilizing power much lower than that of the β anomer. It can be observed in Table 3 that the extraction ability for proteins depends on the linkage between the hydrophobic tail and the sugar head. The *N*-glycosyl carbamates exhibit a much lower solubilizing power than Triton X100. Thus, the inversion of the sugar head and the hydrophobic tail decreases the detergent efficiency. This inversion does not seem to modify in the same way the solubility and the cmc of these compounds. The *N*-glycosyl thiocarbamates show a lower solubiliz-

Table 3
Solubility, critical micelle concentration (cmc), surface tension (γ) and solubilizing properties of the amphiphilic derivatives **1–3** as compared with Triton × 100

Number	Solubility (g L^{-1}) [a]	cmc (mM) [a]	γ (mN m^{-1}) [a]	Solubilization of proteins [b]		
				Nuclear membrane	Mitochondria	Microsomes
1aα	3.6	3.2	35.9	[c]	[c]	[c]
1aβ	3.0	5.0	37.0	62.5	75.4	72.8
1bα	3.8	4.1	32.2	38.9	50.3	55.6
1bβ	3.1	7.0	21.1	64.5	72.5	73.3
1cα	2.9	4.0	29.5	[c]	[c]	[c]
1cβ	2.6	4.6	27.3	60.9	71.7	72.5
2a	12.3	7.1	34.2	40.5	55.1	60.3
2b	12.5	8.3	37.2	37.2	57.2	61.3
2c	11.8	7.1	31.1	32.3	52.2	57.5
3a	2.2	5.4	33.0	42.3	50.5	52.4
3b	1.9	3.4	33.8	40.4	52.6	55.0
3c	1.8	4.9	27.9	37.5	47.1	50.2
Triton × 100	[c]	[c]	[c]	62.2	74.9	76.2

[a] Measured at 20 °C in water.
[b] Percentage of lyophilized material [20].
[c] Not determined.

ing power than Triton X100. The substitution of the oxygen atom by a sulfur atom modifies the solubility, the cmc and the solubilizing power in the same way. The different head group (D-galactose, D-glucose and D-mannose) does not seem to affect the solubilizing properties.

3. Conclusions

The type of linkage between the hydrophobic tail and the sugar head appears to be important in determining the physico-chemical properties of these non-ionic surfactants. It is noteworthy that the anomeric configuration significantly affects the tensioactive properties (solubility, cmc and solubilizing power) of these molecules.

The nature of the head group (D-galactose, D-glucose and D-mannose) does not seem to modify the solubilizing properties but changes the water solubility.

4. Experimental

General methods.—Melting points were determined on an electrothermal 9100 apparatus and are uncorrected. TLC analysis was performed on aluminium sheets coated with Silica Gel 60 F 254 (E. Merck). Compounds were visualised by spraying the TLC plates with dilute 10% H_2SO_4 in EtOH followed by charring at 150 °C for a few min. Column chromatography was performed on Silica Gel Si 60. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell. ^1H and ^{13}C NMR spectra were recorded on a Brucker AC 250 spectrometer working at 250 and 80 MHz, respectively, with Me_4Si as internal reference. Elemental analyses were performed by the "Service Central de Microanalyse de Montpellier" and the "Service Commun de Microanalyse de Saint Jérome, Marseille".

All reagents were of commercial quality and were purchased from Aldrich Chemie.

The cmc values were determined by measurements of surface tension in aq solutions at 25 °C, by the ring method with a Tensiometer Kruss K-12 [21] except for the thiourea compounds **4**, which show a low solubility (< 1 g L^{-1}). The cmc was measured at the break of the slope in the γ versus log$C$ plots as usual.

The solubilizing properties of these products (**1**, **2**, and **3**) were assayed on various liver subcellular fractions: cell membrane and nuclei, mitochondria and microsomes. A 20 mg

sample of freeze-dried membrane/nuclei or 5 mg of freeze-dried mitochondria or microsomes obtained from rat liver was suspended in 1 mL of phosphate buffer (0.05M, pH 7.2) containing a 1 mg mL^{-1} concentration of detergent (lower than the cmc). The suspension was stirred at 37 °C, then centrifuged 10 min at 15,000*g*. Protein titration was achieved by optical density measurements of solution at 280 nm [20].

General procedure for the synthesis of O-β-D-*glycopyranosyl* N-*alkylcarbamates*.—A mixture of the reducing sugar **5a–c** (1 g, 2.87 mmol) [8], heptyl isocyanate (0.405 g, 2.87 mmol) and a catalytic amount of DABCO in toluene (50 mL) was stirred at rt for 18 h. After evaporation to dryness, the mixture was chromatographed on silica gel with 3:2 EtOAc–hexane.

2,3,4,6-Tetra-O-*acetyl*-β-D-*galactopyranosyl* N-*heptylcarbamate* (**6a**β). White powder (94%); mp 87–88 °C; $[\alpha]_D^{20}$ +20.4° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 54.06; H, 7.51; N, 3.00.

2,3,4,6-Tetra-O-*acetyl*-β-D-*glucopyranosyl* N-*heptylcarbamate* (**6b**β). White powder (84%); mp 85–86 °C; $[\alpha]_D^{20}$ +1.3° (*c* 1.2, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 54.15; H, 7.17; N, 3.08.

2,3,4,6-Tetra-O-*acetyl*-β-D-*mannopyranosyl* N-*heptylcarbamate* (**6c**β) *and 2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranosyl* N-*heptylcarbamate* (**6c**α). Syrup (61%); the anomers were separated by chromatography with 7:3 hexane–EtOAc in a 3:1 α–β ratio.

6cβ. $[\alpha]_D^{20}$ +25.7° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 53.95; H, 7.21; N, 3.10.

6cα. $[\alpha]_D^{20}$ +34.1° (*c* 1.2, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 54.00; H, 7.23; N, 3.07.

General procedure for the synthesis of O-α-D-*glycopyranosyl* N-*alkylcarbamates*.—The reducing sugar **5a–c** (1 g, 2.87 mmol) [8], heptyl isocyanate (0.405 g, 2.87 mmol) and Et_3N in MeCN (50 mL) were refluxed for 8 h. After evaporation to dryness, the mixture of α–β anomers was chromatographed on silica gel with 7:3 EtOAC–hexane as eluent to afford the α anomers.

2,3,4,6-Tetra-O-*acetyl*-α-D-*galactopyranosyl* N-*heptylcarbamate* (**6a**α). Amorphous solid (90%); mixture of α–β anomers in a 3:1 ratio; $[\alpha]_D^{20}$ +71.0° (*c* 1.1, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 54.07; H, 7.26; N, 2.95.

2,3,4,6-Tetra-O-*acetyl*-α-D-*glucopyranosyl* N-*heptylcarbamate* (**6b**α). White powder (80%); mp 84–85 °C; mixture of α–β anomers in a 2:1 ratio; $[\alpha]_D^{20}$ +96.7° (*c* 1.1, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 53.98; H, 7.16; N, 3.10.

2,3,4,6-Tetra-O-*acetyl*-α-D-*mannopyranosyl* N-*heptylcarbamate* (**6c**α). Syrup (85%); mixture of α–β anomers in a 3:1 ratio as described above.

General procedure for the synthesis of alkyl N-α-D-*glycopyranosylcarbamates*.—A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromide **7a-c** (1 g, 2.43 mmol), potassium cyanate (0.493 g, 6.09 mmol), heptyl alcohol (0.7 g, 6.07 mmol) in DMF (25 mL) was stirred at rt for 48 h. The solvent was removed and the residue was then diluted with EtOAc. The solution was filtered, washed with water and dried over sodium sulfate. After evaporation to dryness, the mixture was chromatographed on silica gel with 7:3 hexane–EtOAc.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl*-α-D-*galactopyranosyl)carbamate* (**8a**). Syrup (52%); $[\alpha]_D^{20}$ +67.8° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 53.70; H, 7.25; N, 2.86.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl*-α-D-*glucopyranosyl)carbamate* (**8b**). Syrup (35%); $[\alpha]_D^{20}$ +16.6° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 53.88; H, 7.19; N, 2.81.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranosyl)carbamate* (**8c**). White powder (84%); mp 63–65 °C; $[\alpha]_D^{20}$ −4.0° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2.

Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.15; N, 2.86. Found: C, 54.05; H, 7.23; N, 3.01.

General procedure for the synthesis of O-*alkyl* N-D-*glycopyranosylthiocarbamates*.—A solution of the corresponding 2,3,4,6-tetra-*O*-acetyl-D-glycopyranosyl isothiocyanate **9a–c** (0.5 g, 1.28 mmol) [10], heptyl alcohol (0.15 g, 1.28 mmol) and DABCO in toluene (50 mL) was stirred at rt for 8 h. The solvent was removed and the residue was then chromatographed on silica gel with 7:3 hexane–EtOAc.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)thiocarbamate* (**10a**). Syrup (83%); $[\alpha]_D^{20}$ +26.6° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{10}S$: C, 52.27; H, 6.93; N, 2.77. Found: C, 52.18; H, 7.04; N, 2.82.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)thiocarbamate* (**10b**). White powder (92%); mp 95–96 °C; $[\alpha]_D^{20}$ +11.0° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{10}S$: C, 52.27; H, 6.93; N, 2.77. Found: C, 52.06; H, 7.09; N, 2.74.

Heptyl N-*(2,3,4,6-tetra*-O-*acetyl-α*-D-*mannopyranosyl)thiocarbamate* (**10c**). Syrup (83%); $[\alpha]_D^{20}$ +25.7° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{22}H_{35}NO_{10}S$: C, 52.27; H, 6.93; N, 2.77. Found: C, 52.20; H, 7.02; N, 2.76.

General procedure for the synthesis of N-D-*glycopyranosyl*-N′-*alkylthioureas*.—A solution of 2,3,4,6-tetra-*O*-acetyl-D-glycopyranosyl isothiocyanate **9a–c** (0.5 g, 1.28 mmol) [10], octylamine (0.16 g, 1.28 mmol) and DABCO in toluene (50 mL) was stirred at rt for 8 h. The solvent was removed and the residue was then chromatographed on silica gel with 3:2 hexane–EtOAc.

N-*2,3,4,6-Tetra*-O-*acetyl-β*-D-*galactopyranosyl*-N′-*octylthiourea* (**11a**). Syrup (83%); $[\alpha]_D^{20}$ +22.1° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{23}H_{38}N_2O_9S$: C, 53.28; H, 7.33; N, 5.40. Found: C, 53.20; H, 7.35; N, 5.31.

N-*2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl*-N′-*octylthiourea* (**11b**). Syrup (77%); $[\alpha]_D^{20}$ +14.1° (*c* 1.0, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{23}H_{38}N_2O_9S$: C, 53.28; H, 7.33; N, 5.40. Found: C, 53.15; H, 7.47; N, 5.38.

N-*2,3,4,6-Tetra*-O-*acetyl-α*-D-*mannopyranosyl*-N′-*octylthiourea* (**11c**). Syrup (90%); $[\alpha]_D^{20}$ +66.3° (*c* 1, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 1 and 2. Anal. Calcd for $C_{23}H_{38}N_2O_9S$: C, 53.28; H, 7.33; N, 5.40. Found: C, 53.26; H, 7.46; N, 5.40.

General O-deacetylation procedure.—The fully protected glycoside was dissolved in dry MeOH and treated with a catalytic amount of NaOMe. After 2 h at rt, the mixture was neutralised with Amberlite IRC 50 (H^+ form), filtered and evaporated. The compound was obtained in almost quantitative yield and lyophilised.

β-D-*Galactopyranosyl* N-*heptylcarbamate* (**1aβ**). White powder; mp 96-98 °C; $[\alpha]_D^{20}$ +9.8° (*c* 1.0, MeOH); ^1H NMR (CD_3OD, δ): 5.28 (d, 1 H, *J* 7.92); 3.88 (d, 1 H); 3.56–3.70 (m, 5 H); 3.31 (dd, 1 H); 3.11 (t, 2 H); 1.50 (m, 2 H); 1.31 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 157.59 (CONH); 97.28 (C-1); 77.28 (C-5); 74.94 (C-3); 71.37 (C-2); 70.16 (C-4); 62.37 (C-6); 41.83, 32.97, 30.77, 30.13, 27.83 and 23.67 (CH_2); 14.44 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.06; H, 8.37; N, 4.46; O, 35.11.

β-D-*Glucopyranosyl* N-*heptylcarbamate* (**1bβ**). Amorphous solid; $[\alpha]_D^{20}$ +3.0° (*c* 1.0, MeOH); ^1H NMR (CD_3OD, δ): 5.32 (d, 1 H, *J* 7.92); 3.83 (dd, 1 H); 3.67 (dd, 1 H); 3.26–3.44 (m, 5 H); 3.10 (t, 2 H); 1.50 (m, 2 H); 1.31 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 157.47 (CONH); 96.70 (C-1); 78.54 (C-3); 78.07 (C-5); 74.03 (C-2); 71.14 (C-4); 62.42 (C-6); 41.86, 32.97, 30.78, 30.14, 27.84 and 23.68 (CH_2); 14.43 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.01; H, 8.51; N, 4.40; O, 35.09.

β-D-*Mannopyranosyl* N-*heptylcarbamate* (**1cβ**). Amorphous solid; $[\alpha]_D^{20}$ +8.8° (*c* 1.0, MeOH); ^1H NMR (CD_3OD, δ): 5.86 (d, 1 H, *J* 1.5); 3.58–3.80 (m, 6 H); 3.30 (dd, 1 H); 3.08 (t, 2 H); 1.51 (m, 2 H); 1.30 (s, 8 H); 0.89 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 156.91 (CONH); 95.71 (C-1); 76.53 (C-5); 72.34 (C-2); 71.39 (C-3); 68.09 (C-4); 62.76 (C-6); 41.81, 32.97, 30.77, 30.12, 27.84 and 23.67 (CH_2);

14.43 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.03; H, 8.44; N, 4.43; O, 35.10.

α-D-*Galactopyranosyl* N-*heptylcarbamate* (**1a**α). White powder; mp 83–84 °C; $[\alpha]_D^{20}$ + 81.7° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.96 (d, 1 H, *J* 3.9); 3.62–3.94 (m, 6 H); 3.31 (dd, 1 H); 3.10 (t, 2 H); 1.49 (m, 2 H); 1.30 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 157.77 (CONH); 94.64 (C-1); 74.23 (C-5); 71.29 (C-3); 70.77 (C-2); 69.01 (C-4); 62.56 (C-6); 41.83, 32.96, 30.82, 30.15, 27.86 and 23.68 (CH_2); 14.43 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.29; H, 8.51; N, 4.38; O, 34.84.

α-D-*Glucopyranosyl* N-*heptylcarbamate* (**1b**α). Amorphous solid; $[\alpha]_D^{20}$ + 9.1° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.20 (d, 1 H, *J* 2.9); 4.37 (dd, 1 H); 3.64–3.91 (m, 6 H); 3.30 (t, 2 H); 1.59 (m, 2 H); 1.32 (s, 8 H); 0.89 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 159.21 (CONH); 84.75 (C-1); 80.75 (C-2); 72.81 (C-3); 71.66 (C-5); 70.99 (C-4); 64.60 (C-6); 42.07, 32.9330.06,, 28.59, 27.79 and 23.65 (CH_2); 14.42 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.24; H, 8.55; N, 4.31; O, 34.90.

α-D-*Mannopyranosyl* N-*heptylcarbamate* (**1c**α). Amorphous solid; $[\alpha]_D^{20}$ + 38.3° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.86 (d, 1 H, *J* 1.8); 3.55–3.82 (m, 6 H); 3.30 (dd, 1 H); 3.10 (t, 2 H); 1.49 (m, 2 H); 1.30 (s, 8 H); 0.89 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 156.92 (CONH); 95.71 (C-1); 76.53 (C-5); 72.33 (C-2); 71.39 (C-3); 68.09 (C-4); 62.75 (C-6); 41.81, 32.93, 30.77, 30.13, 27.84 and 23.68 (CH_2); 14.43 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.27; H, 8.52; N, 4.31; O, 34.85.

Heptyl N-*(α-D-galactopyranosyl)carbamate* (**2a**). Amorphous solid; $[\alpha]_D^{20}$ + 36.55° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 6.28 (d, 1 H); 5.31–5.34 (m, 2 H); 5.47 (d, 1 H); 4.89 (t, 1 H); 4.31 (t, 1 H); 4.08–4.12 (m, 2 H); 3.10–3.22 (m, 2 H); 1.51 (m, 2 H); 1.29 (s, 8 H); 0.88 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 153.94 (CONH); 90.46 (C-1); 68.36 (C-2); 67.56 (C-3); 67.54 (C-4); 61.33 (C-6); 66.65 (C-5); 41.23, 31.74, 29.01, 28.93, 26.69 and 22.58 (CH_2); 14.04 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.29; H, 8.50; N, 4.38; O, 34.83.

Heptyl N-*(α-D-glucopyranosyl)carbamate* (**2b**). White powder; $[\alpha]_D^{20}$ + 8.0° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 3.98 (t, 1 H); 3.26–3.82 (m, 7 H); 3.12 (t, 2 H); 1.52 (m, 2 H); 1.31 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 157.25 (CONH); 98.25 (C-1); 76.33 (C-2); 73.02 (C-3); 71.93 (C-4); 71.79 (C-5); 65.85 (C-6); 62.78, 32.97, 30.20, 30.11, 26.96 and 23.66 (CH_2); 14.42 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.26; H, 8.51; N, 4.34; O, 34.89.

Heptyl N-*(α-D-mannopyranosyl)carbamate* (**2c**). Syrup; $[\alpha]_D^{20}$ + 6.5° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 3.88 (t, 1 H); 3.21–3.83 (m, 9 H); 1.52 (m, 2 H); 1.30 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 157.23 (CONH); 99.06 (C-1); 73.18 (C-2); 72.15 (C-3); 70.92 (C-4); 70.50 (C-5); 68.42 (C-6); 62.96, 33.61, 30.20, 30.10, 26.85 and 23.61 (CH_2); 14.41 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36; O, 34.85. Found: C, 52.28; H, 8.52; N, 4.33; O, 34.87.

Heptyl N-*(β-D-galactopyranosyl)thiocarbamate* (**3a**). White powder; mp 70–72 °C; $[\alpha]_D^{20}$ + 14.2° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.29 (d, 1 H); 4.42 (t, 1 H); 3.89 (d, 1 H); 3.49–3.71 (m, 5 H); 3.30 (m, 2 H); 1.70 (m, 2 H); 1.30 (s, 8 H); 0.89 (t, 3 H); ^{13}C NMR ($CDCl_3$, δ): 170.51 (CSNH); 87.16 (C-1); 78.55 (C-5); 76.06 (C-3); 71.88 (C-2); 71.51 (C-4); 70.51 (C-6); 62.71, 33.21, 30.37, 30.08, 27.22 and 23.93 (CH_2); 14.70 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_6S$: C, 49.83; H, 8.07; N, 4.15; S, 9.50. Found: C, 49.82; H, 8.03; N, 4.05; S, 9.34.

Heptyl N-*(β-D-glucopyranosyl)thiocarbamate* (**3b**). White powder; mp 93–94 °C; $[\alpha]_D^{20}$ + 5.1° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.33 (d, 1 H); 4.42 (t, 1 H); 3.83 (dd, 1 H); 3.67 (dd, 1 H); 3.29–3.45 (m, 6 H); 1.70 (m, 2 H); 1.31 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR ($CDCl_3$, δ): 170.56 (CSNH); 86.32 (C-1); 79.55 (C-5); 78.80 (C-3); 73.61 (C-2); 71.61 (C-4); 71.29 (C-6); 62.51, 32.97, 30.02, 29.73, 26.88 and 23.59 (CH_2); 14.39 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_6S$: C, 49.83; H, 8.07; N,

4.15; O, 28.45; S, 9.50. Found: C, 49.80; H, 7.91; N, 4.09; O, 28.75; S, 9.45.

Heptyl N-(α-D-*mannopyranosyl)thiocarbamate* (**3c**). White powder; mp 105–107 °C; $[\alpha]_D^{20}$ +44.5° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 5.87 (d, 1 H); 4.42 (t, 1 H); 3.68–3.85 (m, 5 H); 3.46 (m, 1 H); 3.30 (m, 2 H); 1.72 (m, 2 H); 1.31 (s, 8 H); 0.90 (t, 3 H); ^{13}C NMR ($CDCl_3$, δ): 170.99 (CSNH); 84.96 (C-1); 77.03 (C-5); 72.69 (C-2); 71.96 (C-3); 71.71 (C-4); 68.96 (C-6); 62.91, 33.19, 30.36, 30.02, 27.18 and 23.92 (CH_2); 14.67 (CH_3). Anal. Calcd for $C_{14}H_{27}NO_6S$: C, 49.83; H, 8.07; N, 4.15; O, 28.45; S, 9.50. Found: C, 49.83; H, 8.03; N, 4.19; O, 28.53; S, 9.42.

N-β-D-*Galactopyranosyl*-N′-*octylthiourea* (**4a**). White powder; mp 77–78 °C; $[\alpha]_D^{20}$ +4.3° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 4.89 (t, 1 H); 3.89 (t, 1 H); 3.68–3.85 (m, 7 H); 3.46 (m, 1 H); 3.30 (m, 2 H); 1.59 (m, 2 H); 1.32 (s, 10 H); 0.90 (t, 3 H); ^{13}C NMR ($CDCl_3$, δ): 171.59 (CSNH); 85.82 (C-1); 78.17 (C-2); 75.91 (C-3); 71.65 (C-4); 70.80 (C-5); 62.95 (C-6); 33.25, 30.70, 30.62, 30.52, 30.29, 28.26 and 23.96 (CH_2); 14.71 (CH_3). Anal. Calcd for $C_{14}H_{27}N_2O_5S$: C, 51.41; H, 8.63; N, 7.99; S, 9.15. Found: C, 51.39; H, 8.66; N, 7.96; S, 9.15.

N-β-D-*Glucopyranosyl*-N′-*octylthiourea* (**4b**). Amorphous solid; $[\alpha]_D^{20}$ −3.5° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 4.89 (t, 1 H); 3.27–3.85 (m, 8 H); 3.20 (m, 2 H); 1.58 (m, 2 H); 1.31 (s, 10 H); 0.90 (t, 3 H); ^{13}C NMR ($CDCl_3$, δ): 171.44 (CSNH); 86.87 (C-1); 80.03 (C-2); 79.58 (C-3); 74.84 (C-4); 72.34 (C-5); 63.56 (C-6); 33.82, 31.28, 31.20, 31.09, 30.88, 28.84 and 24.54 (CH_2); 15.30 (CH_3). Anal. Calcd for $C_{14}H_{27}N_2O_5S$: C, 51.41; H, 8.63; N, 7.99; S, 9.15. Found: C, 51.38; H, 8.65; N, 7.94; S, 9.13.

N-α-D-*Mannopyranosyl*-N′-*octylthiourea* (**4c**). White powder; mp 111–112 °C; $[\alpha]_D^{20}$ +8.3° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, δ): 4.89 (t, 1 H); 3.27–3.85 (m, 8 H); 3.20 (m, 2 H); 1.57 (m, 2 H); 1.31 (s, 10 H); 0.90 (t, 3 H); ^{13}C NMR (CD_3OD, δ): 170.74 (CSNH); 83.26 (C-1); 79.78 (C-2); 76.10 (C-3); 72.68 (C-4); 68.52 (C-5); 63.11 (C-6); 33.26, 30.70, 30.63, 30.32, 30.27, 28.27 and 23.97 (CH_2); 14.70 (CH_3). Anal. Calcd for $C_{14}H_{27}N_2O_5S$: C, 51.41; H, 8.63; N, 7.99; S, 9.15. Found: C, 51.32; H, 8.60; N, 7.95; S, 9.10.

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