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# Synthesis and Complex Formation Ability of Monomeric and Dimeric Amphiphilic β-Cyclodextrin Derivatives

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**Abstract**—Applying 6-*O*-monotosyl derivative of β-cyclodextrin and hexane-1,6-diamine monomeric and dimeric (bridging) amphiphilic compounds were obtained, and the opportunity was demonstrated of the preparation on their basis of inclusion compounds at the interaction with 2-(4-isobutylphenyl)propionic acid (Ibuprofen).

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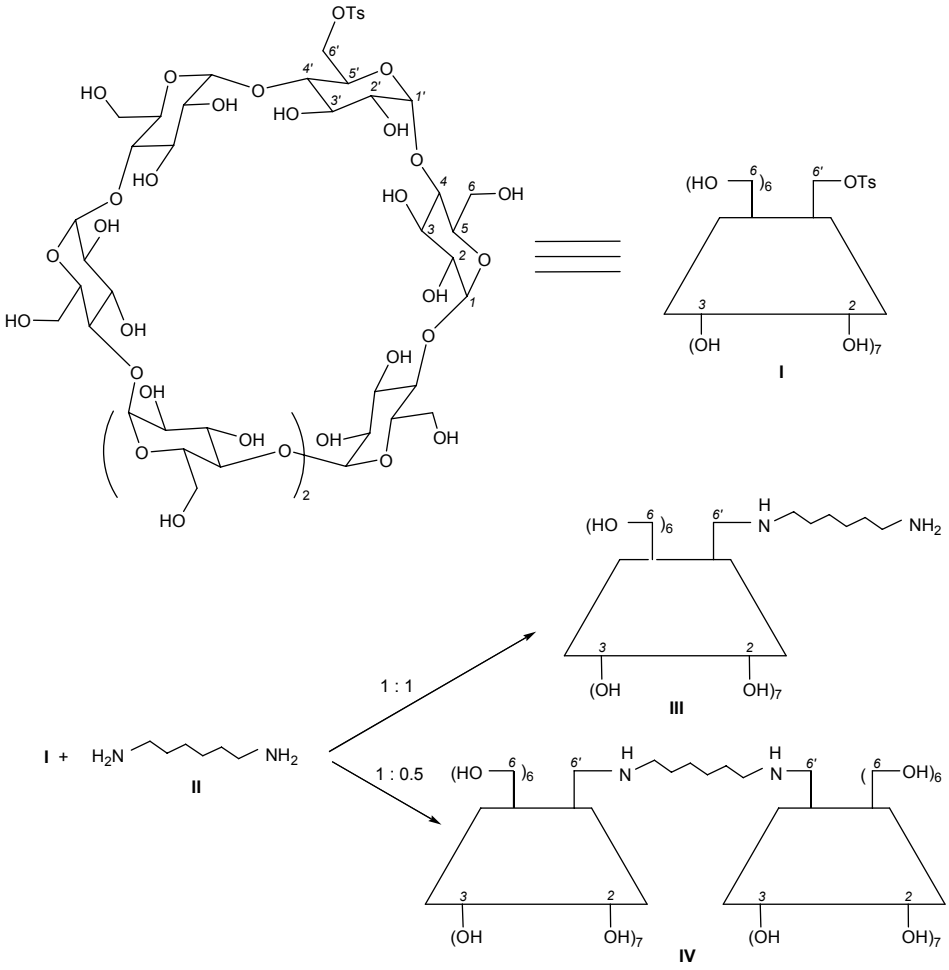
Cyclodextrins, which are cyclic oligosaccharide compounds, due to the presence of internal lipophilic cavity have found widest application in pharmacology mainly as containers of drugs owing to the formation of inclusion compounds of the "guest–host" type with numerous biologically important "guests" [1]. The encapsulation often protects the included compound possessing the drug properties from biodegradation, favors increased solubility, and can also assist to its more prolonged and targeted delivery. We formerly suggested practical ways of manufacturing stable nanosize inclusion complexes of β-cyclodextrin with binuclear "guests" containing two residues of aromatic monocarboxylic acids, promising in the pharmacologic respect [2]. It is assumed that nanosize cyclodextrin derivatives of this type act as bio adhesives on the mucous membrane of the digestive tract, therefore a sufficiently large amount of the administered substance can be imbibed already in its upper part thus accelerating the onset of the pharmacologic effect [3]. Therewith the increase in the efficiency of the drug due to the growing solubility and bio accessibility would result in reducing the therapeutic dose and therefore decrease the overall toxicity of the applied medication. We additionally obtained amphiphilic derivatives of α- and β-cyclodextrins containing covalently linked to the cyclodextrin scaffold residues of pharmacologically important substances (so-called conjugates) [4]. Such conjugated cyclodextrins (prodrugs) may be used for spot specific delivery of drugs, and the amphiphilicity of cyclodextrins may assist in overcoming the biologic barriers, for instance, the hematoencephalic barrier [5].

Considering the above mentioned data we planned in this study to obtain monomeric and dimeric amphiphilic β-cyclodextrin derivatives and to attempt the preparation of inclusion compounds on their basis. As initial compound we chose a monotosyl derivative of β-cyclodextrin **I** prepared along the known procedure from β-cyclodextrin and *N*-tosylimidazole, a reliable monotosylating reagent for the primary hydroxy groups of the β-cyclodextrin [6]. Monotosyl derivative **I** was brought into the reaction with 1,6-hexanediamine (**II**) in stoichiometric ratios 1 : 1 and 1 : 0.5. The corresponding mono-(**III**) and dimeric (**IV**) (bridging) derivatives formed in 35 and 40% yields (Scheme 1).

The preparation of regiodirected monosubstituted cyclodextrin derivatives (in this case at the primary hydroxy groups) is a difficult synthetic task because of the possible substitution also at the secondary hydroxy groups in the positions *2* and *3* of the cyclodextrin scaffold. Therefore we paid a special attention to the study of the structure of obtained compounds **III** and **IV** by NMR spectroscopy. Since at registering the spectra the signals of the residual protons of the deuterated solvents often overlapped the analytical regions of the spectra, to increase the reliability of signals assignment the $^{1}H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ and $D_2O$, and also at 20 and 80°C (for correct assignment of hydroxyl protons and pro-

**Scheme 1.**



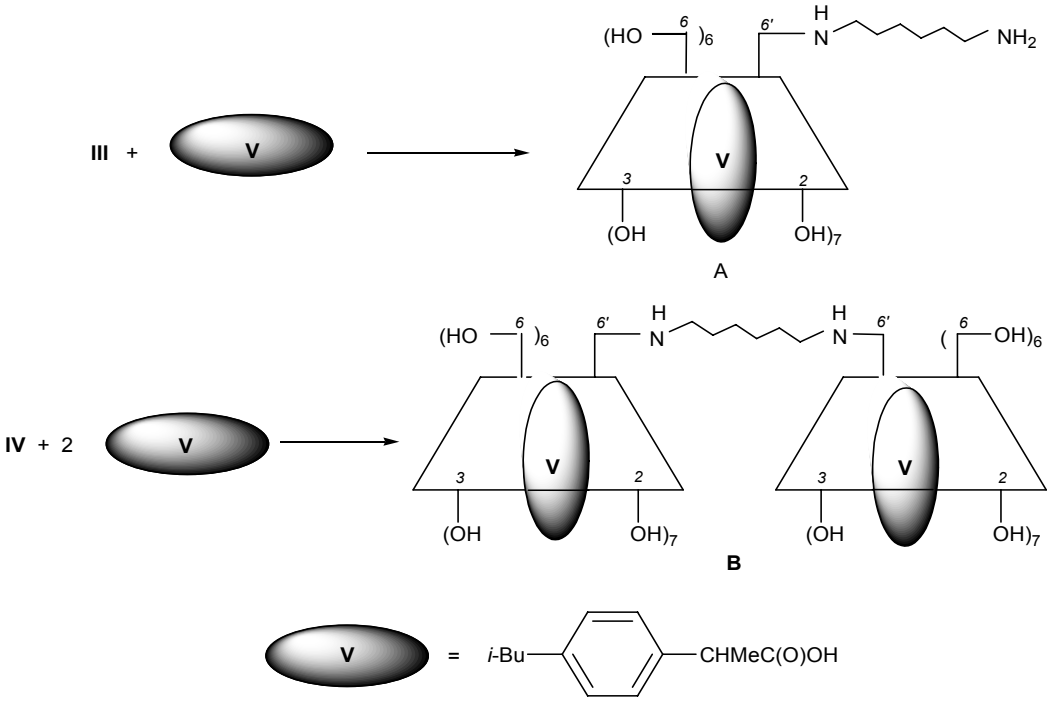

tons at nitrogen atoms) and moreover in acid medium (pH 2). Due to the protonation and the appearance of a positive charge on the nitrogen atom the signals of contiguous protons and carbon atoms considerably shift downfield. The validity of signals assignment was confirmed by the analysis of 2D NMR spectra of homo- (HOMOCOR $\{^1H\text{-}^1H\}$) and heteronuclear (HETCOR $\{^1H\text{-}^{13}C\}$) correlation. In the $^{13}C$ NMR spectrum of compound **III** in DMSO-$d_6$ a signal from carbon atom $C^6$ with unsubstituted hydroxy group is observed at 61.5 ppm, and at 60.8 ppm an upfield signal of atoms $C^{6'}$* appears bearing a diaminoalkyl substituent [in $D_2O$ at 60.8 ($C^6$) and 57.0 ($C^{6'}$) ppm respectively].

After nitrogen protonation ($D_2O$, pH 2) due to the deshielding the signal of atom $C^{6'}$ is displaced in the region 60.2 ppm, and the signals of the methylene carbon atoms contiguous to the nitrogen atoms also shifted downfield. Whereas at the acylation of the hydroxy group at the atom $C^6$ we have observed the downfield shift of $C^{6'}$ signals [4, 7], the substitution by an amino group causes an upfield shift. In the $^1H$ NMR spectrum of compound **III** in acid environment also downfield shifts were observed of the proton signals of methylene groups directly bound to the protonated nitrogen atom.

Analogous changes we observed also in the spectrum of compound **IV**. Since the central hexamethylenediamine bridge binds identic cyclodextrin substituents the methylene fragments in the positions *1* and *6*, *2* and *5*, *3* and *4* are equivalent in pairs, and in this region the $^1H$ and $^{13}C$ NMR spectra are considerably simplified. In the $^{13}C$ NMR spectrum of compound **IV** in DMSO-$d_6$ and $D_2O$ upfield shifts are observed for the signals of atoms $C^{6'}$ at 56.8 and 57.0 ppm (compared to the signals of atoms $C^6$ with unsubstituted hydroxyl at 60.6 and 59.8 ppm); in $D_2O$

* Here and hereinafter the carbon atoms of cyclodextrin are primed when their hydroxy groups are substituted.

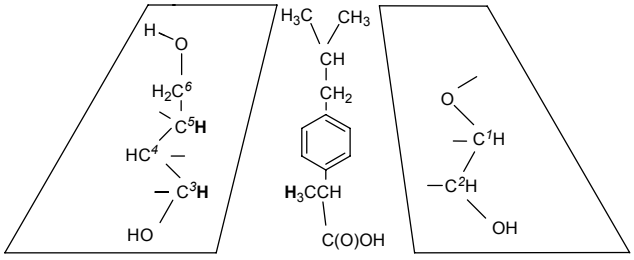
**Scheme 2.**




at pH 2 a downfield shift occurred for the signals of atoms $C^{6'}$ at 60.6 ppm. In the $^1H$ NMR spectra of both compounds **III** and **IV** in acid environment downfield shifts were observed of the protons of methylene groups contiguous to nitrogen atoms.

We considered the possibility of the formation of inclusion compounds with β-cyclodextrin derivatives **III** and **IV** ("host") with the drug Ibuprofen [2-(4-isobutylphenyl)propionic acid (**V**)] ("guest"). To this end we added to the solutions of compounds **III** (0.0188 mol/L) and (0.00942 mol/L) 1 or 2 mol-equiv respectively of compound **V** and analyzed the $^1H$ and $^{13}C$ NMR spectra. It should be noted that water-soluble inclusion complexes **A** and **B** were actually obtained, for without inclusion into the cyclodextrin cavity acid **V** is insoluble in water in this concentration (Scheme 2).

In the $^1H$ NMR spectra of solutions of complexes **A** and **B** we observed the upfield shift of the signals of protons $H^3$ and $H^5$ (Δδ 0.06 ppm), evidencing the




formation of relatively stable (in the NMR time scale) inclusion compounds "guest–host".

At the inclusion into the hydrophobic cavity of β-cyclodextrin of the "guest" molecule, in particular, when it contained an aromatic fragment, the strongest reaction in the $^1H$ NMR spectra is observed in the signals of protons at the atoms $C^3$ and $C^5$ of the glycoside fragments, since just these are oriented inside the cyclodextrin cavity [8]. The signals of bridging methylene protons change their positions due to overlapping with the "guest" signals. Additional confirmation of the formation of inclusion compounds **A** and **B** was obtained from the analysis of 2D $^1H$ NMR spectra ROESY, where the through space interactions (NOE) were observed for protons $H^3$ of the cyclodextrin scaffold and the methyl group of the fragment (O)CCH($C\underline{H}_3$) of the inclusion "guest". At the formation of complex **A** in water solution a competing formation is possible of supramolecular polymers owing to the possible inclusion of the "tail" part of aminohexamethylene fragment into the cavity of the adjacent cyclodextrin [9] resulting in sharp decrease in its complex formation ability. Dimeric complex **B** compared to complex **A** possesses an enhanced (synergic) effect** with respect to inclusion of

** For instance for fast dissolution of acid **V** in the "host" **III** solution heating is required (80°C, 15 min), the same acid in solution of "host" **IV** dissolved quickly already at 20°C.

"guests" into its cyclodextrin cavity [10] that in its turn can favor more efficient spot delivery of drugs.

This study provides an opportunity to prepare dimeric β-cyclodextrin complexes with important pharmaceuticals.

## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were registered on a spectrometer Jeol ECX400 at operating frequencies 400 and 100.53 MHz with respect to external standard TMS. The assignment of proton signals of compounds **III** and **IV** and complex **B** was additionally checked by registering spectra on a spectrometer Bruker Avance 500 at the frequency 500 MHz. Elemental analyses were carried out on an analyzer FlashEA 1112HT. TLC was performed on aluminum plates with the fixed silica gel layer (Silufol UV-254), eluents ethyl acetate–2-propanol–$H_2O$, 7 : 7 : 5 (A), acetonitrile–$H_2O$, 1 : 1 (B). In the study was used β-cyclodextrin purchased from Merck (Germany) that was additionally thoroughly dried.

**6-Deoxy-6-(6-aminohexylamino)-β-cyclodextrin (III)**.[***] To a solution of 0.5 g (0.388 mmol) of monotosyl derivative **I** in 20 mL of DMF was added at stirring 0.034 g of sodium hydrogen carbonate, 0.045 g (0.388 mmol) of diamine **II**, and the reaction mixture was stirred for 30 h at 80°C. The solution was concentrated to 2 mL, filtered, diluted with 10 mL of acetone, the separated precipitate was filtered off, washed in succession with chloroform (2 × 5 mL), ethanol (2 × 3 mL), acetone (2 × 5 mL), ethyl ether (2 × 7 mL), and dried in a vacuum (1 mm Hg) for 4 h at 80°C. Yield 0.167 g (35%), mp 257–260°C (decomp.), $R_f$ 0.35 (A), 0.00 (B). $^1$H NMR spectrum, δ, ppm, in DMSO-$d_6$: 1.03–1.05 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.25–1.39 m (4H, $NCH_2C\underline{H}_2$), 2.36–2.46 m (4H, $NCH_2$), 3.20–3.38 m (14H, $C^2H$, $C^4H$), 3.51–3.74 m (28H, $C^3H$, $C^5H$, $C^6H_2$), 4.08 br.s (6H, $C^6OH$), 4.81 br.s (7H, $C^1H$), 5.31–5.60 br.s (14H, $C^2OH$, $C^3OH$); in $D_2O$: 1.64–1.80 m (4H, $NCH_2\cdot CH_2C\underline{H}_2$), 1.80–2.00 m (4H, $NCH_2C\underline{H}_2$), 3.02–3.10 m, 3.22–3.32 m (4H, $NCH_2$), 3.92–4.12 m (14H, $C^2H$, $C^4H$), 4.22 m (14H, $C^6H_2$), 4.28 m (7H, $C^5H$), 4.32 m (7H, $C^3H$), 5.46 br.s (7H, $C^1H$); in $D_2O$, pH 2: 1.22–1.32 m (4H, $N^+CH_2CH_2C\underline{H}_2$), 1.51–1.67 m (4H, $N^+CH_2C\underline{H}_2$), 2.92 t (2H, $C^6H_2N^+C\underline{H}_2$, $^3J$ 7.8 Hz), 3.35–3.52 m (14H, $C^2H$, $C^4H$), 3.60–3.75 m (28H, $C^3H$, $C^5H$, $C^6H_2$), 3.94 t (2H, $H_2N^+C\underline{H}_2$, $^3J$ 9.6 Hz), 4.90 br.s (7H, $C^1H$). $^{13}$C NMR spectrum, δ, ppm, in DMSO-$d_6$: 26.7, 27.1 ($NCH_2CH_2\underline{C}H_2$), 30.1, 30.2 ($NCH_2\underline{C}H_2$), 50.1, 50.2 ($NCH_2$), 60.8 ($C^{6'}$), 61.5 ($C^6$), 72.7 ($C^5$), 73.2 ($C^2$), 73.7 ($C^3$), 82.3 ($C^4$), 102.6 ($C^1$); in $D_2O$: 25.2, 27.8 ($NCH_2CH_2\underline{C}H_2$), 37.3, 39.1 ($NCH_2\underline{C}H_2$), 46.3, 47.8 ($NCH_2$), 57.0 ($C^{6'}$), 60.8 ($C^6$), 71.6 ($C^5$), 72.6 ($C^2$), 72.8 ($C^3$), 80.6 ($C^4$), 101.4 ($C^1$); in $D_2O$, pH 2: 25.2, 25.3 ($N^+CH_2CH_2\underline{C}H_2$), 26.5, 26.6 ($N^+CH_2\cdot \underline{C}H_2$), 39.4 ($C^6H_2N^+\underline{C}H_2$), 48.3 ($H_3N^+\underline{C}H_2$), 60.2 ($C^{6'}$), 60.3 ($C^6$), 71.8 ($C^5$), 72.1 ($C^2$), 73.2 ($C^3$), 81.1 ($C^4$), 102.0 ($C^1$). Found, %: C 46.55; H 6.73; N 2.20. $C_{48}H_{84}O_{34}N_2$. Calculated, %: C 46.75; H 6.87; N 2.27.

**Di-6,6'-dideoxy-6,6'-(hexane-1,6-diyldiamino)-β-cyclodextrin (IV)** was obtained similarly from 0.25 g (0.194 mmol) of monotosyl derivative **I**, 0.0163 g of sodium hydrogen carbonate in 20 mL of DMF, and 0.011 g (0.097 mmol) of diamine **II**. The mixture was heated at 80°C for 40 h. Yield 0.27 g (40%), mp 348–350°C (decomp.), $R_f$ 0.45 (A), 0.10 (Б). $^1$H NMR spectrum, δ, ppm, in DMSO-$d_6$: 1.15–1.25 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.25–1.38 m (4H, $NCH_2C\underline{H}_2$), 2.50–2.70 m (4H, $NCH_2$), 3.15–3.45 m (28H, $C^2H$, $C^4H$), 3.45–3.78 m (56H, $C^3H$, $C^5H$, $C^6H_2$), 4.43 br.s (12H, $C^6OH$), 4.77 br.s (14H, $C^1H$), 5.74 br.s (28H, $C^2OH$, $C^3OH$); in $D_2O$: 1.78–1.85 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.85–2.08 m (4H, $NCH_2C\underline{H}_2$), 3.20–3.30 m (4H, $NCH_2$), 3.96–4.14 m (28H, $C^2H$, $C^4H$), 4.25 m (28H, $C^6H_2$), 4.30 m (14H, $C^5H$), 4.32 m (14H, $C^3H$), 5.50 br.s (14H, $C^1H$); in $D_2O$, pH 2: 1.19–1.35 m (4H, $N^+CH_2CH_2C\underline{H}_2$), 1.35–1.70 m (4H, $N^+CH_2C\underline{H}_2$), 2.97 t (2H, $C\underline{H}_2N^+H_3$, $^3J$ 7.3 Hz), 3.12 t (2H, $C^{6'}N^+CH_2$, $^3J$ 7.4 Hz), 3.38–3.60 m (28H, $C^2H$, $C^4H$), 3.60–3.90 m (56H, $C^3H$, $C^5H$, $C^6H_2$), 4.94 br.s (14H, $C^1H$). $^{13}$C NMR spectrum, δ, ppm, in DMSO-$d_6$: 27.3 ($NCH_2CH_2\underline{C}H_2$), 33.5 ($NCH_2\underline{C}H_2$), 50.0 ($NCH_2$), 56.8 ($C^{6'}$), 60.6 ($C^6$), 72.8 ($C^5$), 73.2 ($C^2$), 73.8 ($C^3$), 82.3 ($C^4$), 102.7 ($C^1$); in $D_2O$: 25.0 ($NCH_2CH_2\underline{C}H_2$), 27.8 ($NCH_2\underline{C}H_2$), 47.1 ($NCH_2$), 57.0 ($C^{6'}$), 59.8 ($C^6$), 71.4 ($C^5$), 72.1 ($C^2$), 72.8 ($C^3$), 80.7 ($C^4$), 101.4 ($C^1$); in $D_2O$, pH 2: 25.3 ($N^+CH_2CH_2\underline{C}H_2$), 28.1 ($N^+CH_2\underline{C}H_2$), 48.3 ($N^+CH_2$), 60.2 ($C^6$), 60.6 ($C^{6'}$), 71.9 ($C^5$), 72.4 ($C^2$), 73.2 ($C^3$), 81.2 ($C^4$), 102.0 ($C^1$). Found, %: C 46.15; H 6.63; N 1.20. $C_{90}H_{152}O_{68}N_2$. Calculated, %: C 46.00; H 6.52; N 1.19.

**Inclusion compound A**. $^1$H NMR spectrum, δ, ppm, in $D_2O$: 1.25–1.45 m (2H, $C^{6'}NCH_2CH_2C\underline{H}_2$), 1.33 d [6H, $HC(C\underline{H}_3)_2$, $^3J$ 7.0 Hz], 1.70–1.79 m (4H, $C^{6'}NCH_2\cdot C\underline{H}_2CH_2C\underline{H}_2CH_2CH_2NH_2$), 1.81 d [3H, $HC(C\underline{H}_3)C_6H_4$, $^3J$ 6.5 Hz], 2.07–2.18 m (2H, $C\underline{H}_2CH_2NH_2$), 2.24–2.35 m [1H, $\underline{H}C(CH_3)_2$], 2.91 d (2H, $C_6H_4C\underline{H}_2CH$, $^3J$ 7.0 Hz), 3.40–3.46 m (2H, $C\underline{H}_2NH_2$), 3.55–3.70 m (2H, $C^{6'}NCH_2$), 3.85–3.99 m [1H, $(O)CC\underline{H}(CH_3)\cdot$

[***] Monomeric derivative **III** was mentioned in [11], but without reporting characteristics.

$C_6H_4$], 3.92–4.12 m (14H, $C^2H$, $C^4H$), 4.20 m (28H, $C^6H_2$), 4.22 m (14H, $C^5H$), 4.26 m (14H, $C^3H$), 5.46 br.s (7H, $C^1H$), 7.54 d (2H, $C_6H_4$, $^3J$ 7.9 Hz), 7.66 d (2H, $C_6H_4$, $^3J$ 9.9 Hz). $^{13}C$ NMR spectrum, δ, ppm, in $D_2O$: 16.8 [$HC(\underline{C}H_3)_2$], 21.8 [$HC(\underline{C}H_3)C_6H_4$], 25.2 ($NCH_2CH_2\underline{C}H_2$), 25.4 ($NCH_2\underline{C}H_2$), 30.0 ($C_6H_4\underline{C}H_2$ CH), 44.4 [$H\underline{C}(CH_3)_2$], 48.0, 48.2 ($NCH_2$), 57.4 ($C^{6'}$), 59.7 ($C^6$), 67.2 ($C^{5'}$),[****] 71.9 [$(O)C\underline{C}H(CH_3)C_6H_4$], 72.1 ($C^5$), 72.3 ($C^2$), 73.3 ($C^3$), 81.0 ($C^4$), 102.1 ($C^1$), 126.6, 129.1 ($C_6H_4$), 139.4, 140.8 ($C_6H_{4\text{-}ipso}$), 183.0 [C(O)].

**Inclusion compound B**. $^1H$ NMR spectrum, δ, ppm, in $D_2O$: 1.25–1.45 m (2H, $NCH_2CH_2C\underline{H}_2$), 1.34 d [12H, $HC(\underline{C}H_3)_2$, $^3J$ 7.0 Hz], 1.79–1.89 m (4H, $NCH_2$·$C\underline{H}_2C\underline{H}_2CH_2CH_2CH_2N$), 1.80 d [6H, $HC(C\underline{H}_3)C_6H_4$, $^3J$ 6.4 Hz], 2.05–2.15 m (2H, $NCH_2C\underline{H}_2$), 2.22–2.35 m [2H, $\underline{H}C(CH_3)_2$], 2.95 d (4H, $C_6H_4C\underline{H}_2CH$, $^3J$ 7.0 Hz), 3.42–3.45 m (4H, $NCH_2$), 3.80–3.95 m [2H, $(O)CC\underline{H}$·$(CH_3)C_6H_4$], 3.95–4.15 m (28H, $C^2H$, $C^4H$), 4.24 m (14H, $C^5H$), 4.25 m (28H, $C^6H_2$), 4.26 m (14H, $C^3H$), 5.47 br.s (14H, $C^1H$), 7.54 d (4H, $C_6H_4$, $^3J$ 7.9 Hz), 7.67 d (4H, $C_6H_4$, $^3J$ 9.9 Hz). $^{13}C$ NMR spectrum, δ, ppm, in $D_2O$: 18.8 [$HC(\underline{C}H_3)_2$], 21.7 [$HC(\underline{C}H_3)C_6H_4$], 25.3 ($NCH_2CH_2\underline{C}H_2$), 26.0 ($NCH_2\underline{C}H_2$), 29.9 ($C_6H_4$·$\underline{C}H_2CH$), 39.3 ($NCH_2\underline{C}H_2$), 44.4 [$H\underline{C}(CH_3)_2$], 48.2 ($NCH_2$), 59.7 ($C^{6'}$), 60.4 ($C^6$), 67.0 ($C^{5'}$), 71.7 [$(O)C\underline{C}H(CH_3)C_6H_4$], 72.0 ($C^5$), 72.1 ($C^2$), 73.3 ($C^3$), 81.0 ($C^4$), 83.5 ($C^{4'}$), 102.0 ($C^1$), 126.6, 129.1 ($C_6H_4$), 139.5, 140.9 ($C_6H_{4\text{-}ipso}$), 183.3 [C(O)].

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[****] In some cases, the signals of the nuclei of atoms $C^{5'}$ and even $C^{4'}$, that are in the same carbohydrate moiety which contains a substituent at $C^{6'}$ also significantly shifted in compare with the signals $C^4$ and $C^5$ [4, 12].