Carbohydrate Research 406 (2015) 41–45

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

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Functional glycolipid-crown-ethers by click chemistry

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ARTICLE INFO

Article history:
Received 7 November 2014
Received in revised form
29 December 2014
Accepted 30 December 2014
Available online 19 January 2015

Keywords:
Triazole-linked macrocyclic ligand
Copper-catalyzed azide-alkyne cycloaddition (CuAAC)
Surfactant assembly
Alkali complexation

ABSTRACT

A series of glycolipid crown ether analogs was prepared by bis-propargylation of lauryl glycoside followed by subsequent click-coupling with ethylene glycol-based diazides. The triazole-linked macrocycles were obtained in remarkable high yields. While the surfactant assembly was affected by presence of sodium ions, suggesting the formation of complexes, no ion-selectivity was observed for the macrocylic ligands. Computational studies suggest a low but significant cation-binding activity of the macrocycle, involving coordination at both oxygen and nitrogen atoms.

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Recently we proposed the incorporation of macrocyclic ligands into glycolipids to create surfactants that could enable the development of a drug-delivery system with an electrolyte-induced release mechanism.[1] However, despite decent yields in the cation-aided macrocyclization the conventional preparation of crown ethers on glycolipids is uneconomic owing to the number of required reaction steps. In order to reduce the latter, we aimed for a lately reported approach that utilizes click chemistry for an efficient cyclization of crown-ether related macrocycles.[2,3] This concept was previously already utilized for preparation of other macrocycles.[4–6] Closely following the synthetic approach of Stefaniak *et al.*[3] a bispropargylated glycolipid was coupled with different sized oligo-ethylene glycol diazides. The synthetic scheme is displayed in Scheme 1.

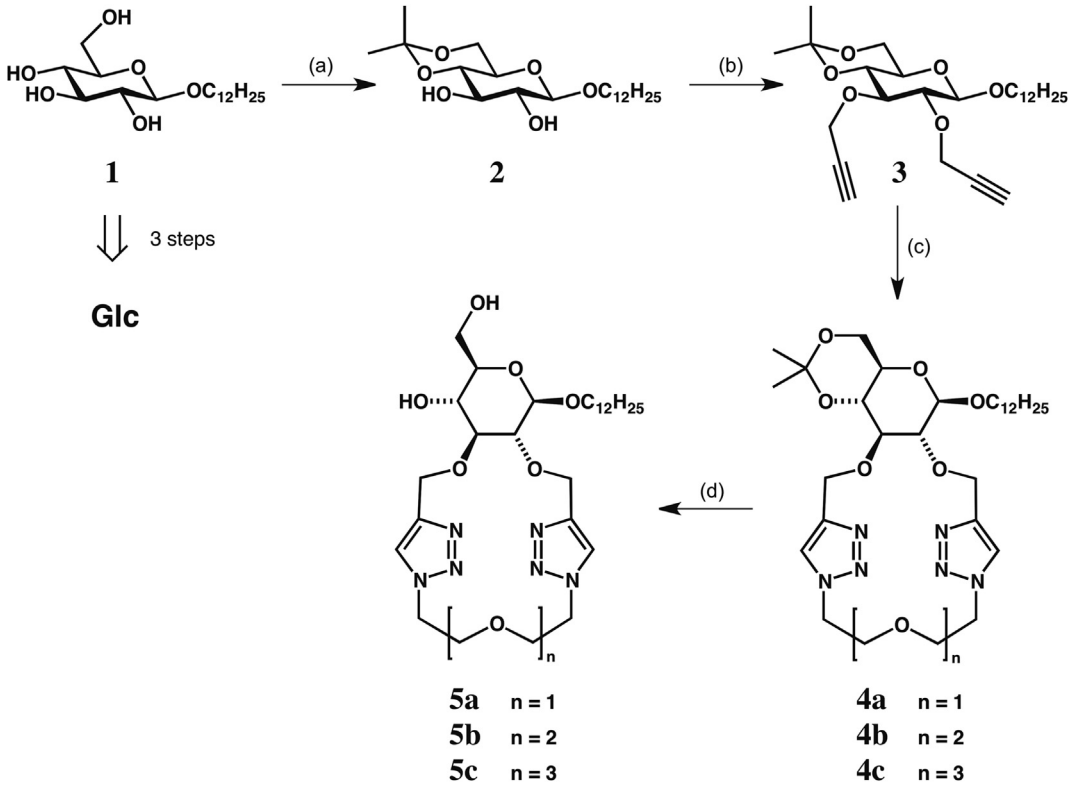
Lauryl β-D-glucoside,[7,8] **1**, was acetonated according to a literature procedure[9] and subsequently alkylated with propargyl bromide under phase transfer conditions[10] to provide the 2,3-bispropargylated precursor **3** in 80% overall yield. The copper catalyzed alkyne-azide cycloaddition (CuAAC)[11,12] furnished the macrocycles, **4**, in yields exceeding 80% in agreement with previous reports on similar compounds.[3] Although no significant material loss was experienced, a slight starting spot on TLC suggests the possibility of minor amounts of polymers from a competing polyaddition process. Despite the use of low reactant-concentrations (up to about 1 mM), the high macrocycle conversion yield is more likely due to a cation templating effect,[13] may be by the copper catalyst, since this metal coordinates well with nitrogen ligands, than reflecting a high dilution approach.[14] Final hydrolysis of the acetone acetal[15] yielded the crown ether analogs **5** in practically quantitative yield. The overall yield for the introduction of the macrocycle exceeds with ~65% our previous yield[1] of below 40% significantly. The higher yield in combination with reduced number of reaction steps and requirement of a single chromatographic purification step only makes the synthetic approach potentially viable.

The synthesis of macrocyle-annelated glycolipids was limited to glucose as the most economic and abundant carbohydrate resource. However, the approach can be applied for both *cis*- and *trans*-configurated vicinal diols. Even the macrocyclization at positions 4 and 6 of glucose succeeded in similar yield. Moreover, the triazole linkage is compatible with a wide range of protection groups, involving esters,[16] acetals as well as benzyl ethers. Details are provided in the Supplementary data.

The surfactant aggregation of **5a**, summarized in Table 1, practically exactly mirrored the behavior of previously investigated lauryl glucoside with 15-cr-5 anellation at the C-2–C-3 bond.[1] Moreover, addition of sodium chloride increased the CMC by about the same factor, whereas a reverse effect has been previously reported for alkyl glycosides without coordinating macrocycles.[17] This indicates **5** as potentially functional surfactant for delivery

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http://dx.doi.org/10.1016/j.carres.2014.12.015
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Scheme 1. Synthesis scheme for glycolipid click-crown ethers (a) $Me_2C(OMe)_2$, pTsOH, DMF, 18 h rt, 90%; (b) $HC{\equiv}CCH_2Br$, Bu_4NBr, tol/NaOH aq, 18 h rt, 90%; (c) $N_3C_2H_4O(-C_2H_4O)_nC_2H_4N_3$ n=1–3, [Cu^+], EtOH aq, 2 h reflux, ~80+%; (d) TFA, THF aq, 2 h 65 °C, >90%.

systems that may be triggered by electrolytes. A previous study[3] described the monitoring of silver cation-binding to the triazole-linked macorcycle by an NMR experiment. However, exposure of **5a** to excess of sodium ions did not alter any of the compounds NMR shifts. This may indicate a weaker coordination, or simply reflects the less sensitive probe owing to a low electron density effect of alkali-binding on the ring-oxygen and its subsequent carbon environment compared the binding of silver on the triazole nitrogen.

Unlike the previously investigated crown ethers,[1] the triazole analogs **5** did not exhibit any selectivity in the complexation of alkali metal ions. Instead of a size depending cation-binding selectivity, only similar affinities for sodium and potassium were detected in all cases. An observed minor trend towards slightly increased sodium affinity upon increasing macrocycle size was considered non-conclusive and statistical insignificant. While previous reports indicate a sandwich coordination of potassium by two 15-crown-5 macrocycles, owing to the size limitation of the ligand,[18,19] the mass spectrometer used in this investigation did not enable the detection of such species owing to a mass limit of m/z=1500. Anyway, the formation of a sandwich complex inside an assembly of lipid **5**, e.g. a micelle, is rather unlikely; hence this coordination type is not expected to exhibit a major effect on the stability of the assembly.

In order to understand the unexpected complexation behavior of **5** a computational study to compare **5a** with its simple crown ether analog 15-cr-5 was conducted. The results, displayed in Table 2, showed a significant reduction of cation binding energy for both sodium and potassium in the triazole containing macrocycle **5a**. This is expected since the triazole is a less efficient ligand compared to an ether-oxygen. However, charge densities for ligand **5a** and its sodium complex still suggest a stabilizing interaction of the triazole with the cation. In contrast to the binding energy, the charge density at the metal center of the sodium complex of **5a** almost matched the 15-cr-5-analog, while the corresponding potassium value remains significantly below that of the 15-cr-5-complex. Both, binding energy and cation charge density, at the complex suggest a preference of sodium over potassium for **5a**. This preference is also reflected in the structures of the two complexes; while the sodium ion is nicely wrapped by the macrocycle in **5a**, the potassium atom remains outside of the macrocycle, which only shields about half of the ion. Images are provided in the Supplementary data. It is not clear why this preference is not reflected in the ratio of mass peaks upon exposure of equimolar concentrations of sodium and potassium. The lower cation affinity, however, may render the applied method insufficiently sensitive to provide accurate information.

Table 1
Surfactant characteristics

	5a aq	**5a** NaCl (1 N aq)
CMC [mmol L^{-1}]	2.8	4.4
γ_{CMC} [mN m^{-1}]	32.7	33.9
A_{Surf} [Å^2]	68	45

Table 2
Cation binding (calcd)

Cation		**5a**	15-cr-5
Na^+	ΔE	68	101
	ρ_q	+0.58	+0.59
K^+	ΔE	49	69
	ρ_q	+0.72	+0.81

ΔE [kJ mol^{-1}], ρ_q [e].

Besides the increase of the CMC upon exposure with sodium ions, Table 1 also indicates a reduced molecular surface area of the surfactant in sodium electrolyte. The latter was calculated from the slope of the concentration depending region in the logarithmic surface tension concentration plot.[20] The optimized structures for **5a** and its sodium complex, shown in Fig. 1, provide a possible explanation for this unexpected result. The coordination of the sodium cation has significant impact on the conformation of the macrocycle, causing it to compress. This may result in the decrease of the molecular surface area.

In conclusion, click-chemistry enables an efficient synthetic approach towards macrocyclic ligands on glycolipids. Despite lower alkali cation complexation activity of triazole containing macrocycles, the assembly behavior of glycolipids with macrocycle-anellation based on CuAAC is affected by electrolytes, thus potentially enabling the development of an electrolyte-stimulated drug delivery system. However, in view of the low cation selectivity of the compounds, click chemistry based ligands cannot replace sugar-anellated crown ethers[1] for applications aiming to regulate local electrolyte concentrations, e.g. drugs aiming on nerves.

1. Experimental

1.1. General

Commercial grade chemicals and solvents of AR grade were applied without prior purification. Chromatographic purifications applied the flash technique on silica gel 60 (35–60 mesh). NMR spectra were recorded on Jeol and Bruker 400 MHz spectrometers at room temperature. ^{13}C-peak-assignments are based on PENDANT and HSQC spectra. High resolution mass spectra were recorded on an Agilent LC-MS with electrospray ionization in presence of HOAc (5 mM), NaCl and KCl (each 1 mM). Critical micelle concentrations were determined based on systematic surface tension measurements using the DuNouy ring method. The intersection of the concentration dependent and the high concentration independent region in the logarithmic plot of surface tension against concentration determined the CMC. Surface tension measurements were recorded in 5 replicates with standard deviations below 0.1 mN m^{-1}.

1.1.1. Dodecyl 4,6-O-isopropylidene-β-D-glucopyranoside (**2**)

A solution of **1** (2.77 g, 8.0 mmol) in DMF (40 mL) was treated with 2.2-dimethoxypropane (1.65 g, 16 mmol) and pTsOH (50 mg). The mixture was stirred at rt for 18 h before the solvent was evaporated. The residue was taken up in EtOAc and extracted with $NaHCO_3$ aq. The organic layer was dried over $MgSO_4$ and subsequently concentrated to leave **2** as yellow syrup (2.78 g, 90%). $[\alpha]_D^{25}$ −30 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 4.33 (d, H-1), 3.91 (dd, H-6eq), 3.86 (dt, α-CH_2), 3.79 (dd, H-6ax), 3.66 (dd~t, H-3), 3.58 (dd~t, H-4), 3.53 (dt, α′-CH_2), 3.44 (dd, H-2), 3.26 (ddd~dt, H-5), 2.90, 2.72 (2bs, 2H, OH), 1.62 (m_c, 2H, β-CH_2), 1.50, 1.44 (2s, 2×3H, ^{i}Prdn), 1.25 (m_c, 18H, bulk-CH_2), 0.88 (t, 3H, CH_3); $^3J_{1,2}$=7.5, $^3J_{2,3}$=9.0, $^3J_{3,4}$=9.0, $^3J_{4,5}$=9.5, $^3J_{5,6ax}$=10.0, $^3J_{5,6eq}$=5.5, $^2J_6$=11.0, ^2J_a=9.5, $^3J_{a,b}$=7.0 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 103.2 (C-1), 99.8 (^{i}Prdn-C), 74.7, 73.5, 73.2, 67.3 (C-2–C-4), 70.5 (α), 62.1 (C-6), 31.9 (ω-2), 29.6 (2), 29.5, 29.4, 29.3 (bulk-CH_2), 29.0, 19.1 (^{i}Prdn-CH_3), 25.9 (β), 22.7 (ω-1), 14.1 (ω).

1.1.2. Dodecyl 4,6-O-isopropylidine-2,3-di-O-propargyl-β-D-glucopyranoside (**3**)

A solution of **2** (1.3 g, 3.3 mmol) in toluene (20 mL) was treated with aqueous NaOH (20 mL, 50%) and Bu_4NBr (0.53 g, 1.67 mmol). Propargyl bromide (1.59 g, 13 mmol) was added drop-wise and the mixture was stirred for 18 h at rt. TLC indicated complete conversion of the starting material. The organic layer was separated, washed with water and dried over $MgSO_4$. Evaporation of the solvent provided **3** (1.4 g, 90%) as pale yellow syrup. $[\alpha]_D^{25}$ −40 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 4.43 (m_c, 4H, propargyl-CH_2), 4.37 (d, H-1), 3.89 (dd, H-6aq), 3.85 (dt, α-CH_2), 3.75 (dd~t, H-6ax), 3.61 (dd~t, H-3), 3.51 (dt, α′-CH_2), 3.50 (dd~t, H-4), 3.30 (dd, H-2), 3.18 (ddd~dt, H-5), 2.44 (2t~m_c, 2H, propargyl-CH), 1.59 (m_c, 2H, β-CH_2), 1.47 & 1.40 (2s, 2×3H, ^{i}Prdn), 1.25 (m_c, 18H, bulk-CH_2), 0.87 (t, 3H, CH_3); $^3J_{1,2}$=7.5, $^3J_{2,3}$=9.5, $^3J_{3,4}$=9.5, $^3J_{4,5}$=9.5, $^3J_{5,6ax}$=10.0, $^3J_{5,6eq}$=5.5, $^2J_6$=11.0, ^2J_a=9.5, $^3J_{a,b}$=7.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 103.5 (C-1), 99.4 (^{i}Prdn-C), 81.2 (C-2), 80.2 & 79.9 (propargyl-C), 80.3 (C-4), 74.2 & 74.1 (propargyl-CH_2), 73.6 (C-3), 70.5 (α), 66.7 (C-5), 62.1 (C-6), 60.0 (2, propargyl-CH), 31.9 (ω-2), 29.7, 29.6 (3), 29.5, 29.4, 26.3 (bulk-CH_2), 29.0 & 19.0 (^{i}Prdn-CH_3), 25.9 (β), 22.7 (ω-1), 14.1 (ω).

1.2. General procedure for click-cyclization

A solution of **3** and an oligoethyleneglycol diazide (1 equiv) in EtOH (90% aq) was treated with $Cu(OAc)_2$ (0.3 equiv) and Na-ascorbate (1.1 equiv) and the reaction mixture was heated to reflux for 2 h, when TLC indicated compete conversion. After evaporation of the solvent the remaining mixture was taken up in CH_2Cl_2 and water. The organic layer was washed twice with EDTA (0.5 M aq) to remove copper contents, before dried over $MgSO_4$. After evaporation of the solvent the product was purified by chromatography using EtOAc/acetone 5–6:1.

1.2.1. Dodecyl 4,6-O-isopropylidine-2,3-O-[bis-triazolo-19-crown-5]-β-D-glucopyranoside (**4a**)

3 (1.0 g, 2.2 mmol) and diethylene glycol diazide[3,21] (0.33 g, 2.2 mmol) were coupled in EtOH (90% aq, 150 mL) using $Cu(OAc)_2$ (120 mg, 0.65 mmol) and Na-ascorbate (0.43 g, 2.2 mmol) according to general procedure 1.3. to give **4a** (1.12 g, 84%) as a colorless syrup. $[\alpha]_D^{25}$ −27 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 7.42 & 7.39 (2s, 2H, triazole), 5.10 & 5.07 (2d, 2H, CH_2O-sugar-A&B),

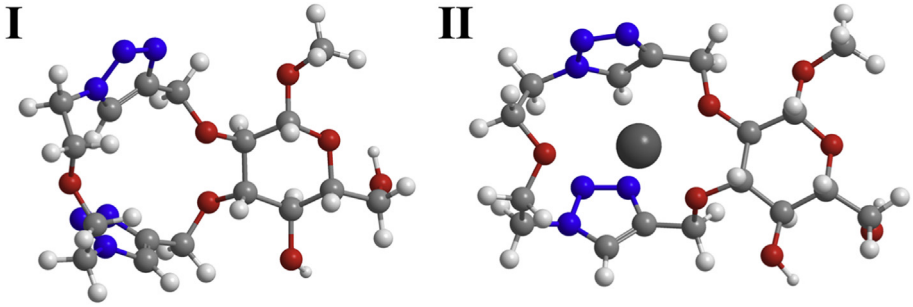


Fig. 1. Optimized structures for **5a** (I) and its Na-complex (II).

4.70 & 4.66 (2d, 2H, CH_2O-sugar-A′&B′), 4.55–4.44 (m, 4H, CH_2N), 4.42 (d, H-1). 3.90 (dd, H-6eq), 3.87–3.77 (m, 5H, α+4EG), 3.77 (dd~t, H-6ax), 3.70 (dd~t, H-3), 3.59–3.50 (m, 2H, H-4 & α′), 3.35 (dd, H-2), 3.22 (ddd~dt, H-5), 1.63 (m_c, 2H, β), 1.49 & 1.41 (2s, 2×3H, ^{i}Prdn), 1.33 (m_c, 2H, γ), 1.22 (m_c, 16H, bulk-CH_2), 0.84 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{2,3}$=9.0, $^{3}J_{3,4}$=9.0, $^{3}J_{4,5}$=10.0, $^{3}J_{5,6ax}$=10.0, $^{3}J_{5,6eq}$=5.5, $^{2}J_{6}$=11.0, $^{2}J_{CH2O}$=12.0 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 146.0, 145.7 (triazole-C), 123.3 (2 triazole-CH), 104.1 (C-1), 99.2 (^{i}Prdn-C), 81.7 (C-2), 80.6 (C-4), 74.8 (C-3), 70.4 (α), 69.2, 69.1 (EG), 66.7 (C-5), 66.6, 66.2 (CH_2O), 62.1 (C-6), 50.1 (CH_2N), 31.8 (ω-2), 29.7, 26.5 (3), 29.4, 29.3, 29.2 (bulk-CH_2), 29.1 & 19.1 (^{i}Prdn-CH_3), 25.9 (β), 22.6 (ω-1), 14.0 (ω).

1.2.2. Dodecyl 4,6-O-isopropylidine-2,3-O-[bis-triazolo-22-crown-6]-β-D-glucopyranoside (**4b**)

3 (0.4 g, 0.86 mmol) and triethylene glycol diazide[3,8] (0.17 g, 0.86 mmol) were coupled in EtOH (90% aq, 120 mL) using $Cu(OAc)_2$ (50 mg, 0.26 mmol) and Na-ascorbate (0.17 g, 0.86 mmol) according to general procedure 1.3. to give **4b** (0.48 g, 85%) as a pale yellow syrup. $[\alpha]_D^{25}$ +52 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 & 7.65 (2s, 2h, triazole), 5.07 & 5.05 (2d, 2H, CH_2O-sugar-A&B), 4.81 & 4.79 (2d, 2H, CH_2O-sugar-A′&B′), 4.59–4.42 (m, 4H, CH_2N), 4.41 (H-1), 3.89 (dd, H-6eq), 3.87–3.79 (m, 5H, α+4EG), 3.75 (dd~t, H-6ax), 3.66 (dd~t, H-3), 3.59–3.51 (m, 5H, α′+4EG), 3.50 (dd~t, H-4), 3.31 (dd, H-2), 3.19 (ddd~dt, H-5), 1.63 (m_c, 2H, β), 1.48 & 1.41 (2s, 2×3H, ^{i}Prdn), 1.34 (m_c, 2H, γ), 1.22 (m_c, 16H, bulk-CH_2), 0.85 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{2,3}$=9.0, $^{3}J_{3,4}$=9.0, $^{3}J_{4,5}$=10.0, $^{3}J_{5,6ax}$=10.0, $^{3}J_{5,6eq}$=5.0, $^{2}J_{6}$=11.0, $^{2}J_{CH2O}$=12.0 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 145.6, 145.2 (triazole-C), 123.5, 123.4 (triazole-CH), 103.9 (C-1), 99.3 (^{i}Prdn-C), 81.2 (C-2), 80.5 (C-4), 74.4 (C-3), 70.6 (α), 70.3, 70.2, 69.5 (2, EG), 66.7 (C-5), 66.5, 66.4 (CH_2O), 62.1 (C-6), 50.2 (CH_2N), 31.8 (ω-2), 29.7, 29.6 (2), 29.5 (2), 29.3 (2) (bulk-CH_2), 29.1 & 19.0 (^{i}Prdn-CH_3), 25.9 (β), 22.6 (ω-1), 14.0 (ω).

1.2.3. Dodecyl 4,6-O-isopropylidine-2,3-O-[bis-triazolo-25-crown-7]-β-D-glucopyranoside (**4c**)

3 (0.35 g, 0.75 mmol) and tetraethylene glycol diazide[3,22] (0.18 g, 0.75 mol) were coupled in EtOH (90% aq, 120 mL) using $Cu(OAc)_2$ (40 mg, 0.23 mmol) and Na-ascorbate (0.15 g, 0.86 mmol) according to general procedure 1.3. to give **4c** (0.42 g, 79%) as a pale yellow syrup. $[\alpha]_D^{25}$ −13 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 & 7.77 (2s, 2H, triazole), 4.98 & 4.97 (2d, 2H, CH_2O-sugar-A&B), 4.86 (2d~d, 2H, CH_2O-sugar-A′&B′), 4.50 (m_c, 4H, CH_2N), 4.40 (d, H-1), 3.89 (dd, H-6eq), 3.88–3.82 (m, 5H, a+4EG), 3.75 (dd~t, H-6ax), 3.66 (dd~t, H-3), 3.58–3.42 (m, 10H, H-4+α+8EG), 3.32 (dd, H-2), 3.19 (ddd~dt, H-5), 1.62 (m_c, 2H, β), 1.48 & 1.40 (2s, 2×3H, ^{i}Prdn), 1.32 (m_c, 2H, γ), 1.23 (m_c, 16H, bulk-CH_2), 0.86 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{2,3}$=9.0, $^{3}J_{3,4}$=9.0, $^{3}J_{4,5}$=10.0, $^{3}J_{5,6ax}$=10.0, $^{3}J_{5,6eq}$=5.5, $^{2}J_{6}$=11.0, $^{2}J_{CH2O}$=12.0 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 145.5, 145.0 (triazole-C), 124.0, 123.9 (triazole-CH), 104.0 (C-1), 99.3 (^{i}Prdn-C), 81.2 (C-2), 80.5 (C-4), 74.4 (C-3), 70.7 (2), 70.6 (2), 70.5 (α+EG), 69.7 (2) (EG), 66.7 (C-5), 66.2 (2, CH_2O), 62.1 (C-6), 50.3 (CH_2N), 31.8 (ω-2), 29.7, 29.6 (3), 29.5, 29.4, 29.3 (bulk-CH_2), 29.1 & 19.1 (iPrdn-CH_3), 26.0 (β), 22.6 (ω-1), 14.1 (ω).

1.3. General procedure for deacetonation

A solution of crown ether **4** in THF (80% aq) was treated with CF_3CO_2H (1.5 equiv) and heated to 65 °C for about 2 h, when TLC indicated complete conversion. THF was evaporated in vacuum and the aqueous solution was subsequently extracted with ^{n}BuOH. The organic layer was washed with satd $NaHCO_3$ (aq), dried over $MgSO_4$ and the solvent was evaporated in vacuum. The final products **5** were finally dried in vacuum over P_2O_5 to remove water and left-over ^{n}BuOH.

1.3.1. Dodecyl 2,3-O-[bis-triazolo-19-crown-5]-β-D-glucopyranoside (**5a**)

4a (0.47 g, 0.7 mmol) was treated with TFA (0.13 g, 1.1 mmol) in THF (80% aq, 15 mL) according to general procedure 1.4. to provide syrupy **5a** (0.42 g, 96%). $[\alpha]_D^{25}$ +28 (*c* 0.05, MeOH). ^{1}H NMR (400 MHz, CD_3OD) 7.78, 7.51 (triazole), 4.98 (d, CH_2O-A), 4.94 (d, CH_2O-B), 4.78 (d, CH_2O-A′), 4.78 (d, CH_2O-B′), 4.59 (mc, 4H, EG), 4.45 (d, H-1), 3.99 (dt, α), 3.94–3.76 (m, 5H, H–6A & CH_2N), 3.70 (dd, H-6B), 3.60 (dt, α′), 3.48 (dd~t, H-3), 3.41 (dd~t, H-4), 3.34–3.27 (m, 2H, H-2 & H-5), 1.66 (m_c, 2H, β), 1.43 (m_c, 2H, γ), 1.28 (m_c, 16H, bulk-CH_2), 0.90 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{2,3}$=9.0, $^{3}J_{3,4}$=9.0, $^{3}J_{4,5}$=9.0, $^{3}J_{5,6B}$=10.0, $^{3}J_{5,6eq}$=5.5, $^{2}J_{6}$=12.0, $^{2}J_{a,b}$=6.5, $^{2}J_{a}$ 9.5 Hz, $^{2}J_{CH2O\text{-}A}$=13.0, $^{2}J_{CH2O\text{-}B}$=12.0 Hz. ^{13}C NMR (100 MHz, CD_3OD) 147.1, 147.0 (triazole-C), 126.1, 126.0 (triazole-CH), 105.3 (C-1), 85.4, 82.7, 77.9, 72.1 (C-2, C-3, C-4, C-5), 71.0 (α), 70.2, 70.0 (EG), 67.0, 66.1 (CH_2O), 62.7 (C-6), 51.6, 51.3 (CH_2N), 33.0 (ω-2), 30.8, 30.7 (2), 30.6 (2), 30.5, 30.4 (bulk-CH_2), 27.2 (β), 23.6 (ω-1), 14.2 (ω). HRMS: Calc. for $C_{28}H_{48}N_6O_7$ [M+H] 581.3663, [M+Na] 603.3482, 604.3516 (31%), [M+K] 619.3222, 620.3255 (31%); found [M+H] 581.3607, [M+Na] 603.3475, 604.3513 (32%), [M+K] 619.3219, 620.3253 (32%).

1.3.2. Dodecyl 2,3-O-[bis-triazolo-22-crown-6]-β-D-glucopyranoside (**5b**)

4b (0.10 g, 0.15 mmol) was treated with TFA (30 mg, 0.2 mmol) in THF (80% aq, 15 mL) according to general procedure 1.4. to provide syrupy **5b** (0.09 g, 94%). $[\alpha]_D^{25}$ +10 (*c* 0.05, MeOH). ^{1}H NMR (400 MHz, CD_3OD) 7.92, 7.85 (2s, 2H, triazole), 5.08 (d, CH_2O-A), 4.91 (m_c, 2H, CH_2O-B), 4.79 (d, CH_2O-A′), 4.59 (m_c, 4H, EG), 4.46 (d, H-1), 3.99 (m_c, α), 3.93–3.82 (m, 5H, H-6A, CH_2N), 3.71 (dd, H-6B), 3.66–3.54 (m, 5H, α′+EG), 3.47 (dd~t, H-3), 3.40 (dd~t, H-4), 3.35–3.29 (m, H-5), 3.27 (dd, H-2), 1.67 (m_c, 2H, β), 1.42 (m_c, 2H, γ), 1.30 (m_c, 16, H, bulk-CH_2), 0.91 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{2,3}$=9.0, $^{3}J_{3,4}$=9.0, $^{3}J_{4,5}$=9.0, $^{3}J_{5,6B}$=5.5, $^{2}J_{6}$=12.0, $^{2}J_{CH2O}$=12.0 Hz. ^{13}C NMR (100 MHz, CD_3OD) 147.0, 146.8 (triazole-C), 126.0, 125.7 (triazole-CH), 105.0 (C-1), 85.4, 83.1, 77.8, 71.6 (C-2, C-3, C-4, C-5), 71.7, 71.6 (EG), 71.1 (α), 70.6, 70.5 (EG), 67.1, 66.7 (CH_2O), 62.7 (C-6), 51.5 (CH_2N), 33.0 (ω-2), 30.8, 30.7 (2), 30.6 (2), 30.5, 30.4 (bulk-CH_2), 27.2 (β), 23.6 (ω-1), 14.3 (ω). HRMS: Calc. for $C_{30}H_{52}N_6O_8$ [M+H] 625.3925, 626.3958 (33%), [M+Na] 647.3744, 648.3778 (33%), [M+K] 663.3484, 664.3517 (33%); found [M+H] 625.3916, 626.3931 (41%), [M+Na] 647.3728, 648.3759 (39%), [M+K] 663.3466, 664.3527 (35%).

1.3.3. Dodecyl 2,3-O-[bis-triazolo-25-crown-7]-β-D-glucopyranoside (**5c**)

4c (0.18 g, 0.26 mmol) was treated with TFA (40 mg, 0.4 mmol) in THF (80% aq, 15 mL) according to general procedure 1.4. to provide syrupy **5c** (0.16 g, 93%). $[\alpha]_D^{25}$ −8 (*c* 0.05, MeOH). ^{1}H NMR (400 MHz, CD_3OD) 8.00, 7.95 (2s, 2H, triazole), 4.98 (d, CH_2O-A), 4.88 (d, CH_2O-B), 4.78 (d, 2H, CH_2O-A′ & CH_2O-B′), 4.56 (m_c, 4H, EG), 4.41 (d, H-1), 3.96 (dt, α), 3.91–3.82 (m, 5H, H-6A, CH_2N), 3.66 (dd, H-6B), 3.61–3.44 (m, 9H, α′+EG), 3.45–3.36 (m, 2H, H-3 & H-4), 3.29–3.22 (m, 2H, H-2 & H-5), 1.63 (m_c, 2H, β), 1.41 (m_c, 2H, γ), 1.28 (m_c, 16, H, bulk-CH_2), 0.89 (t, 3H, CH_3); $^{3}J_{1,2}$=7.5, $^{3}J_{5,6B}$=5.0, $^{2}J_{6}$=11.5, $^{3}J_{ab}$=7.0, $^{2}J_{a}$=9.0, $^{2}J_{CH2O}$=12.0 Hz. ^{13}C NMR (100 MHz, CD_3OD) 147.0, 146.8 (triazole-C), 126.2 (triazole-CH), 105.0 (C-1), 85.9, 82.9, 77.8, 71.6 (C-2, C-3, C-4, C-5), 71.8 (2), 71.7, 71.6 (EG), 71.0 (α), 70.7, 70.6 (EG), 67.0, 66.4 (CH_2O), 62.7 (C-6), 51.6 (CH_2N), 33.0 (ω-2), 30.8, 30.7 (3), 30.5, 30.4 (bulk-CH_2), 27.2 (β), 23.6 (ω-1), 14.3 (ω). HRMS: Calc. for $C_{32}H_{56}N_6O_9$ [M+H] 669.4187, 670.4221 (36%), [M+Na] 691.4006, 692.4040 (36%), [M+K] 707.3746, 708.3779 (36%); found [M+H] 669.4172, 670.4215 (45%), [M+Na] 691.3996, 692.3031 (38%), [M+K] 707.3733, 708.3763 (39%).

1.4. Molecular modeling

Structure optimization calculations were performed using Gaussian 09 based on density function theory B3LYP applying basis set 6-31G. Input configurations were obtained by MOPAC minimization in Chem3D using AM1. In order to reduce the calculation time a methyl glucoside analog of **5a** was applied. Ion-binding energies were determined by subtracting the total energies of the structure-optimized ligand and an isolated sodium ion from the total binding energy of the structure optimized complex.

Acknowledgment

This work was supported by the University of Malaya under research grants RP024-2012B and RG264-13AFR, and the Malaysian Ministry of Education under research grants RP024-2012B, RG264-13AFR and FP032-2013B.

Supplementary data

Supplementary data (complementary cyclization experiments on bispropargylated carbohydrates differing in regio- and stereochemistry, images of NMR spectra, details for cation binding from MS experiments, as well as surface tension measurements and additional modeling results and images) related to this article can be found at http://dx.doi.org/10.1016/j.carres.2014.12.015.

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