ELSEVIER

Carbohydrate Research 299 (1997) 49–57

CARBOHYDRATE RESEARCH

Synthesis and surface-active properties of amphiphilic 6-aminocarbonyl derivatives of D-glucose

Valérie Maunier [a], Paul Boullanger [a,*], Dominique Lafont [a], Yves Chevalier [b]

[a] *Laboratoire de Chimie Organique 2 (U.M.R. 5622 du C.N.R.S.), Université de Lyon 1, Ecole Supérieure de Chimie Physique Electronique de Lyon, 43 Bd du 11 Novembre 1918, F-69622 Villeurbanne, France*

[b] *Laboratoire des Matériaux Organiques à Propriétés Spécifiques (U.P.R. 9031 du C.N.R.S.), B.P. 24, F-69390 Vernaison, France*

Received 30 September 1996; accepted 13 December 1996

Abstract

Several 6-amido-6-deoxy derivatives of methyl α-D-glucopyranoside and D-glucopyranose were prepared via peracetylated 6-azido-6-deoxy or 6-deoxy-6-isocyanato intermediates. These compounds displayed high Krafft temperatures which could result from hydrogen bonding between NH and O-5. Their tensio-active properties above the Krafft temperature were compared with Hecameg (methyl 6-*O*-(*N*-heptylcarbamoyl)-α-D-glucopyranoside).

Keywords: Surfactants; 6-Amino-6-deoxy carbohydrates; Amphiphile

1. Introduction

In the frame of a programme devoted to amphiphilic carbohydrate derivatives, substituents in which the hydrophilic and hydrophobic moieties are linked by a carbamate or amide functionality at C-6 are of interest. From modification in the conformational flexibility around the C-5–C-6 bond, which could result from hydrogen bonding with the NH group, the formation of supramolecular assemblies, the organization at the surface of liposomes or monolayers [1,2] or the molecular recognition of the carbohydrate by a lectin could be affected. In addition, 6-*N*-carbamoyl derivatives offer structural similarities with Hecameg **1** [methyl 6-*O*-(*N*-heptylcarbamoyl)-α-D-glucopyranoside], a surfactant of current use in the extraction of membrane proteins [3].

2. Results and discussion

Synthesis.—In contrast to 1-amino or 2-amino deoxy analogues, only a few examples of mesomorphic derivatives of the 6-amino-6-deoxyhexoses are reported in the literature. Among them are the alkyl 6-alkylamino-6-deoxy-D-galactopyranosides [4], 6-alkylamido-6-deoxy-D-galactopyranoses [4] or (6,6′-

* Corresponding author.

0008-6215/97/$17.00
PII S0008-6215(96)00336-9

Table 1
Reaction conditions and yields for the reaction of octanoic acid or octanoyl chloride with azido derivatives **10** and **14** (1 equiv), in 0.06–0.08 M solutions unless otherwise stated

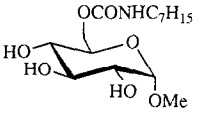
Starting material	PPh_3 (equiv)	$C_7H_{15}COX$ (X (equiv))	Solvent	T (°C)	Time (h)	Yield product (%) [a]
10	1.13	OH (1.08)	DMF	80	24	**3** (traces)
10	1.20	OH (1.20)	C_6H_6	82	24	**3** (traces)
10	1.00	OH (1.00)	C_6H_6	82	48	**3** (traces)
14	1.00	OH (1.20)	C_6H_6	82	72	**17** (19)
14	1.50	OH (1.80)	C_6H_6	82	72	**17** (40)
14	2.00	OH (5.00)	C_6H_6	82	72	**17** (50)
14	1.50	OH (1.80)	dioxane	110	72	none
14	1.50	OH (1.80)	toluene	117	72	**17** (20)
14	1.20	Cl (1.20)	CH_2Cl_2	25	48	**17** (73)
14	1.20	Cl (1.60)	C_6H_6	35	22	**17** (77)
14 [b]	1.20 [b]	Cl (1.60) [b]	C_6H_6 [b]	35	3	**17** (83)

[a] Reactions were stopped at consumption of the starting material; yields are given for separated, purified and characterized derivatives.
[b] Reaction performed in 0.2 M solution.

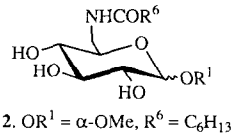
hexadecylamino) bis(6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose) [5]. This paper reports on the synthesis of new compounds of this family (**2–6**), together with some of their surface-active properties.

The key intermediates for these syntheses were the 6-azido-6-deoxy derivatives of D-glucose and methyl α-D-glucopyranoside, or methyl 6-isocyanato-6-deoxy-α-D-glucopyranoside. The latter were obtained by nucleophilic displacement on derivatives bearing a leaving group at C-6 (halogen **7**, **8** [6,7] or sulfonate **9**, **19** [8,9]). Among methods tested for the substitution of the leaving group by azide [10,11], the best result was obtained by substitution of the chlorodeoxy derivative **7** with sodium azide in refluxing dimethylformamide allowing the preparation of methyl 6-azido-6-deoxy-α-D-glucopyranoside (**10**) in almost quantitative yield. Nevertheless, handling and purification of the 6-halogeno and 6-*O*-tosyl derivatives were better achieved in their acetylated forms. Compounds **7**, **8**, **9** and **19** were therefore acetylated to **11**, **12**, **13** and **20**, respectively. The nucleophilic substitution was performed on the latter with sodium azide, either in refluxing dimethylformamide (for **11** and **12**) or in dimethyl sulfoxide at 50 °C (for **13** and **20**). The 6-azido-6-deoxy derivative **14** and **21** were obtained in almost quantitative yields.

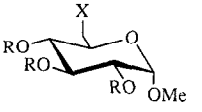
The synthesis of amide or carbamate derivatives from azido intermediates most often involved hydrogenolysis to amines [10,11], followed by reaction with acyl halides or anhydrides. In order to minimize the number of steps and to avoid side-reactions (e.g. acyl migrations), we decided to use the Staudinger [12] reaction to effect this transformation. The azido compound **14** or **21** was reacted in the presence of triphenylphosphine, either with heptanoic (or octanoic) acid [13] or a with heptanoyl (or octanoyl) chloride [14] affording the expected derivatives **16**, **17**, **22** or **23**. The intermediate iminophosphoranes were formed easily; however, their reactions with carboxylic acids or acyl chlorides were strongly dependent on reaction conditions. The results of experiments with **10** and **14**, summarized in Table 1, show that better yields are obtained from the fully acetylated derivative **14** rather than **10**, in apolar solvents and with octanoyl chloride rather than octanoic acid.



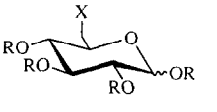
HECAMEG
1



2. OR^1 = α-OMe, $R^6 = C_6H_{13}$
3. OR^1 = α-OMe, $R^6 = C_7H_{15}$
4. OR^1 = α-OMe, $R^6 = OC_7H_{15}$
5. OR^1 = OH, $R^6 = C_6H_{13}$
6. OR^1 = OH, $R^6 = C_7H_{15}$



7. R = H, X = Cl
8. R = H, X = Br
9. R = H, X = OTs
10. R = H, X = N_3
11. R = Ac, X = Cl
12. R = Ac, X = Br
13. R = Ac, X = OTs
14. R = Ac, X = N_3
15. R = Ac, X = NCO
16. R = Ac, X = $NHCOC_6H_{13}$
17. R = Ac, X = $NHCOC_7H_{15}$
18. R = Ac, X = $NHCO_2C_7H_{15}$



19. R = H, Z = OTs
20. R = Ac, Z = OTs
21. R = Ac, Z = N_3
22. R = Ac, Z = $NHCOC_6H_{13}$
23. R = Ac, Z = $NHCOC_7H_{15}$

Table 2
^{1}H NMR data for the amphiphilic derivatives and their acetylated precursors [a]

No.	Solvent	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{6,6'}$)	H-6′ ($J_{5,6'}$)	NH ($J_{NH,6'}$)	OMe	CH_2–CH_2–$(CH_2)_n$–CH_3			
2	D_2O (70 °C)	5.21 *(3.7)*	3.99 *(9.7)*	4.09 *(9.3)*	3.71 *(9.2)*	4.0–4.1 *(7.6)*	3.83 *(14.6)*	4.0–4.1 *(nd)*	exch.	3.84	2.71	2.03	1.72	1.30
3	C_5D_5N	5.07 *(3.7)*	4.05 *(9.5)*	4.46 *(9.1)*	3.85 *(9.1)*	4.12 *(6.3)*	3.97 *(13.8)*	4.20 *(2.7)*	8.65 *(6.0)*	3.37	2.22	1.61	1.30	0.88
3	CD_3OD	4.64 *(3.6)*	3.38 *(9.3)*	3.60 *(9.3)*	3.09 *(9.3)*	3.5–3.6 *(nd)*	3.3–3.4 *(nd)*	3.5–3.6 *(nd)*	8.02 *(5.5)*	3.39	2.45	1.78	1.20	0.80
4	CD_3OD	4.64 *(3.8)*	3.37 *(9.5)*	3.58 *(9.3)*	3.12 *(9.2)*	3.5–3.6 *(7.3)*	3.25 *(14.2)*	3.5–3.6 *(nd)*	6.84 *(5.5)*	3.36	4.02	1.53	1.31	0.90
5-α [b]	D_2O (70 °C)	5.20 *(3.7)*	3.1–3.7 *(9.7)*	3.70 *(9.2)*	3.1–3.7 *(9.9)*	3.84 *(6.7)*	3.1–3.7 *(nd)*	3.1–3.7 *(3.3)*	exch.	–	2.27	1.56	1.28	0.86
5-β [b]	D_2O (70 °C)	4.95 *(7.8)*	3.1–3.7 *(nd)*	3.1–3.7 *(nd)*	3.1–3.7 *(nd)*	3.1–3.7 *(nd)*	3.1–3.7 *(nd)*	3.1–3.7 *(nd)*	exch.	–	2.27	1.56	1.28	0.86
6-α [b]	D_2O (70 °C)	5.64 *(3.8)*	3.7–4.0 *(9.5)*	4.16 *(9.4)*	3.7–4.0 *(9.7)*	4.30 *(6.4)*	3.7–4.0 *(nd)*	4.00 *(3.1)*	exch.	–	2.70	2.03	1.73	1.31
6-β [b]	D_2O (70 °C)	5.05 *(7.8)*	3.7–4.0 *(nd)*	3.65 *(nd)*	3.7–4.0 *(nd)*	3.98 *(nd)*	3.7–4.0 *(13.6)*	4.07 *(2.3)*	exch.	–	2.70	2.03	1.73	1.31
10	C_5D_5N	5.11 *(3.7)*	4.09 *(9.6)*	4.45 *(9.2)*	3.94 *(9.0)*	4.22 *(6.6)*	3.75 *(13.0)*	3.88 *(2.3)*	–	3.45	–	–	–	–
14	$CDCl_3$	4.95 *(3.6)*	4.86 *(10.2)*	5.47 *(9.8)*	4.96 *(10.0)*	3.97 *(6.1)*	3.30 *(13.5)*	3.41 *(3.3)*	–	3.44	–	–	–	–
15	$CDCl_3$	5.01 *(3.7)*	4.95 *(9.9)*	5.48 *(9.5)*	5.07 *(9.6)*	3.89 *(5.3)*	3.31 *(13.0)*	3.35 *(3.0)*	–	3.46	–	–	–	–
16	$CDCl_3$	4.92 *(3.6)*	4.83 *(9.8)*	5.46 *(9.7)*	4.86 *(9.7)*	3.87 *(6.2)*	3.31 *(14.4)*	3.61 *(2.8)*	5.80 *(6.1)*	3.39	2.19	1.61	1.30	0.88
17	$CDCl_3$	4.92 *(3.6)*	4.83 *(9.9)*	5.45 *(9.8)*	4.87 *(9.8)*	3.88 *(6.2)*	3.32 *(14.4)*	3.61 *(2.7)*	5.88 *(6.1)*	3.39	2.19	1.60	1.29	0.90
18	$CDCl_3$	4.91 *(3.8)*	4.83 *(9.9)*	5.47 *(9.7)*	4.90 *(9.4)*	3.85 *(6.2)*	3.45 *(nd)*	3.24 *(3.0)*	5.00 *(5.5)*	3.38	4.04	1.59	1.29	0.88
21-α [b]	$CDCl_3$	6.35 *(3.6)*	5.08 *(9.4)*	5.46 *(9.8)*	5.10 *(9.4)*	4.08 *(5.4)*	3.3–3.6 *(nd)*	3.3–3.6 *(3.0)*	–	–	–	–	–	–
21-β [b]	$CDCl_3$	5.72 *(7.9)*	5.14 *(9.1)*	5.25 *(9.2)*	5.07 *(9.4)*	3.81 *(4.8)*	3.3–3.6 *(nd)*	3.3–3.6 *(4.4)*	.	–	–	–	.	–
22-α [b]	$CDCl_3$	6.28 *(3.7)*	5.03 *(10.0)*	5.45 *(9.9)*	4.92 *(9.9)*	4.02 *(5.6)*	3.59 *(nd)*	3.33 *(2.8)*	5.73 *(m)*	–	2.18	1.59	1.26	0.89
22-β [b]	$CDCl_3$	5.66 *(8.1)*	5.10 *(9.4)*	5.23 *(9.4)*	4.92 *(9.5)*	3.70 *(6.4)*	3.61 *(nd)*	3.32 *(2.3)*	5.73 *(m)*	–	2.18	1.59	1.26	0.89
23-α [b]	$CDCl_3$	6.28 *(3.7)*	5.04 *(10.2)*	5.46 *(9.9)*	4.91 *(9.6)*	4.03 *(5.8)*	3.3–3.6 *(nd)*	3.3–3.6 *(2.7)*	5.71 *(m)*	–	2.17	1.63	1.28	0.86
23-β [b]	$CDCl_3$	5.65 *(8.1)*	5.14 *(9.3)*	5.23 *(9.4)*	4.92 *(9.5)*	3.69 *(6.4)*	3.58 *(nd)*	3.33 *(2.6)*	5.71 *(m)*	–	2.17	1.63	1.28	0.86

[a] Spectra recorded at room temperature, unless otherwise stated; nd: not determined attributions; exch.: exchangeable protons.
[b] Mixtures of α and β anomers.

The reaction was then extended to the azido derivative **21** and to heptanoyl chloride. Compounds **16**, **18**, **22** and **23** were prepared in similar yields.

Intermediates **12** and **14** were also used for the synthesis of carbamate **18**. This reaction involved the isocyanate **15** obtained in 63% yield by reaction of triphenylphosphine-carbon dioxide [15,16] on the azido derivative **14**. Unfortunately, the condensation of heptanol with **15**, by the procedures described in the literature [17,18], failed in our hands. Nevertheless, compound **18** was obtained by a one-pot reaction of **12** with a mixture of potassium cyanate-heptanol in dimethyl sulfoxide [19,20].

Compounds **16**, **17**, **18**, **22** and **23** were finally de-*O*-acetylated using the Zemplén procedure [21] to afford the expected compounds **2–6** in almost quantitative yields.

The structures of the intermediates and final products were confirmed by ^{1}H and ^{13}C NMR (Tables 2 and 3). The linkage between the glucose residue and the alkyl chain displays a preferred conformation which can be assigned by ^{1}H NMR. As seen from the values of $^{3}J_{5,6}$ and $^{3}J_{5,6'}$ coupling constants (6.9 ± 0.7 Hz and 2.8 ± 0.5 Hz, respectively), the C-5–C-6 bond is slightly distorted in a gauche–gauche conformation [28] which could result from hydrogen bonding between the NH group and O-5 [29,30].

This assumption is in agreement with the infrared spectra of the derivatives in the solid state. Thus, for example, characteristic absorptions bands for **3** can be assigned as follow (3506 cm^{-1}). ($\nu_{NH\text{-free}}$ and/or ν_{OH}), 3335 and 3072 ($\nu_{NH\text{-bound}}$), 1698 (amide I), 1551 (amide II, bound C–N), 1538 (amide II, free C–N). By comparison Hecameg, in which no intramolecular hydrogen bond between NH and O-5 occurred in the solid state, displayed absorptions at 3200–3600 cm^{-1} ($\nu_{NH,OH}$), 1698 cm^{-1} (amide I) and one band only at 1541 cm^{-1} (amide II, free C–N).

Tensioactive properties.—The physico-chemical properties of the above derivatives were evaluated and compared with Hecameg as a reference compound. The Krafft boundary temperature, critical micellar concentration (cmc), interfacial area per surfactant molecule at the air–water interface and surface tension at the cmc were measured for each surfactant (Table 4). Krafft temperatures were determined by slow heating of aqueous mixtures containing 0.01 M, 0.1 M and 1 M of amphiphilic compounds respectively. Surface tension (γ) measurements were carried out by the ring method of Lecomte du Nouÿ [22] and corrected according to Harkins and Jordan [23]. In order to allow direct comparison for all compounds, all measurements were performed at 70 °C,

Table 3
^{13}C NMR data of the amphiphilic derivatives and their acetylated precursors [a]

No.	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	OMe	CH_2	CH_2	$(CH_2)_n$	CH_3
2	D_2O	99.6	71.7	73.3	70.5	71.7	40.3	55.4	36.2	25.9	31.2, 28.4, 22.3	13.8
3	C_5D_5N	101.4	73.8	74.7	72.1	73.2	41.2	55.0	36.6	26.3	31.9, 29.6, 29.3, 22.8	14.2
3	CD_3OD	101.2	73.6	74.9	71.9	73..2	66.0	55.5	43.0	26.9	33.0, 30.2, 30.1, 23.7	14.4
4	CD_3OD	101.2	73.5	74.8	71.8	73.2	66.0	52.2	43.0	26.9	33.0, 30.2, 30.0, 23.7	14.4
5-α [b]	D_2O	92.5	73.0	72.0	70.3	71.6	40.3	–	36.5	26.3	31.9, 29.6, 29.3, 22.8	14.2
5-β [b]	D_2O	96.4	74.6	75.8	71.5	74.6	40.5	–	36.5	26.3	31.9, 29.6, 29.3, 22.8	14.2
6-α [b]	C_5D_5N	94.2	73.8	74.6	73.3	74.5	41.4	–	36.5	26.3	31.9, 29.6, 29.3, 22.8	14.2
6-β [b]	C_5D_5N	99.0	76.3	77.7	71.7	76.9	41.4	–	36.5	26.3	31.9, 29.6, 29.3, 22.8	14.2
10	C_5D_5N	101.5	73.5	75.0	72.5	72.5	52.6	55.2	–	–	–	–
14	$CDCl_3$	96.6	70.8	69.9 [c]	69.8 [c]	68.5	51.0	55.6	–	–	–	–
15	$CDCl_3$	96.8	70.6	70.1	69.7	68.5	46.8	55.6	–	–	–	–
16	$CDCl_3$	96.7	71.0	69.9	69.4	67.9	38.8	55.4	36.7	25.6	31.5, 29.0, 22.5	14.1
17	$CDCl_3$	96.7	71.0	69.9	69.4	67.9	38.8	55.4	36.7	25.6	31.7, 29.3, 29.0, 22.6	14.1
18	$CDCl_3$	96.6	71.0	70.0	69.5	68.0	65.4	55.4	40.9	25.8	31.7, 29.0, 22.6	14.1
21-α [b]	$CDCl_3$	88.9	69.1	69.7	69.0	70.9	50.7	–	–	–	–	–
21-β [b]	$CDCl_3$	91.5	70.9	72.7	69.0	73.8	50.6	–	–	–	–	–
22-α [b]	$CDCl_3$	88.9	69.3	69.7	68.7	70.6	38.7	–	33.9	25.5	31.4, 28.7, 24.7	14.1
22-β [b]	$CDCl_3$	91.9	70.3	72.7	68.6	73.7	38.9	–	36.6	25.5	31.5, 28.9, 22.5	14.1
23-α [b]	$CDCl_3$	89.0	69.4	69.7	68.8	70.7	38.7	–	36.6	25.6	31.7, 29.3, 29.0, 22.6	14.1
23-β [b]	$CDCl_3$	91.9	70.3	72.7	68.6	73.7	38.9	–	36.6	25.6	31.7, 29.3, 29.0, 22.6	14.1

[a] Spectra recorded at room temperature.
[b] Mixtures of α and β anomers, tentative attributions.
[c] Attributions could be inverted.

Table 4
Physico-chemical parameters for amphiphilic derivatives **1–6**

No.	T_{Krafft} (°C)	cmc [a] (mM)	a_0 at the interface (Å^2) [a]	(γ) at the cmc (mN·m^{-1}) [a]
1	< 20	19	49	30.8
1	< 20	19 [b]	41 [b]	32.2 [b]
2	45	93	55	34.3
3	65	34	49	32.2
4	57	14	49	30.2
5	35	148	47	34.4
6	41	55	57	32.9

[a] Measured at 70 °C unless otherwise stated.
[b] Measured at 25 °C.

above the highest Krafft temperature of the series. The cmc was determined at the break of the slope in the γ versus log(C) plots (Fig. 1) as usual. The interfacial area per surfactant molecule (a_0) was calculated for concentrations just below the cmc as inversely proportional to the surface excess (Γ) given by the Gibbs law

$$\Gamma = -\frac{1}{RT}\frac{d\gamma}{d\ln(C)} = \frac{1}{N_{Av}a_0}$$

The cmc of Hecameg was shown not to depend on temperature, since the same values were found at 25 °C and 70 °C (Table 4), in agreement with literature data [3]. A slight increase of a_0 upon increasing temperature was observed, as has already been reported for other carbohydrate surfactants [24]. This could be simply attributed to thermal motion of the surfactant molecules. The surface tension at the cmc decreases slightly with temperature, but the fall in the surface tension is less than that of pure water. Thus, the surface lateral pressure $\Pi = \gamma_{water} - \gamma_{cmc}$ decreases with temperature, which is as expected since a_0 increases.

In spite of their close similarity with Hecameg (**1**), which displays a Krafft temperature below 0 °C, compounds **2–6** show a low solubility in water at room temperature and Krafft temperatures (T_{Krafft}) higher than 40 °C (Table 4). The latter increases as the number of carbon atoms in the alkyl chain increases, which is expected because of the larger thermodynamic stability of crystals of long linear alkyl chain compounds. Given the alkyl chain length (7 carbon atoms for compounds **3**, **4** and **6**), the presence of a methoxy group at the anomeric position increases the Krafft temperature (compare **3** and **6**) and the substitution of an amide group by a carbamate reduces the Krafft temperature. The position of the nitrogen atom seems to be the key parameter since high Krafft temperatures are observed with **2–6**, compounds which have their nitrogen atom directly linked to C-6, while Hecameg **1** is fairly soluble in water. In particular, one may notice the large difference of Krafft temperature between compounds **1** and **4** which are both carbamates with an *n*-heptyl chain.

The surface tension curves (γ versus log(C), Fig. 1) are typical of micelle-forming surfactants, but a

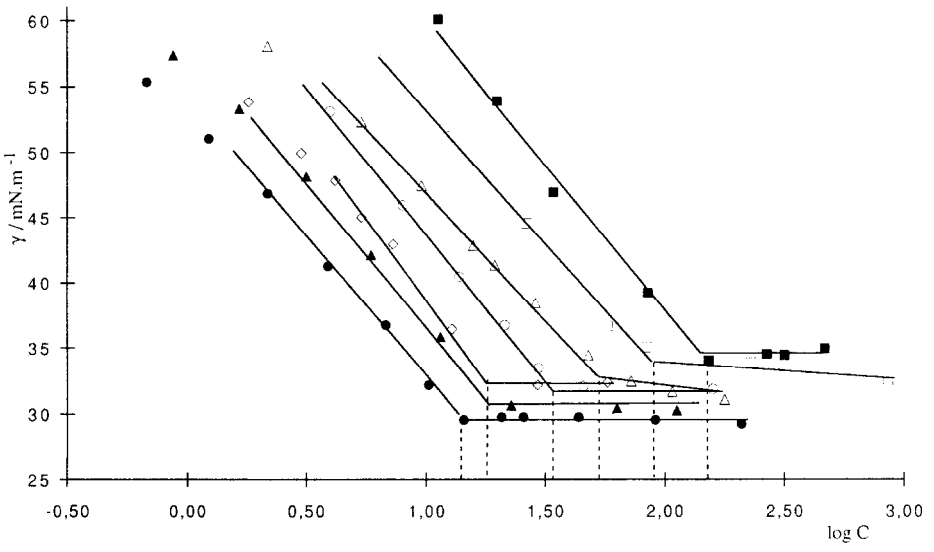


Fig. 1. Surface tension (γ)/mN · m^{-1} as a function of log of surfactant concentration (in mmol); only the linear portions of the curves at low concentrations were drawn for clearness. The measurements were done at 70 °C, unless otherwise stated; ◇ **1** (25 °C), ▲ **1**, □ **2**, ○ **3**, ● **4**, ■ **5**, △ **6**.

slight decrease of the surface tension was observed above the cmc for compounds **2**, **5** and **6**. For compounds **2** and **5**, this phenomenon may result from a non-micellar aggregation because of the short length of their hydrophobic hexyl chain. It was indeed reported that true micellar aggregation requires tensioactive molecules having hydrophobic chains longer than 5 to 6 carbon atoms [25]. For compound **6** with a heptyl chain, the α/β equilibrium could be responsible for the surface tension decrease above the cmc.

The values of the cmc measured at 70 °C are in the expected range for non-ionic monosaccharide surfactants with a hexyl or heptyl chain. The cmc variation as a function of alkyl chain-length agrees with the expected value found for nonionic surfactants [26]. In the heptyl series, the cmc increase in the order **4** < **1** < **3** < **6**. For methyl glucosides, both carbamates have cmc values of comparable magnitude, much lower than that of the amide **3**. The additional oxygen atom of the carbamate surfactants then acts as a hydrophobic group being transferred from water to a hydrophobic environment during micelle formation. The amide **6** having a hydroxyl group at the anomeric position shows a much higher cmc, which reflects the more hydrophilic character of the hydroxyl group with respect to a methoxy substituent.

Molecular areas at the air–water interface a_0 are small (less than 50 Å^2/molecule for heptyl surfactants) for all compounds, which is a general trend for carbohydrate surfactants [3,24] and can be attributed to intermolecular hydrogen bonding of surfactant head-groups at the interface [27]. The larger a_0 value found for **6** could result from the anomeric equilibrium favoring the β anomer (68% at 70 °C, from ^{1}H NMR data) in which the carbohydrate moiety is roughly perpendicular to the alkyl chain and is then constrained to lay flat at the interface. Lastly, the surface tensions at the cmc are similar in magnitude, which is a direct consequence of the close similarity of a_0 values.

The preferred conformation, which could be stabilized by an intramolecular hydrogen bond between NH and O-5, has already been discussed in the section devoted to synthesis. It is noteworthy that the latter remained unchanged when the surfactant concentration was increased above the cmc; the coupling constants remained identical, the chemical shifts being affected only by the changes in molecular organization. The presumed intramolecular hydrogen bond, which is not replaced by an intermolecular one when molecules aggregate into micelles, may also persist in the crystalline state below the Krafft temperature. The overall shape of the molecule is determined by this conformation, at the linkage between the polar head and the hydrophobic alkyl chain.

The high Krafft temperatures, which were systematically found for the surfactants with a nitrogen atom (amide or carbamate) directly linked to carbon C-6 of the glucose residue, may be related to the high thermodynamic stability of the crystalline state originating from the shape of the surfactant molecule. The origin of the low Krafft temperature of Hecameg, which has its nitrogen atom in a γ position from C-6, may be due to a lower thermodynamic stability of its crystalline state arising from its inability to form such a strong intramolecular hydrogen bond [31].

3. Conclusion

Amphiphilic 6-aminocarbonyl derivatives of D-glucose represent a new class of tensio-active materials which can be prepared from easily available 6-azido-6-deoxy (and 6-deoxy-6-isocyanato) intermediates. When azido derivatives were used, the Staudinger reaction, performed in the presence of fatty acids, allowed the direct conversion to amide derivatives in quite reasonable yields. The latter one-step reaction avoids the need for reduction of the azido group before condensation.

The Krafft temperatures of compounds **2–6** are higher than the corresponding alkyl D-glucopyranosides or D-glucopyranose alkyl monoethers for the same chain length. This could be due to an intramolecular hydrogen bond between NH-6 and O-5; however this assumption has to be confirmed by the synthesis or other derivatives, molecular modelling and other physical measurements as well. Within this series, it could be noticed that the 'reverse-Hecameg' derivative **6**, despite a lower solubility, displayed a lower cmc and a lower surface tension at the plateau than Hecameg **1**.

4. Experimental

Melting points were determined on a Büchi apparatus and were uncorrected. TLC analyses were performed on aluminium sheets coated with Silica Gel 60 F 254 (E. Merck). Compounds were visualized by spraying the TLC plates with dilute 20% H_2SO_4 in MeOH followed by charring at 150 °C for a few min. Column chromatography was performed on Silica Gel Geduran Si 60 (E. Merck). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell. ^{1}H and ^{13}C NMR spectra were recorded on a

Bruker AC-200 or AM-300 spectrometer working at 200 or 300 MHz and 50 or 75.5 MHz respectively, with Me_4Si as the internal reference. Elemental analyses were performed by the 'Laboratoire Central d'Analyses du CNRS' (Vernaison, France).

Methyl 6-azido-6-deoxy-α-D-glucopyranoside (**10**). —Compound **7** [6] (6.9 g, 32.7 mmol) and sodium azide (10.7 g, 167 mmol) were refluxed for 48 h in dry DMF (100 mL). After filtration and evaporation to dryness, the mixture was dissolved in CH_2Cl_2 (100 mL) and filtered again, concd to 50 mL and filtered once more. Compound **10** was obtained as an amorphous solid (7.1 g, 99%); $[\alpha]_D^{21}$ +126° (*c* 1.0, MeOH); ^1H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_7H_{13}N_3O_5$: C, 38.36; H, 5.98; N, 19.17. Found: C, 38.45; H, 6.27; N, 18.98.

Methyl 2,3,4-tri-O-acetyl-6-azido-6-deoxy-α-D-glucopyranoside (**14**).—The same experimental procedure was applied to **11** (11.2 g, 33.1 mmol) [6]. Compound **14** was obtained in almost quantitative yield (11.1 g, 97%) after recrystallisation from ether; mp 103 °C, lit. 103 °C [11]; $[\alpha]_D^{21}$ +133° (*c* 1.0, MeOH), lit. 155.4° [11]; ^1H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{13}H_{19}N_3O_8$: C, 45.22; H, 5.55; N, 12.17. Found: C, 45.35; H, 5.67; N, 12.40.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-isocyanato-α-D-glucopyranoside (**15**).—Compound **14** (202 mg, 0.57 mmol) and triphenylphosphine (145 mg, 0.56 mmol) were refluxed for 3 h in dry THF (2 mL) under a stream of carbon dioxide. After evaporation to dryness, the mixture was chromatographed on silica gel with 1:1 EtOAc–light petroleum ether (bp 40–60 °C) as eluent. Compound **15** was obtained as an unstable amorphous solid (128 mg, 63%) which was not fully characterized; ^1H and ^{13}C NMR, Tables 2 and 3.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-heptanamido-α-D-glucopyranoside (**16**).—Triphenylphosphine (7.2 g, 27 mmol) in anhyd CH_2Cl_2 (20 mL) was added, at room temperature, to a mixture of **14** (7.3 g, 21 mmol) and heptanoyl chloride (5.1 mL, 33 mmol) in anhyd CH_2Cl_2 (120 mL). After 5 h at room temperature, the mixture was filtered, washed with an aq soln of $NaHCO_3$ (5 g/100 mL) and dried over magnesium sulfate. After evaporation to dryness, the mixture was chromatographed on silica gel with 2:1 EtOAc–light petroleum ether (bp 40–60 °C) as the eluent to afford **16** (6.2 g, 68%). Syrup; $[\alpha]_D^{21}$ +107° (*c* 1.1, CH_2Cl_2); ^1H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{20}H_{33}NO_9$: C, 55.67; H, 7.71; N, 3.25. Found: C, 55.53; H, 7.63; N, 3.18.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-octanamido-α-D-glucopyranoside (**17**).—The same experimental procedure was applied to **14** (6.9 g, 20 mmol), using octanoyl chloride (5.0 mL, 29 mmol); the same work up procedure and chromatographic purification afforded **17** (6.5 g, 73%); mp 84 °C; $[\alpha]_D^{21}$ +113° (*c* 1.1, MeOH); ^1H and ^{13}C NMR, Tables 2 and 3). Anal. Calcd for $C_{21}H_{35}NO_9$: C, 56.62; H, 7.92; N, 3.14. Found: C, 56.52; H, 7.79; N, 3.14.

Methyl 2,3,4-tri-O-acetyl-6-N-carbamoylheptyl-6-deoxy-α-D-glucopyranoside (**18**).—A mixture of the 6-bromo derivative **12** [6] (8.0 g, 20.9 mmol), potassium cyanate (4.3 g, 53.0 mmol) and heptyl alcohol (6.16 g, 53.0 mmol) in Me_2SO (54 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was poured on to icy water and extracted with ether (3 × 40 mL). The organic extracts were washed once with water and then dried over magnesium sulfate. After evaporation to dryness, the mixture was flash-chromatographed on silica gel with 1:2 EtOAc–light petroleum ether (bp 40–60 °C) as the eluent to afford **18** (2.4 g, 25%) as a syrup; $[\alpha]_D^{21}$ +106° (*c* 1.2, MeOH); ^1H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{21}H_{35}NO_{10}$: C, 54.65; H, 7.64; N, 3.03. Found: C, 54.65; H, 7.46; N, 2.95.

1, 2, 3, 4 - Tetra - O - acetyl - 6 - azido - 6 - deoxy - D - glucopyranose (**21**).—1,2,3,4-Tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-D-glucopyranose **20** [9] (14.0 g, 27.9 mmol) and sodium azide (10.0 g, 154 mmol) dissolved in dry Me_2SO (100 mL) were stirred at 50 °C for 4 h and then at room temperature for 16 h. The mixture was poured on to icy water and extracted with ether (4 × 100 mL). The organic extracts were washed twice with water and then dried over calcium chloride. After evaporation to dryness, compound **21** was recovered as a mixture of α/β anomers in 1:4 ratio (9.3 g, 89%) as a white powder which was used without further purification; ^1H and ^{13}C NMR (Tables 2 and 3).

1,2,3,4-Tetra-O-acetyl-6-deoxy-6-heptanamido-D-glucopyranose (**22**).—The same experimental procedure as was used for the synthesis of **16** from **14** was extended to the preparation of **22** from **21** (8.0 g, 21.5 mmol). After evaporation to dryness, the mixture was chromatographed on silica gel with 3:2 EtOAc–light petroleum ether (bp 40–60 °C) as the eluent to afford compound **22** as a syrupy mixture of α and β anomers in 1:2 ratio (7.2 g, 73%); ^1H and ^{13}C NMR (Tables 2 and 3). Anal. Calcd for $C_{21}H_{33}NO_{10}$: C, 54.89; H, 7.24; N, 3.05. Found: C, 54.66; H, 7.34; N, 3.05.

1,2,3,4-Tetra-O-acetyl-6-deoxy-6-octanamido-D-glucopyranose (**23**).—The previous experimental procedure was applied to **21** (7.0 g, 18.8 mmol).

After evaporation to dryness, the mixture was chromatographed on silica gel with 1:1 EtOAc–light petroleum ether (bp 40–60 °C) as the eluent to afford compound **23** as a syrupy mixture of α and β anomers in 1:9 ratio (6.5 g, 74%); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{22}H_{35}NO_{10}$: C, 55.80; H, 7.45; N, 2.96. Found: C, 55.57; H, 7.44; N, 2.96.

Preparation of **2–6**; *general* O-*deacetylation procedure.*—The fully protected glucoside (**16**, **17** or **18**) (3.0 g) or glucose derivative (**22** or **23**) (3.0 g) was dissolved in dry MeOH (100 mL) and treated with a catalytic amount of NaOMe (20 mg). After 16 h at room temperature, the mixture was neutralized with Amberlite IR 120 (H^+ form), filtered and evaporated. The OH-free compound (**2–4**) was obtained pure, in almost quantitative yield, and did not require any purification. Compound **5** or **6** was chromatographed on silica gel with 5:1 $CHCl_3$–MeOH as the eluent.

Methyl 6-deoxy-6-heptanamido-α-D-*glucopyranoside* (**2**).—White powder (2.0 g, 94%); mp 142–143 °C; $[\alpha]_D^{21}$ +93° (*c* 1.1, MeOH); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{14}H_{27}NO_6$: C, 55.07; H, 8.91; N, 4.59. Found: C, 55.17; H, 8.97; N, 4.56.

Methyl 6-deoxy-6-octanamido-α-D-*glucopyranoside* (**3**).—White powder (2.1 g, 97%); mp 135 °C; $[\alpha]_D^{21}$ +91° (*c* 1.0, MeOH); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{15}H_{29}NO_6$: C, 56.41; H, 9.15; N, 4.39. Found: C, 56.57; H, 9.29; N, 4.62.

Methyl 6-N-carbamoylheptyl-6-deoxy-α-D-*glucopyranoside* (**4**).—White powder (2.0 g, 92%); mp 105 °C; $[\alpha]_D^{21}$ +94° (*c* 1.0, MeOH); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{15}H_{29}NO_7$: C, 53.72; H, 8.72; N, 4.18. Found: C, 53.48; H, 8.72; N, 4.09.

*6-Deoxy-6-heptanamido-*D-*glucopyranose* (**5**).—Amorphous solid (1.35 g, 71%); $[\alpha]_D^{25}$ mutarotation → +31° (*c* 0.5, H_2O); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.84; H, 8.74; N, 4.46.

*6-Deoxy-6-octanamido-*D-*glucopyranose* (**6**).—Amorphous solid (1.6 g, 82%); $[\alpha]_D^{25}$ mutarotation → +26° (*c* 0.5, H_2O); ^{1}H and ^{13}C NMR, Tables 2 and 3. Anal. Calcd for $C_{14}H_{27}NO_6$: C, 55.07; H, 8.91; N, 4.59. Found: C, 55.07; H, 8.87; N, 4.48.

Acknowledgements

The authors are grateful to the 'Groupe de Recherche: Systèmes Colloïdaux Mixtes (CNRS)' for a generous gift of Hecameg.

References

[1] L. Lebeau, P. Oudet, and C. Mioskowski, *Helv. Chim. Acta*, 74 (1991) 1697–1706.
[2] M.-R. Sancho, P. Boullanger, and R. Létoublon, *Colloids Surfaces B, Biointerfaces*, 1 (1993) 373–381.
[3] D. Plusquellec, C. Chevalier, R. Talibart, and H. Wroblewski, *Anal. Biochem.*, 179 (1989) 145–153; D. Plusquellec and H. Wroblewski, *US Patent* 5 223 411 (1993); *Chem. Abstr.*, 119 (1993) p 154466u; for recent applications in studies of membrane proteins or lipids, see for example: J.W. Lee, M. Chan, T.V. Law, H. Joo Kwon, and B.K. Jap, *J. Mol. Biol.*, 252 (1995) 15–19, and refs. therein; M.B. Ruiz, A. Prado, F.M. Goni, and A. Alonso, *Biochim. Biophys. Acta*, 1193 (1994) 301–306.
[4] P. Stangier, V. Vill, S. Rohde, U. Jeschke, and J. Thiem, *Liq. Crystals*, 17 (1994) 589–595.
[5] L. Sharma and S. Singh, *Carbohydr. Res.*, 270 (1995) 43–49.
[6] R.L. Whistler and M. Anisuzzaman, *Methods Carbohydr. Chem.*, 8 (1980) 227–231.
[7] A. Kashem, M. Anisuzzaman, and R.L. Whistler, *Carbohydr. Res.*, 61 (1978) 511–518.
[8] (a) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, 92 (1959) 384–391; (b) F.D. Cramer, *Methods Carbohydr. Chem.*, 2 (1963) 244–245.
[9] E. Hardegger and R. Montavon, *Helv. Chim. Acta*, 29 (1946) 1199–1203.
[10] D. Beaupère, B. Stasik, R. Uzan, and G. Demailly, *Carbohydr. Res.*, 191 (1989) 163–166.
[11] S. Hanessian, D. Ducharme, R. Massé, and M.-L. Capmau, *Carbohydr. Res.*, 63 (1978) 265–269.
[12] H. Staudinger and E. Hauser, *Helv. Chim. Acta*, 4 (1921) 861–886.
[13] M. Vaultier, N. Knouzi, and R. Carrié, *Tetrahedron Lett.*, 24 (1983) 763–764.
[14] Y. Golobolov, I.N. Zhmurova, and L.F. Kasukhin, *Tetrahedron*, 37 (1981) 437–472.
[15] P. Molina, M. Alajarin, and A. Arques, *Synthesis* (1983) 596–597.
[16] O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 49 (1984) 2688–2691.
[17] D. Plusquellec, G. Chevalier, R. Talibart, and H. Wroblewski, *Anal. Biochem.*, 179 (1989) 145–153.
[18] M.E. Duggan and J.S. Imagire, *Synthesis* (1989) 131–132.
[19] P.A. Argabright, H.D. Rider, and R. Sieck, *J. Org. Chem.*, 30 (1965) 3317–3320.
[20] F. Effenberger, K. Drauz, S. Förster, and W. Müller, *Chem. Ber.*, 114 (1981) 173–189.
[21] A. Thompson and M.L. Wolfrom, *Methods Carbohydr. Chem.*, 2 (1963) 215–220.
[22] P. Lecomte du Nouÿ, *J. Gen. Physiol*, 1 (1918) 521–524.
[23] W.D. Harkins and H.F. Jordan, *J. Amer. Chem. Soc.*, 52 (1930) 1751–1772.
[24] P. Boullanger and Y. Chevalier, *Langmuir*, 12 (1996) 1771–1776.
[25] J.B. Rosenholm, *Adv. Colloid Interface Sci.*, 41 (1992) 197–239.

[26] C. Tanford, *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, Wiley, New York, 1973.
[27] A.R. van Buuren and H.J.C. Berendsen, *Langmuir*, 10 (1994) 1703–1713.
[28] K. Bock and J.Ø. Duus, *J. Carbohydr. Chem.*, 13 (1994) 513–543.
[29] R.U. Lemieux, P.H. Boullanger, D.R. Bundle, D.A. Baker, A. Nagpurkar, and A. Venot, *New J. Chem.*, 2 (1978) 321–329.
[30] (a) R.U. Lemieux and A.A. Pavia, *Can. J. Chem.*, 47 (1969) 4441–4446; (b) R.U. Lemieux and J.T. Brewer, *Adv. Chem. Ser.*, 117 (1973) 121–146.
[31] S.B. Engelsen, S. Perez, L. Toupet, and D. Plusquellec, *Carbohydr. Res.*, 264 (1994) 161–171.