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ORIGINAL PAPER

Synthesis and self-assembly behavior of amphiphilic methyl α-D-glucopyranoside-centered copolymers

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Abstract A series of well-defined polymers with various content of reactive oxirane groups (25–100 mol%) were synthesized via atom transfer radical polymerization (ATRP). The acetal derivatives of methyl α-D-glucopyranoside used as bi-, tri-, and tetrafunctional initiators allowed us to design macromolecules containing a sugar moiety in the center with V- and star-shaped topologies, and a length of each polymethacrylate segment in the range of 30–75 units. Various degrees of oxirane ring opening via aminolysis with mono- and diamines (20–100 %) or azidation (100 %) have demonstrated that the reactivity of pendant epoxide groups incorporated into the polymer was strongly dependent on the nucleophile agent and reaction environment. The complete transformation in the reaction with ethylenediamine and sodium azide yielded amphiphilic copolymers with differential solubility (diamine-functionalized polymers in polar protic solvents, e.g., water, versus azide-functionalized polymers in polar aprotic solvents, e.g., dimethylformamide). A few polymeric forms, that is unimers (0.5–1 nm), micelles (5–30 nm), aggregates (170–290 nm) and superaggregates (> 4,500 nm), were indicated by DLS measurements of water-soluble ethylenediamine derivatives of copolymers. Both the epoxy-functionalized polymers and their modified derivatives are potential materials for biomedical applications.

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Introduction

Polymers containing moieties with special properties can be obtained directly by the polymerization of functionalized monomers and the chemical reaction of specific groups in polymer with low molecular weight compounds, or via the functionalization of polymers (*post-polymerization modification*). The latter method corresponds to substitution or elimination reactions, which leads to changes in solubility, surface nature, and other properties [1].

The epoxy polymers represent one of the most known groups of reactive and functional macromolecules, which can be obtained by the epoxidation of unsaturated alkenyl moieties with formic acid [2, 3] or by a reaction between carboxylated moieties and diepoxides [4]. Alternatively, the epoxide-functionalized polymers can be prepared by the conventional and controlled radical polymerization of glycidyl methacrylate (GMA). The crosslinkable capacity of GMA-based polymers are usually generated with a diamine to get networks and gels, as it was studied for epoxy resins technologies [5]. The other ring-opening reaction, hydrolysis, transforms the epoxide groups into glycerol (bis-alcohol) groups [6, 7]. The poly(glycidyl methacrylate)s (PGMAs) were also modified by phosphonation with diphenylphosphinic chloride [8], and silylation with tris(trimethylsilyl) methyl lithium [9], whereas the reaction with monothiol-functionalized polyhedral silsesquioxane yielded the cage-like inorganic materials in an organic cylindrical matrix [10]. The grafting reactions via epoxy groups in the short PGMA segment in block copolymers were achieved with silanol functionality of silica

nanoparticles [11], or aminosililated quartz wafer surfaces [12]. The macroinitiators based on PGMA after modifications contained one bromine and hydroxyl group [13, 14] or an azide group [15] at every unit of the polymer, which were then selectively used in a polymerization or "click" reaction yielding the asymmetric centipede-like polymer brushes.

The modified GMA-based (co)polymers have been found to be potentially useful as membranes for fluid separation [9], membranes of hollow-fiber forms, ion-exchange resins, chelate-forming macromolecules, and pseudoaffinity ligands [16], or as polymeric catalysts for the epoxidation of cyclohexene with hydrogen peroxide [17], whereas the photoreactive copolymers containing pendant chlorocinnamoyl moieties were tested as negative photoresists in some industries [18]. The epoxide groups can be also used for several subsequent couplings, i.e. biofunctionalization via the attachment of amine functionalized biological molecules, such as peptides, antibodies, and DNA [7, 19–21].

There are a few reports for the epoxide-functionalized star block copolymers, which were synthesized by controlled radical polymerization of GMA in the presence of macroinitiators, i.e., bromine-terminated, four-armed poly(methyl methacrylate) and polystyrene [5] or porphirin-(polystyrene)$_4$ [22], as well as bromine-functionalized, three-armed [23] or chlorine-terminated, four-armed poly(ε-caprolactone) [24].

Here, we present the synthesis and modification of epoxide-functionalized copolymers with various topologies (two-segmented V-shaped as well as three-, and four-armed stars) containing acetal derivatives of methyl α-D-glucopyranoside in the center. The presence of a hydrophilic, biodegradable, and biocompatible sugar unit evaluates the polymer properties, providing a stereochemistry. Carbohydrate functionalized polymers are in great demand for biomedical applications, especially in pharmaceutical areas, molecular recognition processes, and as biomimetics or surfactants [25]. The multifunctionality of D-glucopyranoside derivatives used for the initiation of polymerization allowed us to obtain the well-defined topologies with predetermined numbers of segments/arms using the core-first strategy, which was previously studied in test polymerizations of the equimolar ratio of methacrylate comonomers [26]. This work was developed by using various ratios of comonomers, glycidyl methacrylate (GMA), and methyl methacrylate (MMA), which made it possible to predict the number of oxirane moieties in the copolymers (25–100 mol%) in relation to polymerization degrees. The further studies on the epoxide-functionalized and sugar-centered copolymers were based on the biorelevant chemical modifications, i.e., nucleophilic aminolysis and azidation were applied as the ring-opening reactions to introduce a proper amount of water-soluble groups and generate amphiphilic character. Additional studies on the amine derivatives of copolymer behavior in aqueous solution have been performed to obtain the characteristics of the effective size of particles, as well as to investigate their response to a change in pH values or salt interaction.

Experimental

Materials

Glycidyl methacrylate (GMA, Sigma-Aldrich 97 %) and methyl methacrylate (MMA, Sigma-Aldrich, 98 %) were dried over molecular sieves and stored in a freezer under nitrogen. Copper (I) chloride (CuCl, Fluka, 97 %) was purified by stirring in glacial acetic acid, followed by filtration and washing with ethanol and diethyl ether, and finally, the solid was dried under vacuum. Benzylaldehyde (BZA, Sigma-Aldrich ≤ 98 %) and salicylaldehyde (SLA, Sigma-Aldrich ≤ 98 %) were distilled prior to use. Methyl α-D-glucopyranoside (MeαDGlu, ≤ 99 %), *p*-toluenesulfonic acid (*p*TSA, ≤ 98.5 %), terephthalaldehyde (TPhA, 99 %), 2-bromoisobutyryl bromide (BriBuBr, 98 %), copper (II) chloride ($CuCl_2$, 97 %), 4,4′-dinonyl-2,2′-dipyridyl (dNdpy, 97 %), diethylamine (DEA, >99 %), triethylamine (TEA, >99 %), ethylenediamine (EDA, Alfa-Aesar, 99 %), and sodium azide (NaN_3, 97 %) were purchased from Sigma-Aldrich and used as received. *N,N*-Dimethylformamide (DMF, POCh) was used after distillation over P_2O_5. The other reagents and solvents were applied without purification.

Synthesis of methyl α-D-glucopyranoside-based initiators (GI1, GI2, GI3)

ATRP sugar initiators based on methyl α-D-glucopyranoside were prepared according to previously described procedures [26]. The condensation of MeαDGlu and BZA (1:2) or SLA (1:4) or TPhA (2:1) in a benzene/DMF containing catalyst *p*TSA (0.2 g for GI1; 0.4 g for GI2 and GI3) was performed in argon with stirring, and then water was removed by a Dean–Stark apparatus, whereas the catalyst was deactivated with $CaCO_3$, and filtered off. The products were precipitated with distilled water, and extracted in a Soxhlet apparatus using diethyl ether or ethanol. It yielded acetal derivatives of methyl α-D-glucopyranoside (methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, methyl 4,6-*O*-salicylidene-α-D-glucopyranoside, and 4,6:4′,6′-*O*-terephtalidene-bis-(methyl α-D-glucopyranoside), respectively). In the next step, BriBuBr (1.2 equiv. per –OH group in acetal) was added to the cooled solution of acetal (1.0 g) in pyridyne or methylene chloride and stirred at room temperature overnight. The precipitated ammonium salt was removed by filtration. The bromoester functionalized products were extracted with CH_2Cl_2, washed with distilled water and 5 % Na_2CO_3 (to neutral), dried over anhydrous $MgSO_4$, evaporated, and precipitated in ethanol.

GI1: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.90–1.93 (dd, 12H, -CH_3), 3.45 (s, 3H, -OCH_3), 3.75–3.84 (m, 2H, H-4, H-6), 3.98 (dt, 2H, J=9.8 Hz, J=4.7 Hz, H-5), 4.35 (dd, 1H, J=10.2 Hz, J=4.5 Hz, H-6), 4.96–5.02 (m, 2H, H_{an}, H-2), 5.56 (s, 1H, -OCHO-), 5.69 (t, 1H, J=9.3 Hz, H-3), 7.33–7.35 (m, 3H, $H_{C,D}$), 7.43–7.45 (m, 2H, H_B); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.4–30.8 (*C*H_3), 55.3–55.4 (*C*–Br), 55.9 (O*C*H_3), 62.4 (C–6), 68.9 (C–5), 70.3 (C–4), 72.7 (C–2), 79.1 (C–3), 97.4 (C–1), 101.3 (–O*C*HO–), 125.9 (C_B), 128.2 (C_C), 128.9 (C_A), 136.9 (C_D), 170.4–171.1 (*C*=O); ESI-MS (*m/z*): calcd for $C_{22}H_{28}O_8Br_2$ 579.3; found for $[M+H]^+$ 580.4. Anal. calcd: C 45.54, H 4.86, O 22.06, Br 27.54; found: C 45.73, H 4.96.

GI2: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.77–2.18 (m, 18H, -CH_3), 3.38–3.49 (m, 3H, -OCH_3), 3.68–3.84 (m, 2H, H-4, H-6), 3.98 (dt, 1H, J=9.9 Hz, J=4.8 Hz, H-5), 4.28 (dd, 1H, J=10.2 Hz, J=4.8 Hz, H-6), 4.93–5.03 (m, 2H, H_{an}, H-2), 5.69 (t, 1H, J=9.9 Hz, H-3), 5.76 (s, 1H, -OCHO-), 7.06 (d, 1H, J=8.1 Hz, H_C), 7.27 (t, 1H, J=6.0 Hz, H_E), 7.38 (t, 1H, J=8.1 Hz, H_D), 7.66 (d, 1H, J=7.5 Hz, H_F); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.3–30.8 (-*C*H_3), 55.3–55.9 (-*C*-Br), 62.2 (-O*C*H_3), 69.0 (C-6), 70.1 (C-4), 72.5 (C-5), 77.2 (C-2), 79.1 (C-3), 97.1 (C-1), 97.3 (-O*C*HO-), 121.8 (C_C), 126.5 (C_E), 127.6 (C_{AF}), 128.9 (C_A), 130.2 (C_D), 147.9 (C_B), 168.7–171.0 (*C*=O); ESI-MS (*m/z*): calcd for $C_{26}H_{33}O_{10}Br_3$ 745.2; found for $[M+Na]^+$ 768.2. Anal. calcd: C 41.90, H 4.46, O 21.47, Br 32.16; found: C 41.71, H 4.09.

GI3: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.91 (dd, 24H, J=9.1 Hz, J=1.9 Hz, -CH_3), 3.44 (s, 6H, -OCH_3), 3.72–3.82 (m, 4H, H-4, H-6), 3.95 (dt, 2H, J=9.9 Hz, J=4.7 Hz, H-5), 4.33 (dd, 2H, J=10.2 Hz, J=4.8 Hz, H-6), 4.94–5.01 (m, 4H, H_{an}, H-2), 5.53 (s, 2H, -OCHO-), 5.67 (t, 2H, J=9.6 Hz, H-3), 7.42 (s, 4H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.4–30.8 (-*C*H_3), 55.3–55.4 (-*C*-Br), 55.7 (-O*C*H_3), 62.3 (C-6), 68.8 (C-5), 70.1 (C-4), 72.6 (C-2), 79.0 (C-3), 97.4 (C-1), 101.0 (-O*C*HO-), 125.9 (C_B), 137.5 (C_A), 170.4–171.0 (*C*=O); ESI-MS (*m/z*): calcd for $C_{38}H_{50}O_{16}Br_4$ 1081.4, found for $[M+H]^+$ 1082.0. Anal. calcd: C 42.17, H 4.66, O 23.65, Br 29.53; found: C 42.53, H 4.69.

Synthesis of s-P(GMA-co-MMA) (example for copolymer VI)

Sugar initiator GI2 (77.4 mg contains 0. 1 mmol of initiating sites), GMA (1.0 ml, 7.6 mmol), and MMA (2.5 ml, 23.4 mmol), anisole (2.5 ml, 70 vol.% of monomer), dNdpy (127.7 mg, 0.3 mmol), and $CuCl_2$ (1.1 mg, 8.1 μmol, 5 mol% of Cu^+) were placed in a Schlenk flask and degassed by three freeze-pump-thaw cycles. Then, CuCl (15.5 mg, 0.2 mmol) was added and the reaction flask was immersed in an oil bath at 30 °C. The reaction was stopped by exposing the reaction mixture to air. Then, it was dissolved in $CHCl_3$ and passed through a neutral alumina column to remove the copper catalyst. The mixture was concentrated by rotary evaporation and the rest of solution was further purified by precipitation in cold methanol. The copolymers were isolated by decantation and dried under vacuum at room temperature to a constant mass. Yields: 65–78 %.

Epoxide ring-opening reactions

Aminolysis (method IA, XV): Copolymer (201.2 mg, including 0.8 mmol epoxide groups) was dissolved in DMF (7 ml), and then DEA (0.25 ml, 2.4 mmol) was added, filled out by inert gas, and stirred for 72 h at 50 °C (yield: 24 %). Aminolysis (method IB, XVI): Copolymer (249.8 mg, including 1.0 mmol epoxide groups) was dissolved in DMF (7 ml). Next, DEA (0.31 ml, 3.0 mmol) and TEA (0.14 ml, 1.0 mmol) were added, filled out by inert gas, and stirred for 48 h at 50 °C (yield after 24 h: 30 %). In both cases the modified copolymers were precipitated in hexane and dried under vacuum to constant mass. Aminolysis (method IC, XVII): Copolymer (250.0 mg, including 1.0 mmol epoxide groups) was dissolved in DMSO (7 ml) and DEA (1.02 ml, 9.8 mmol) was added. After heating at 80 °C for 2 h, the volatiles were removed in a rotary evaporator. Residue was dissolved in methanol and purified by ultrafiltration through a membrane (3.5 kDa cutoff), than the residue was evaporated (yield: 14 %). Aminolysis (method ID, XVIII-XIX): Copolymer (250.0 mg, including 1.1 mmol epoxide groups) was dissolved in THF/DMF mixture (5 ml, 50/50 vol.%). Next, EDA (3 ml, 45 mmol) and TEA (0.6 ml, 4.3 mmol) were added and stirred at 55 °C for 72 h. The remaining solution was precipitated and washed with diethyl ether prior to being redissolved in 15 ml of deionized water. The product was purified by ultrafiltration (6 kDa cutoff membrane) and aqueous solution was lyophilized (2 days) to obtain the crude product (yield: 80 %). Azidation (method II, XX): Copolymer (201.0 mg, including 0.8 mmol epoxide groups) was dissolved in DMF (7 ml). Next, NaN_3 (155.3 mg, 2.4 mmol) and NH_4Cl (127.9 mg, 2.4 mmol) were added, filled out by inert gas, and stirred for 24 h at 50 °C. The modified copolymer was precipitated in water and dried under vacuum to constant mass (yield: 80 %).

Characterization

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a UNITY/INOVA (Varian) spectrometer operating at 300 MHz, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Fourier transform infrared (FT-IR) analysis was conducted with a BIORAD FTS 175L spectrophotometer at room temperature using KBr tablets. Molecular weights and dispersities were determined by gel permeation chromatography (GPC) using an 1100 Agilent isocratic pump, autosampler, degasser, thermostatic box for columns, a photometer MALLS DAWN EOS (Wyatt Technology Corporation, Santa Barbara, CA), and differential

refractometer Optilab Rex. ASTRA 4.90.07 software (Wyatt Technology Corporation) was used for data collecting and processing. Two PLGel 5-μm MIXD-C columns were used for separation. The calibration of the DAWN EOS was carried out by p.a. grade toluene and normalization with a polystyrene standard of 30,000 g/mol. The measurements were carried out in methylene chloride as the solvent at room temperature with a flow rate of 0.8 mL/min. The refractive index increments of copolymers were calculated from the weight composition and d*n*/d*c* for PGMA and PMMA, which were measured in CH_2Cl_2 and they reached values of 0.082 and 0.068 mL/g, respectively. The additional GPC measurements in tetrahydrofuran were performed at the same starting parameters and calibration standards using an 1100 Agilent 1260 Infinity system with a differential refractometer MDS RI Detector and column system for separation (pre-column guard 5 μm 50×7.5 mm and PLGel 5 μm MIXED-C 300×7.5 mm). Addon Rev. B.01.02 data analysis software (Agilent Technologies) was used for data collecting and processing. The morphology was observed by scanning electron microscopy (SEM) with a Hitachi TM 3000 tabletop microscope in the standard mode. Hydrodynamic diameter (D_h) values were determined using a Malvern Zetasizer Nano S90, equipped with a 4 mW He-Ne ion laser operating at λ=633 nm, running the Dynamic Light Scattering (DLS) method. The samples were studied at a concentration of 0.4 g/L at 25 °C. Deionized water, phosphate buffer solution (PBS, pH=6, 7.4, 10) and 150 mM solution of NaCl (physiological concentration) were used as solvents. All polymer solutions were equilibrated for approximately 12 h before measurement. Polymer solutions (0.4 mg mL^{-1}) were filtered through a 0.45-mm syringe filter prior to measurement and each experiment was repeated four times to obtain the average value.

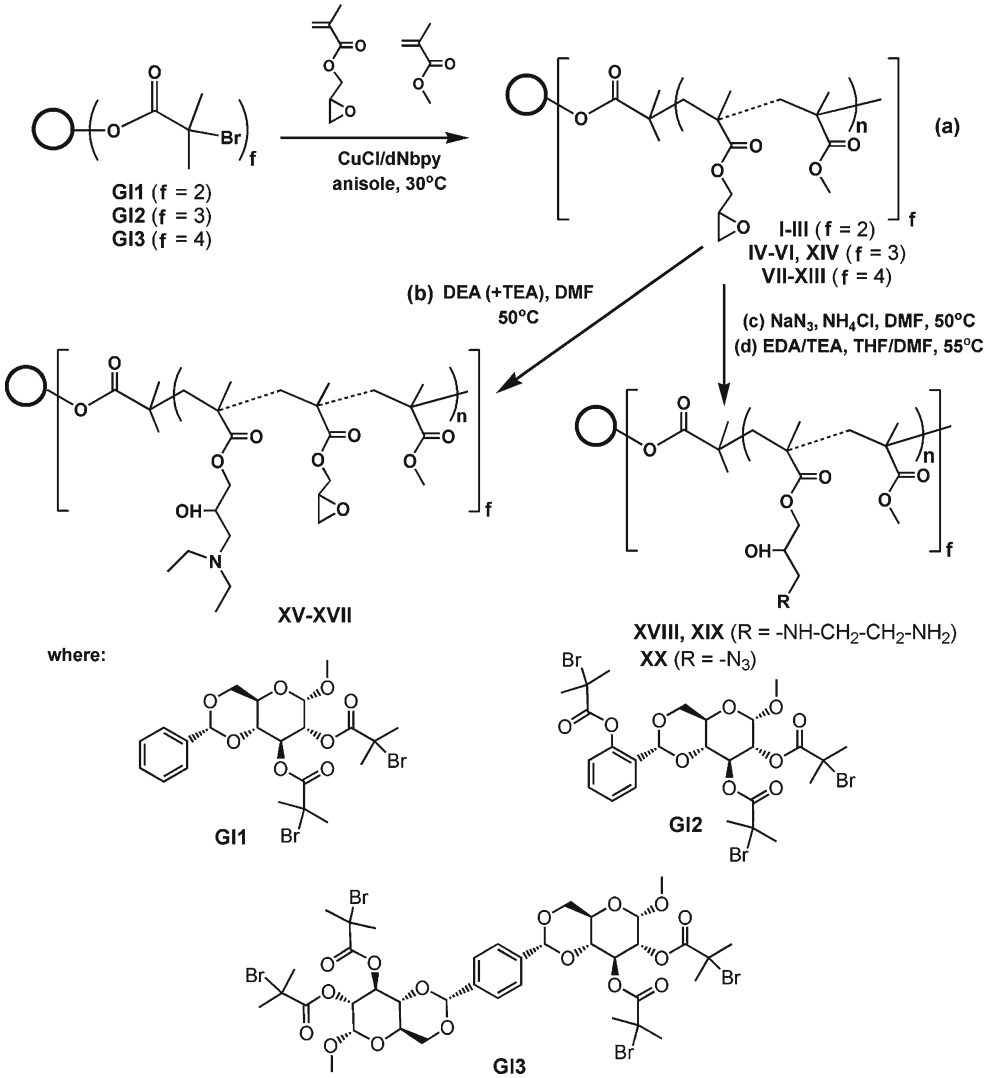
Results and discussion

Sugar-based copolymers with oxirane pendant groups

The initiators (GI1-GI3) based on the acetal derivatives of methyl α-D-glucopyranoside with 2-bromoisobutyryl groups (f_{Br}=2–4, Scheme 1), which are optically active and therefore indicating positive values of the specific rotation ($[\alpha]_D$=+32° – +44°), were applied [26]. They were prepared in a two-step procedure, that is *i)* the condensation of methyl α-D-glucopyranoside with benzaldehyde, salicylaldehyde, and terephthalaldehyde catalyzed by *p*-toluenesulfonic acid, and *ii)* the esterification of secondary hydroxyl groups by 2-bromoisobutyryl bromide. The acetalization process was used to regulate the number of the pre-initiating groups and improve the degradation properties of star copolymers via acetal groups in the sugar core. The bromoester groups were located in C-2 and C-3 positions of sugar in the acetal derivatives (GI1), whereas one additional initiating group is supplied by the salicylic unit (GI2) or doubly increased in the case of dialdehyde with terephthalic unit (GI3). The various numbers of initiating groups made it possible to design V- and star-shaped copolymers with sugar cores sheltered by two, three, and four polymethacrylate segments, respectively. The ATR (co)polymerization of GMA with MMA was performed at 30 °C using CuCl/dNbpy as a catalyst system in anisole (Scheme 1a). Before starting the reaction, 5 mol% of $CuCl_2$ (in relation to CuCl) was also added to introduce a deactivated form of complex $CuCl_2$/dNbpy without waiting for its generation by the transfer of a halogen atom from the initiator to the catalyst system CuCl/dNbpy, and avoiding an initiation reaction that is too fast.

A series of V-shaped copolymers s-[P(GMA-*co*-MMA)]$_2$ (I-III), three-armed stars of s-[P(GMA-*co*-MMA)]$_3$ (IV-VI) and P(GMA)$_3$ (XIV), as well as four-armed s-[P(GMA-*co*-MMA)]$_4$ (VII-XIII) were obtained using bi-, tri- and tetrafunctional sugar initiators, respectively (Table 1). The dependence of monomer conversion in a function of reaction time in Fig. 1a shows that the initial proportions of GMA/MMA have influenced the polymerization rate, which increases with the amount of GMA added to the system. This effect is observed especially in the comparison of 25 % vs. 50 % (IV vs. V), whereas 75 % of GMA did not make significant changes in relation to VI vs. V. The kinetics exhibit a slightly higher consumption of GMA than MMA (inset in Fig. 1a), which can explain faster polymerizations at f_{GMA}=0.5 and 0.75. The samples taken during polymerization V were analyzed by GPC to monitor changes of the copolymer molecular weight and dispersity. GPC traces present monomodal signals, which are shifted into higher molecular weights and becomes narrower (inset in Fig. 1b). This means that the dispersity value was reduced (Đ=1.43–1.31) with the increase in polymerization degree and the slightly changing GMA content in the copolymer (DP_{GMA}=48–84; F_{GMA}=0.56–0.49), whereas molecular weight was in good agreement with $M_{n,th}$ calculated by NMR (Fig. 1b). It is also worth noting that comparison of the copolymers IV-VI, obtained at 60 % of comonomer conversion and at various feeds of GMA, demonstrate the opposite tendency, where dispersity increases (Đ=1.25–1.37) with GMA content (DP_{GMA}=52–137; F_{GMA}=0.27–0.76).

Low values of dyspersities observed for V-shape and four-arm star copolymers made it possible to conclude that it was independent of the arm length and GMA content. This effect is different than that for the three-arm star copolymers with broader molecular distributions, which can be explained by the fact that in bi- and tetrafunctional initiators, all bromoester groups are located directly at the methyl α-D-glucopyranoside, whereas in a trifunctional initiator, one of the initiating groups is placed at the aromatic ring as a spacer



Scheme 1 Synthesis of epoxide-functionalized copolymers with methyl α-D-glucopyranoside in the center, and their modifications via aminolysis and azidation reactions

with a sugar moiety. Because of that it can be postulated that different character of initiating groups causes significant disproportion in the initiation reaction and the formation of short propagating chains, evidenced by higher dispersity, and next at longer chains, the growth of the arms is not involved by the ester initiating unit, which minimizes this discrepancy with chain lengths. However, the same level of dispersity cannot be reached, as it resulted in the case of the V-shape and four-arm star copolymers with a homogeneous neighborhood of initiating groups in the acetal derivative of methyl α-D-glucopyranoside with symmetrical structures ($Đ_{2\text{-}arm} \approx Đ_{4\text{-}arm} < Đ_{3\text{-}arm}$).

Relative reactivity ratios of comonomers

Slightly higher consumption of GMA than of MMA allowed us to conclude small differences in the reactivities of methacrylate monomers in the studied systems of copolymerization. The relative reactivity ratios of monomers were estimated by the Jaacks method [27]. The values were calculated from the plots: $-\ln(1-x_{GMA}) = r_{GMA} \times -\ln(1-x_{MMA})$, yielding $r_{GMA}=1.03\pm0.03$ (Fig. 2a) and $-\ln(1-x_{MMA}) = r_{MMA} \times -\ln(1-x_{GMA})$, yielding $r_{MMA}=0.78\pm0.03$ (Fig. 2b). These results are in good agreement with the earlier reports in the literature describing the synthesis of linear copolymers by ATRP, initiated by ethyl 2-bromoisobutyrate, which showed a slightly higher reactivity of GMA in the pair with allyl methacrylate ($r_{GMA}=1.22$, $r_{M2}=0.82$) [28] or methyl methacrylate ($r_{GMA}=1.21$, $r_{MMA}=0.85$) [29]. The relation $r_1 \geq r_2$ for the comonomer pair GMA/MMA, where $r_{GMA} \geq 1$ and $r_{MMA} < 1$, means that both free radical types GMA and MMA easily react with the GMA monomer, which instantaneously causes the copolymer to be slightly richer in GMA than the monomer mixture that it originates from.

Table 1 ATR (co)polymerization of GMA and MMA initiated by bi- (GI1), tri- (GI2), and tetrafunctional (GI3) sugar initiators at 30 °C

	Initiator (In)	f_{GMA}	Time [h]	Conversion [%]		DP_{GMA}	DP_{arm}	$M_{n,th.}$ [a] [g/mol]	F_{GMA}	GPC[b]		GPC-MALLS[c]	
				x_{GMA}	x_{MMA}					M_n [g/mol]	M_w/M_n	M_n [g/mol]	M_w/M_n
I	GI1	0.50	2.0	18	13	36	31	8300	0.58	9900	1.30	11120	1.19
II	GI1	0.50	4.2	29	30	58	59	14800	0.49	18000	1.34	17300	1.23
III	GI1	0.50	3.0	50	40	50	45	11700	0.56	13000	1.24	13200	1.24
IV	GI2	0.25	5.0	69	62	52	64	22100	0.27	21300	1.25	22700	1.14
V	GI2	0.50	2.5	56	58	84	57	21400	0.49	19000	1.31	18900	1.58
VI	GI2	0.75	2.5	61	59	137	61	24700	0.76	18600	1.37	22800	1.28
VII	GI3	0.25	3.5	50	37	50	40	19300	0.31	20300	1.21	22600	1.15
VIII	GI3	0.75	2.0	53	47	159	52	28400	0.77	28200	1.22	–	–
IX	GI3	0.25	4.0	79	83	59	61	28200	0.24	25800	1.22	23100	1.29
X	GI3	0.75	2.7	75	85	169	58	31500	0.73	27500	1.22	34100	1.23
XI	GI3	0.25	8.0	49	39	37	31	15100	0.30	18300	1.22	18100	1.14
XII	GI3	0.75	5.0	53	52	119	40	21900	0.75	21700	1.24	26600	1.12
XIII	GI3	0.50	21.3	78	72	156	75	37700	0.52	34900	1.18	–	–
XIV	GI2	1.0	1	57	–	171	57	25100	1.0	18200	1.33	–	–

I, II, XIII: $[GMA+MMA]_0:[In]_0:[CuCl]_0:[dNdby]_0$ = 400:1:0.75:1.5; III: 200:1:1.5:3; IV-VI, IX, X, XIV: 300:1:1.5:3; VII, VIII: 400:1:1.5:3; XI, XII: 300:1:0.75:1.5; anisole 70 % vol. of monomer, $CuCl_2$ 5 % mol. of CuCl

[a] Calculated on the basis of conversion determined by NMR

[b] CH_2Cl_2, RI detector, PS standards

[c] CH_2Cl_2, MALLS detector, *dn/dc*=0.082–0.068 mL/g

Additionally, the product of r_{GMA} and r_{MMA} is less than 1, which suggests that longer sequences of GMA units in the copolymer chain can be formed. The plot of instantaneous monomer-copolymer composition (F_{GMA} vs. the initial amounts of GMA used for polymerization (f_{GMA}) diagram) in Fig. 2c (solid line) shows deviation from the typical dependence for "random copolymer" (dashed line).

Modification via aminolysis reaction

Most of the ring opening reactions were performed in the presence of the nucleophilic agent DEA. According to the literature, the rings in linear PGMA were gradually attenuated, and finally, the reaction at a feed molar ratio of $[epoxy\ group]_0:[DEA]_0$ = 1:1.5 in dioxane was essentially complete

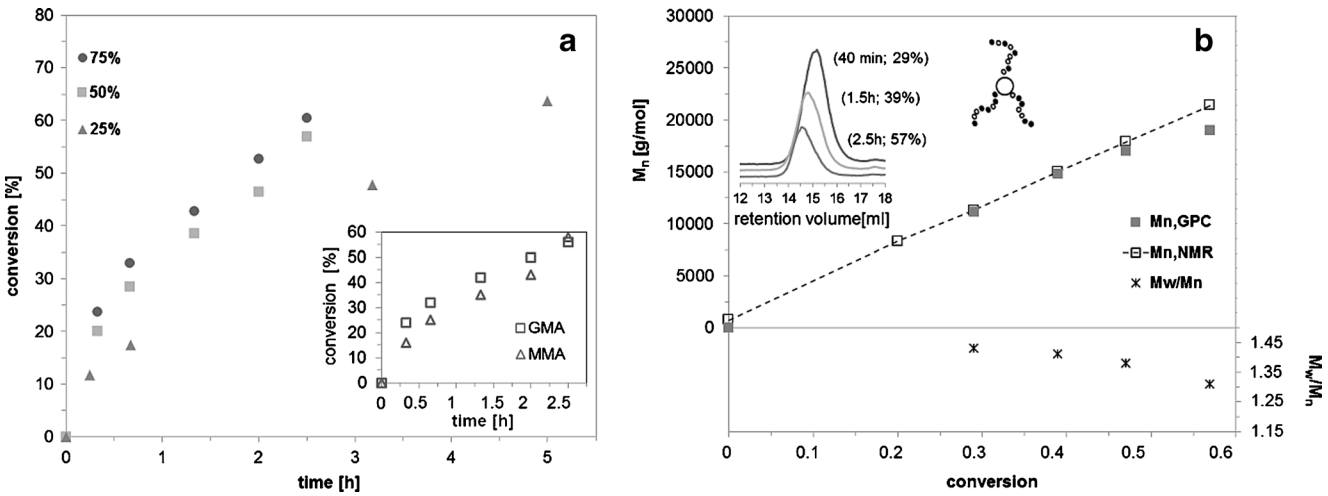


Fig. 1 Conversion vs. time curves for copolymerizations (IV-VIII) with a different initial amount of GMA (**a**); conversion of GMA and MMA in the copolymerization (II) at an initial ratio of GMA/MMA = 50/50 (inset **a**), dependence of the molecular weight (M_n) and molecular weight distribution (M_w/M_n) on monomer conversion (**b**); and GPC traces of 3-arm star copolymers (V) (inset **b**). Initial conditions presented in Table 1

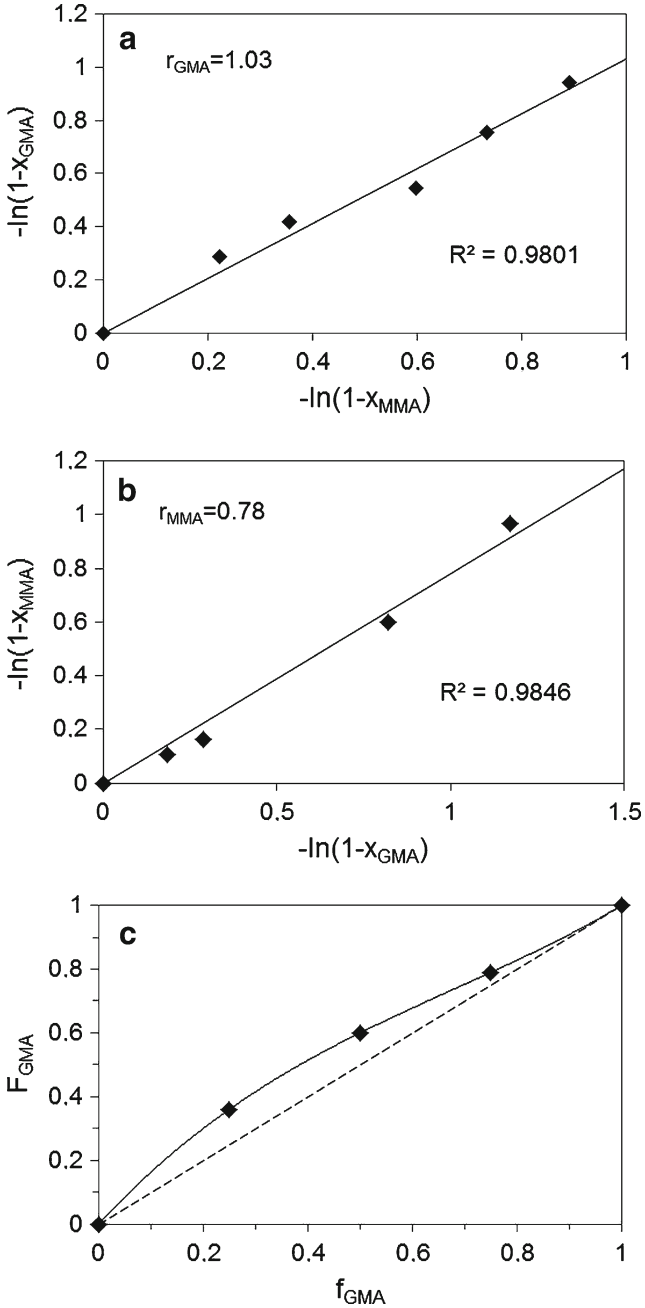


Fig. 2 Jaacks plots for the determination of reactivity ratios r_{GMA} (**a**) and r_{MMA} (**b**); instantaneous monomer–copolymer composition (F_{GMA} vs. initial amounts of GMA used for polymerization (f_{GMA}) diagram) (**c**) for the ATR copolymerization of GMA and MMA

at 30 °C within 72 h [30]. However, the efficiency of transformation via aminolysis of the copolymer V as the representative for the resulting sugar-centered structures was not satisfied even at more stringent conditions (larger excess of amine and higher temperature), because only 20 % of the opened rings within 72 h were observed at a feed molar ratio of [epoxy group]$_0$:[DEA]$_0$ = 1:3 in DMF at 50 °C (Table 2). This method was modified to enhance the effectiveness of the ring-opening reaction by the addition of TEA as catalyst, giving 40 % of 2-hydroxy-3-diethylaminopropyl methacrylate units (HAmPMA) after 24 h, but after a longer time the polymer was cross-linked. In both cases it led to copolymers still containing epoxide groups P(GMA-*co*-HAmPMA-*co*-MMA)$_3$ XV, and XVI (Scheme 1b). In the ^{1}H NMR spectrum (Fig. 3b) the new proton signals at 4.00 ppm (>C*H*OH), 1.04 ppm (-N(CH_2CH_3)$_2$), and in the range 2.3–2.8 ppm (-CH_2N(CH_2CH_3)$_2$), as well as at 3.85 ppm (-OCH_2CH(OH)CH_2N<) were detected, indicating the incorporation of diethylamino and hydroxyl groups, whereas the intensities of signals corresponding to the oxirane ring at 2.65, 2.86, and 3.24 ppm, as well as at 4.34 ppm (1H in -CH_2-C_{ox}) were significantly reduced in comparison to the copolymer before modification (Fig. 3a).

Subsequently, the post-polymerization treatment of V was carried out in DMSO at 80 °C with an higher excess of DEA (10-fold), which after 2 h gave a 78 % epoxide conversion. Unfortunately, the copolymer XVII turned out to be unstable and the formation of gel occurred within less than 24 h of storage after completion of the ring-opening reaction. A crosslinking process has been previously reported for the modification of GMA units in linear polymers, as a concurrent reaction of the anionic oxirane ring-opening polymerization occurring between the unreacted epoxy groups initiated by tertiary amines that originated from the reaction of diethylamine with the epoxy groups at 80 °C [31], or by the self-initiated crosslinking of oxirane rings in block copolymers of PGMA and poly(diethylamine-functionalized methacrylate) by thermal treatment [30]. However, in the studied star-shape copolymer, the branched topology is an additional factor supporting intermolecular side reactions, which can occur even at lower temperatures when the level of incorporated amine groups is properly high.

However, the modification without crosslinking was performed for linear PGMAs with primary amines, 2-amino-1-butanol and 4-amino-1-butanol [19], or ethanolamine and EDA [32], yielding the well-defined water-soluble amphiphilic diamino derivatives of GMA polymers. The ring-opening reaction with the EDA agent was also applied in our study to ensure complete functionalization of the epoxy groups in sugar star polymers using the molar ratio [EDA]$_0$:[GMA]$_0$ = 41:1, which led to the full conversion and elimination of intra- or intermolecular crosslinking. The modified polymer containing 2-hydroxy-3-[(2-aminoethyl)amine]propyl substituents s-P(HAmPMA-*co*-MMA) (XVIII) and s-P(HAmPMA) (XIX) was well-soluble in water. Figure 3c presents the ^{1}H NMR spectrum of XVIII, which was made in deuterated water. The new signals located at 3.3–2.5 ppm can be assigned to methylene protons neighboring with amine groups (-CH_2-NH-, -CH_2-NH_2), whereas the signal of the methanetriyl proton adjacent to the hydroxyl group (>C*H*-OH) is observed at 4.05 ppm.

Table 2 Modification of GMA-based polymers by ring-opening reactions

No.	GMA-based polymer	Ring-opening reaction	Agent	Time [h]	Conversion [%]	Copolymers with OH groups
XV	V	Aminolysis (met. IA)	DEA	12	8	s-P(GMA-*co*-HAmPMA-*co*-MMA)
				24	11	
				48	16	
				72	20	
XVI	V	Aminolysis (met. IB)	DEA/TEA	24	40	
				48	Insoluble	
XVII	V	Aminolysis (met. IC)	DEA	2	78	
XVIII	XIII	Aminolysis (met. ID)	EDA/TEA	72	100	s-P(HAmPMA-*co*-MMA)
XIX	XIV	Aminolysis (met. ID)	EDA/TEA	72	100	s-P(HAmPMA)
XX	V	Azidation (met. II)	NaN_3/NH_4Cl	12	49	s-P(HAzPMA-*co*-MMA)
				24	100	

The morphological evolution of the sugar-centered GMA-based polymers during modification with EDA is elucidated by SEM images. After a reaction taking 72 h, the assemblies form broken sheets/layers, which totally cover the substrate surface. There is no significant difference between the three-armed PGMA star (Fig. 4a) and the four-armed s-P(GMA-co-MMA) (Fig. 4b). A shorter reaction time by one-half made it possible to distinguish particle aggregations (Fig. 4c), which in the magnification reveals individual assemblies with a diameter of 50 nm and a specific shape (selected squares in Fig. 4d).

Modification via azidation reaction

A higher degree of oxirane-ring opening in GMA star-shaped copolymers was also obtained in the azidation reaction in DMF at 50 °C with NaN_3/NH_4Cl (Table 2). A 49 % conversion occurred after 12 h, whereas the reaction was completed after 24 h, yielding a copolymer with 2-hydroxy-3-azidopropyl substituents s-P(HAzPMA-*co*-MMA) XX (Scheme 1c). The structure of the modified copolymer was confirmed by ^{1}H NMR and IR spectroscopy. Figure 3d shows the ^{1}H NMR spectrum of the copolymer with azide units, where the proton peaks of the epoxide ring (2.65, 2.87 and 3.23 ppm), and the methylene group in $–COOCH_2–C_{ox}$ at 4.34 ppm disappeared, whereas new peaks corresponding to the methylene protons next to the azide group $-CH_2N_3$ (3.45 ppm) and the methin next to the hydroxyl group –*CH*-OH (which were overlapped with methylene protons next to the ester group $–COOCH_2–CH(OH)$ in the range 3.75–3.98 ppm) are observed. The IR spectra of the copolymers before and after azidation in Fig. 5a show the peaks at 1,175–1,245 cm^{-1} and 1,727 cm^{-1} , recognized as the stretching vibration of C-O and C=O groups in polymethacrylate, respectively. In the CH stretching region (3,100–2,800 cm^{-1}), bands characteristic for $\nu(CH_2)$ and $\nu(CH_3)$ are observed, and the bands coming from $\delta(CH_2)$ are also identified at 1,450 cm^{-1}. The peak at 909 cm^{-1}, which is associated with

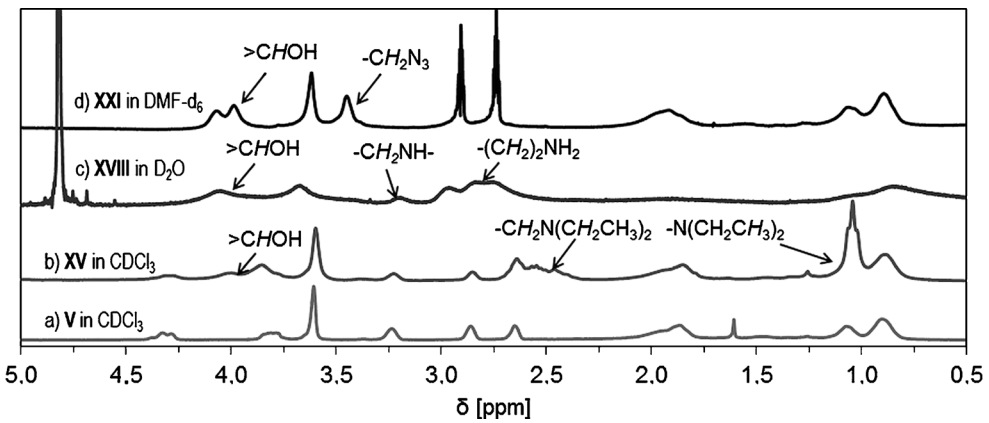


Fig. 3 ^{1}H NMR spectra of GMA copolymer V in $CDCl_3$ before modification (**a**), XV in $CDCl_3$ after aminolysis with DEA (**b**), XVIII in D_2O after aminolysis with EDA (**c**) and XX in DMF-d_6 after azidation (**d**)

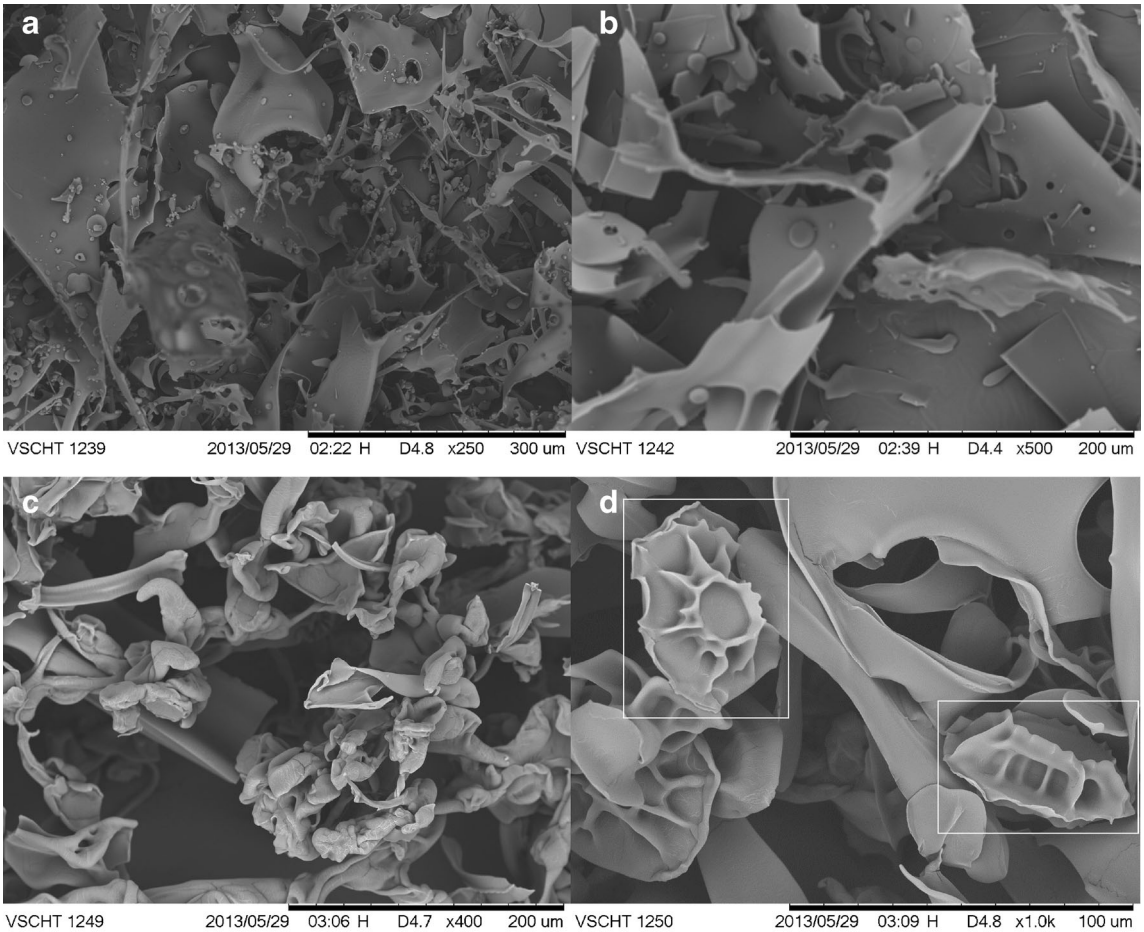


Fig. 4 SEM images of the sugar-centered GMA-based polymers after modification with EDA within 72 h, 3-armed XIX (**a**), 4-arm star-shaped copolymer XVIII (**b**), and after 36 h of aminolysis XVIII with different magnification (**c**, **d**)

the presence of epoxide in GMA units, disappeared for s-P(HAzPMA-*co*-MMA) (XX), while a broad hydroxyl band in region 3,100–3,650 cm^{-1}, a new azide absorption band at 2,109 cm^{-1} $\nu(N_3)$, and bands coming from ν(C–N) at 1,070 cm^{-1} are present, indicating the efficient transformation of star-shaped copolymers. Figure 5b shows GPC traces of V and XX, which were also sufficiently soluble in THF, showing both monomodal signals with similar values of molecular weights and their distributions with regard to maximum peak values (M_w=11 400 g/mol; M_w/M_n=1.34; M_p=11 300 g/mol after azidation, and M_w=11 700 g/mol; M_w/M_n=1.24; M_p=11 400 g/mol before azidation).

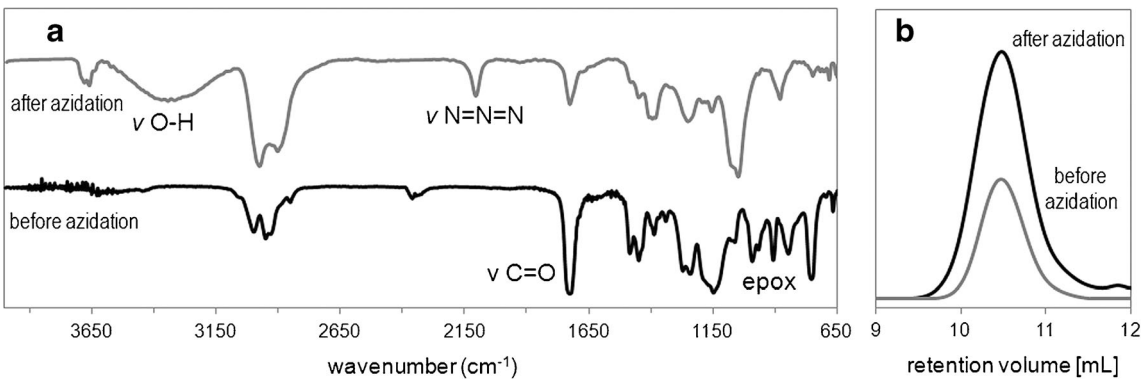


Fig. 5 FT-IR spectra (**a**) and GPC traces (**b**) of copolymer s-P(GMA-*co*-MMA) before modification (V) and after azidation (XX)

Table 3 The averaged particle size distribution data based on intensity and volume calculation methods, as well as polydispersities of XVIII-XIX determined via DLS at T=25 °C

	Solvent	D_h int. [nm]	% intensity	PdI	D_h vol. [nm]	% volume
XVIII	Deionized water	251±30	68.6±4.8	1.000	3.6±0.7	99.7±0.1
		28±23	15.4±4.9		29±11	0.3±0.2
		9±9	11.9±1.5		–	–
	With NaCl	215±20	75.9±0.2	1.000	11±2	99.3±0.4
		13±1	21.9±0.3		182±17	0.3±0.1
		4834±230	2.2±0.1		5090±132	0.3
	PBS (pH=7.4)	290±7	66.0±2.7	0.83±0.295	0.6±0.2	100
		20±2.3	28.7±2.7			
		0.7±0.03	6.0±0.2			
	PBS (pH=10)	203±9	82.7±1.1	0.708±0.011	9±1	99.7±0.1
		11±2	16.8±1		152±16	0.3±0.1
		4979	1.4		5172	0.1
XIX	Deionized water	267±27	100	0.259±0.037	288±31	100
	With NaCl	215±25	93.9±4.1	0.493±0.031	16±10	93.9±4.1
		16±10	7.4±0.9		175±26	4.8±3.3
		5009	2		5193	1.2±1.5
	PBS (pH=7.4)	216±45	49.4±1.9	0.981±0.033	0.9±0.3	99.9±0.6
		17±4	37.5±2.7		14±1.3	0.1±0.6
		0.9±0.3	13±2.6		–	–
	PBS (pH=10)	178±24	79.7±4.6	0.845±0.169	71±26	1.7±0.6
		14±3	17.7±3.9		12±2	97.9±0.7
		4791±470	3.9±2.5		5075±269	0.4±0.3

Results are presented in descending order as mean D_h value ± sd

After modification, the prepared copolymer XX presents amphiphilic character, which in the future can be used to form micelles. The presence of hydroxyl groups in the copolymer make it able to crosslink, which can be useful for micelle stabilization. In addition, the presence of azide groups creates the possibility to change the copolymer properties by the attachment of an alkynyl terminated polymer via the Huisgen 1,3-dipolar cycloaddition "click" reaction.

Self-assembly behavior of EDA-modified copolymers

The hydrodynamic diameters (D_h) and polydispersity indices (PdI) of copolymers XVIII-XIX in aqueous solutions were determined at different pH values, in phosphate buffer or deionized water (conductivity >0.08 μs/cm), and with/without salt interaction using DLS. The data presented in Table 3 are averaged diameters by intensity (D_h int) as well as averaged diameters by volume (D_h vol). As it can be noticed that the PdI values ranged from 0.259 to 1.000, indicating rather large variability in the particle size. In PBS at physiological pH polymers existed as unimers (U, <13 %), but they also formed micelles (M, 30–40 %) and aggregates (A, 50–70 %), which was similar to the behavior of sample XVIII in deionized water, whereas the aggregate self-assembling form in 100 % for particles based on XIX (Fig. 6a–b) was related to the narrowest PdI. At other pH value and in the presence of salt a small fraction of super-aggregates (SA) up to 5 % can be also distinguished. Additionally, the particles in the main fraction of both copolymers were in similar sizes in a neutral environment of deionized water, whereas in PBS with pH=7.4, larger aggregates were created for XVIII, which can be related to the content of amine-functionalized GMA units (100 % vs. 50 %). The addition of NaCl to the aqueous solutions of XVIII and XIX had an influence on the reduction of aggregate sizes due to the salt interaction with nitrogen atoms in the amine group. A similar behavior to that of copolymers yielding smaller aggregates was also detected at higher pH value, which is typical for polybases with a tendency to shrink in unionized deprotonated form. In these specific conditions the unimer form disappeared as it is shown in histograms for copolymer XVIII in Fig. 6c vs. e, and Fig. 7a vs. c), indicating a sensitivity to pH changes and salt interactions.

In relation to the volume of particles, the major fraction (94–100 %) demonstrated sizes in the range of 0.6–16 nm for all measurements. This is associated with the fact that small particles scatter light much less than large particles. Taking into consideration the Rayleigh approximation, the intensity of scattering of a particle is proportional to the sixth power of its diameter.

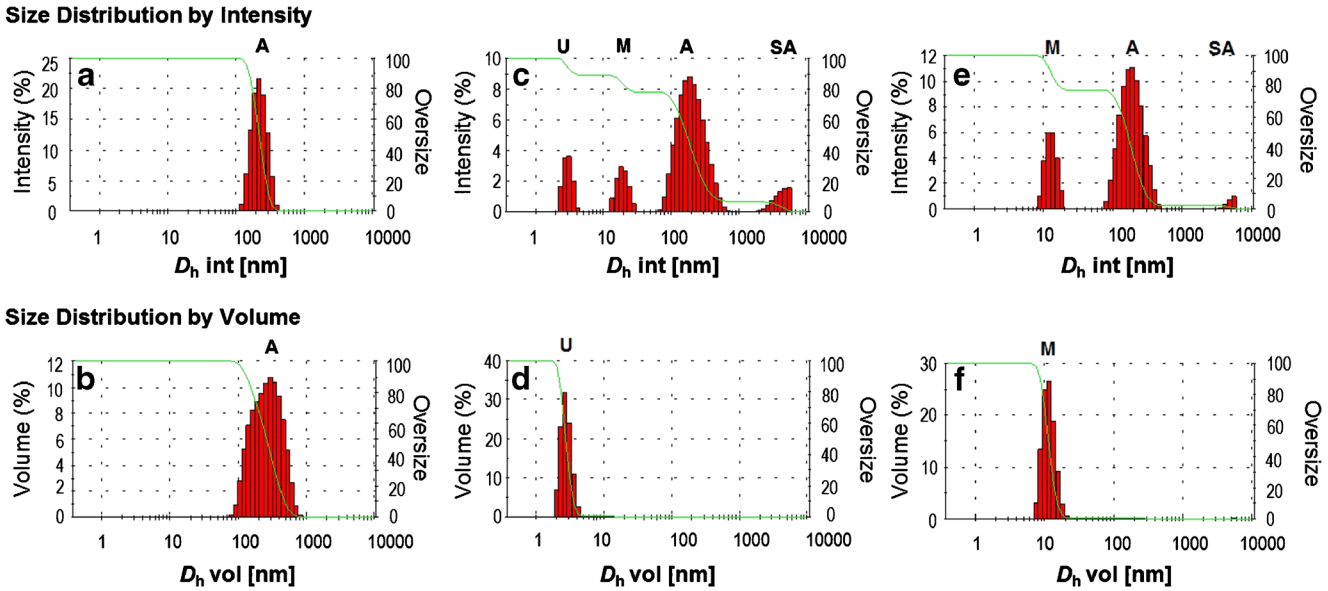


Fig. 6 Size-distribution plots by intensity and volume for XIX in deionized water solution (**a**, **b**), and XVIII in deionized water solution (**c**, **d**) in deionized water solution, as well as XVIII with NaCl addition (**e**, **f**)

Conclusions

The methyl α-D-glucopyranoside-centered copolymers with various topologies (V-shape, and three- and four-armed stars), arm lengths (DP_{arm}=31–75), and contents of oxirane rings (25–100 mol%), characterized by low dispersities, were prepared by ATR (co)polymerization of GMA initiated by acetal derivatives of sugar with a designed number of functionalities as pre-initiating groups. The relative reactivity ratios of comonomers determined by the Jaacks method ($r_{GMA} \geq r_{MMA}$) have suggested the formation of chains/arms slightly richer in GMA units. The incorporated epoxide groups were modified via ring-opening reactions, i.e., aminolysis with diethylamine and ethylenediamine or azidation, but the first method resulted in nucleophilic oxirane ring-opening to a maximum of 40 %, whereas the two latter ones achieved complete conversion. The efficiency dependence on the type of ring-opening agent and GMA content influenced the degree of hydrophilic fraction and the character of copolymers, which became water-soluble only in the case of EDA-functionalized ones. The

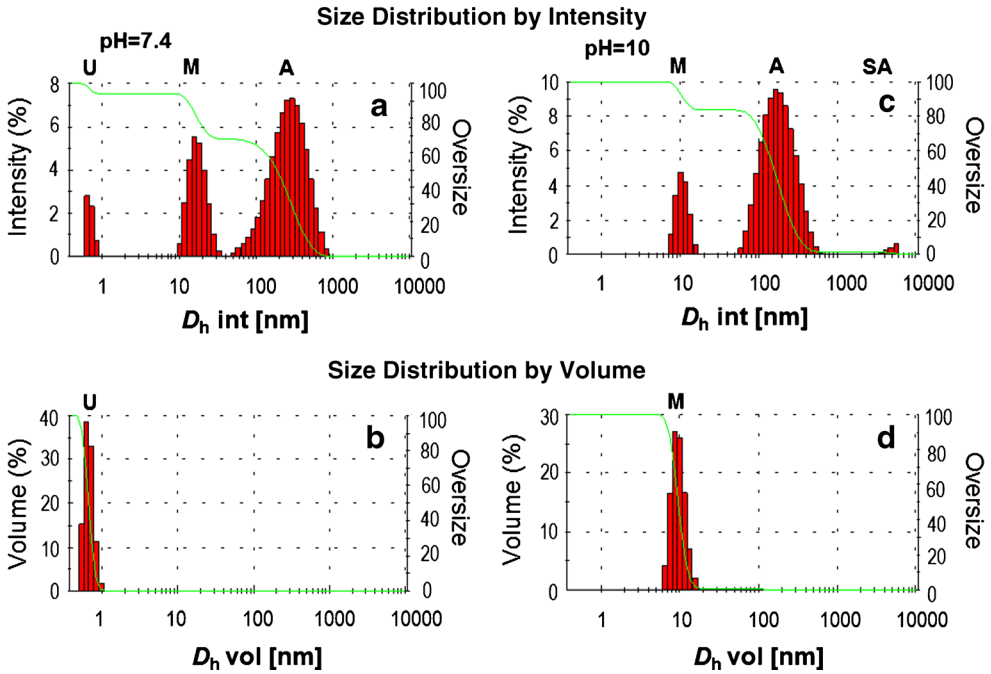


Fig. 7 Size-distribution plots by intensity and volume for XVIII in PBS at physiological pH (**a**, **b**), and in basic conditions (**c**, **d**)

analysis of the effective size of particles provided by DLS indicated that aggregates (178–290 nm) were predominated in relation to the other forms presented by unimers (< 5 nm), micelles (5–50 nm), and super-aggregates (> 1,000 nm). The star copolymers with diamine groups in aqueous solutions were responding to pH value and salt ion stimuli, changing the macromolecular conformation from a stretched to shrunken form. Both the epoxide groups and the modified hydroxyl and amine/azide groups can be used for future covalent bonding; specifically, functionalized compounds (dyes, drugs) or the water-soluble polymers can form micelles/aggregates loaded with those compounds.

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