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Supramolecular Glycopolymers with Thermo-Responsive Self-Assembly and Lectin Binding

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Incorporating monomers into sequence-defined synthetic macromolecules endows them to mimic nature that results in key residues being anchored in the molecular recognition pattern. Developing controlled carbohydrate sequences has a critical importance in understanding the multivalent binding motifs of oligosaccharide and sequence-controlled glycopolymers to various lectins. Here, we describe the development of thermo-responsive copolymer scaffolds bearing adamantane groups that enable to form an inclusion complex with mono and hepta mannosylated-cyclodextrin molecules through host-guest interaction. We have demonstrated the synthesis of triblock copolymer via RAFT polymerization, the complexation of the adamantane containing thermoresponsive copolymer and α-D-mannose-CD, as well as their interactions with ConA.

Introduction

Biomacromolecules, such as proteins, nucleic acids and polypeptides, are largely responsible for the complexity and diversity of the biological materials mainly due to their precisely controlled secondary and tertiary structures. Controlling the monomer sequence is a key strategy in synthetic polymer science towards mimicking biomacromolecules. In recent years, there is an increasing tendency for the preparation of well-defined sequence-controlled polymers. Precise positioning of monomer units along a polymer chain allows the generation of precisely tailored materials through self-assembly, with control over nanoscale-domain geometry, packing symmetry and chemical composition. Recently, new methodologies have emerged for multi-block copolymer synthesis based on one-pot sequential addition of monomers while targeting near full conversion per block, thus removing the need for intermediate purification steps. Precise monomer units along a polymer chain allows the generation of precisely tailored materials through self-assembly, with control over nanoscale-domain geometry, packing symmetry and chemical composition. Recently, new methodologies have emerged for multi-block copolymer synthesis based on one-pot sequential addition of monomers while targeting near full conversion per block, thus removing the need for intermediate purification steps. Perrier and co-workers demonstrated that reversible addition-fragmentation chain transfer (RAFT) polymerization is very useful to make macromolecules featuring a large number of block sequences in a controlled fashion. Importantly, the authors nicely demonstrated, the livingness of a RAFT process depends on knowledge of polymerization kinetics. Similarly, stimuli-responsive or smart behavior can also be imparted to synthetic polymers by incorporation of functional groups that can undergo changes in physical properties, which allow the conjugation of other molecules, such as peptides, carbohydrates, targeting vectors or drugs, onto the polymer backbone. Interest in smart polymers has been maintained over many decades, which display great promise in numerous nanotechnological and biomedical applications. Smart polymers show rapid and reversible changes in response to small changes of their environment (e.g., pH, temperature, salt concentration, and co-solvent). The most commonly investigated stimuli has been the temperature, which is achieved by simply incorporating thermo-responsive groups in the polymer structure that exhibits LCST (lower critical solution temperature) behavior. Thermo-responsive polymers, such as poly(N-isopropyl acrylamide) (PNIPAM), undergo a reversible phase transition from hydrophilic to hydrophobic when their solution temperature is raised above their LCST, changing from an extended chain conformation below LCST into a collapsed chain above LCST. Aqueous solutions of PNIPAM exhibit LCST behavior around 32 °C. In general, the LCST of PNIPAM can be influenced by several factors, e.g. molecular weight (Mw), polydispersity, end groups, topology and incorporating hydrophilic or hydrophobic character by copolymerization with hydrophilic or hydrophobic comonomers. According to these studies, well-defined aqueous solutions of high molecular weight PNIPAM samples with precise end groups, shows dramatic decrease in cloud point due to the reduced entropy of mixing with increasing Mw. Moreover, by increasing the hydrophilic nature of the polymers, the overall hydrogen bonding ability of the macromolecules is increased, which leads to higher transition temperatures. Incorporating hydrophobic groups causes a disruption of the structure of water around the macromolecules and lowers the cloud point. This enhances the interaction of hydrophobic species, further facilitating aggregation. With the same approach, Ritter and coworkers investigated the LCST behavior of both hydrophobic...
Scheme 1. Synthesis of triblock copolymer by sequential RAFT polymerization and its host-guest interaction with self-assembly behaviour. (a) Schematic representation of the synthesis of the triblock copolymer by RAFT in a one pot sequential fashion. (b) Molecular structure of synthesized \( P_1 \) triblock copolymer and its self-assembly micelle formation in water. For simplicity, these structural formulae display only the average DMA, Adac composition of the polymers and do not give information about the localization of the Adac units in the chains. (c) Schematic representation and molecular structures of \( \beta \)-CD derivatives. (d) Self-assembly micelle formation of \( P_1 \) triblock copolymer and equimolar \( \beta \)-CD derivatives in water.

Glycopolymers are synthetic polymers with sugar moieties attached and have a great potential for mimicking the biopolymers.\(^{10,11}\) The recognition event of carbohydrates and lectins is critical in a wide variety of intercellular processes.\(^{6,32-37}\) In general, the interaction of a lectin with a carbohydrate is quite weak, but can be dramatically enhanced by the multivalent effect of glycopolymers, which is known as the "glycocluster effect".\(^{38}\) The multivalency has a significant effect in carbohydrate-lectin binding through intermolecular crosslinking through lectin receptors.\(^{39,40}\) Parameters, such as the density of sugar units, the type of the sugar units and the architecture of the glycopolymers, have even larger impact on binding.\(^{41-43}\) Although some advanced techniques, such as isothermal titration calorimeter (ITC), quartz crystal microbalance (QCM), and surface plasmon resonance (SPR) have been employed to explore the lectin-glycopolymer
interactions, traditional and more widely employed methods (quantitative precipitation, turbidimetry, fluorescence quenching assays, etc.) have also been used to understand these interactions. Recently, extensive reports have been published on this topic, emphatically the synthesis of different thermoresponsive glycopolymers with variety of shapes and compositions. Furthermore, as a result of the thermoresponsive behaviour of these kind of polymers, different conformations of the polymers below and above the cloud point temperature influenced the lectin–polymer interactions. This journal is © The Royal Society of Chemistry 20xx

In order to synthesize sugar decorated β-CD derivatives from azide functionalized β-CD derivatives via CuAAC, the preparation of sugar alkynes are required. Since the discovery of Fischer glycosylation, sulfuric acid immobilized on silica was used as a catalyst for the preparation of alkyl glycosides from free sugar. Thus, alkyne functionalized α-D-mannose was synthesized according to literature. The preparation of β-CD-OTs and β-CD-N$_3$ was well described by Ritter and the same route was adopted to synthesize mono-azide functional CD (β-CD-N$_3$). In the $^1$H NMR spectrum of β-CD-OTs two peaks at 7.42 and 7.75 ppm are assigned to the phenyl protons. The ratio of these two peaks and the peaks corresponding to 2,3-positioned hydroxyl groups of the β-CD ring approaches to 1:1:7, suggesting that only one TsCl is reacted with the 6-positioned hydroxyl group of the β-CD ring. In further reaction, the characteristic phenyl protons in β-CD-OTs disappear, which verifies the complete replacement of paratoluensulfonyl group by azide group (Supplementary Fig. S1, S2). Hepta-azide functional CD (β-CD-(N$_3$)$_7$) was prepared according to our previously published paper. The ratios of all hydroxyl groups and CH$_2$Br or CH$_2$N$_3$ protons in $^1$H NMR spectra indicating the quantitative functionalization of end-groups (Supplementary Fig. S3, S4). The CuAAC of β-CD-N$_3$ and β-CD-(N$_3$)$_7$ with alkyne functionalized α-D-mannose was carried out using a CuBr/$\text{Me}_3$TREN catalyst system in DMSO as solvent to yield the β-CD-Mannose (CD$_1$) and β-CD-(mannose)$_n$ (CD$_n$) glyoclusters, respectively. The $^1$H NMR spectra for both CD substances showed the presence of triazole proton at approximately 7.9 ppm and CD residues at 6.0 ppm (OH) and 5.2 ppm (H-1) indicated the success of the CuAAC reaction (Supplementary Fig. S5, S6). FT-IR spectra (Supplementary Fig. S8, S9) confirmed the disappearance of azide functionalities at 2100 cm$^{-1}$ following the click reaction. DMF SEC analysis (Supplementary Fig. S10) revealed the shift of elution traces after reaction due to the change of hydrodynamic volume.

Recently, Perrier and coworkers were able to synthesize one-pot, sequence-controlled multi-block copolymers from the RAFT methodology. They focused on acrylamide monomers because acrylamide monomers show high propagation rate (high $k_p$) despite the low initiator concentration to keep the number fraction of dead chains at minimum. Junkers and coworkers mapped end-group compositions of RAFT polymers obtained from consecutive polymerizations. Consecutive chain extensions of methyl acrylate polymers were carried out under variation of initiator concentrations and investigated in detail via ESI-MS to carefully map the end-group composition evolution. Consequently, this procedure appears to be very efficient for the polymerization of both acrylamide and high $k_p$ acrylate monomers.

In our study, adamantane modified thermo-responsive triblock copolymer (P1) was synthesized via reversible addition–fragmentation chain transfer (RAFT) polymerization in a sequential addition fashion. We focused on three different monomers, which two of them are commercially available; N,N-dimethylacrylamide (DMA) and N-isopropylacrylamide (NIPAM) and the third one is adamantane acrylate (Adac), which is used after modification of 1-adamantane methanol with acryloyl chloride.

The optimized polymerization conditions were chosen as 65 °C in dioxane, and experiments revealed that an optimal monomer concentration of 1M for the first and second block and 0.4M for the third block, which enables rapid polymerization at moderate viscosity of solution.

2-(((dodecylthio)carbonythiophenyl)thio)propan-2-yl pentanoate and AIBN were chosen as chain transfer agent (CTA) and radical initiator, respectively (Scheme 1). Accordingly, the necessary time to achieve quantitative monomer conversion, which reduces the quantity of initiator required (e.g., the amount of dead chains is decreased), was minimized. [CTA]/[AIBN]$_0$ ratio was kept as 130:1 to avoid dead-end polymerization, which is a polymerization where all initiator is decayed before full conversion is reached. When the AIBN concentration is lowered, the polymerization eventually requires a longer reaction time before reaching to full conversion. Therefore, increasing reaction times were applied based on lower AIBN concentrations, so that in all cases almost full conversions are reached (in practice ≥ 91–99%) was achieved as measured by gas chromatography). DMA and Adac showed similar conversion rates, increased in linear relation by time (Table S1 for the quantity of reagents needed for the triblock copolymer). To obtain full monomer conversion reaction time was increased, but conversion and molecular weight kept constant.

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Thermal phase transition temperature of the polymer solution, expressed as LCST, was measured as a function of temperature at a specific wavelength ($\lambda$) 500 nm using a UV-Vis spectrometer. In order to obtain clear solution, the polymer concentration was chosen as 2.5 mg.mL$^{-1}$. $P_1$ polymer showed distinct heat-induced phase transition with 50% transmittance point at about 24 °C (Fig. 1a). By increasing the hydrophilic nature of the polymers, the overall hydrogen bonding ability of the macromolecules is increased, which leads to higher transition temperatures. Incorporating hydrophobic groups lowers the LCST. Furthermore, the addition of hydrophobic groups causes a disruption of the structure of water around the macromolecules. This enhances the interaction of hydrophobic species, further facilitating aggregation. Compared to the literature value of 32 °C reported for high-molecular weight linear PNIPAM, the decreased LCST of $P_1$ can be attributed to both the rather low molecular weight and the presence of hydrophilic (DMA) and hydrophobic (Adac) units along the backbone. The measured hydrodynamic diameters of this ‘hydrophobic’ conjugated copolymer below its LCST indicate that it exist as unimers in solution, suggesting that the expected increase in LCST is as a consequence of the formation of micelles (Fig. 1b).

Analysis of the molecular weight distributions by size-exclusion chromatography (SEC) revealed monomodal distributions with a clear shift to higher molecular weights after each monomer addition. However, in all cases molecular weights are low and do not differ significantly from each other as should be expected (Fig. 1c). Low molecular-weight tailing was observed after each block extension, ascribed to the accumulation of initiator-derived chains. In each step, dispersity continuously increased from 1.1 to 1.3. This increase in dispersity could be caused by the nature of different monomers used in the copolymerization (Table S2). Two different monomers were used for the first and third block. Vinyl protons overlapped with each other and the monomer conversions could not be calculated by $^1$H NMR spectra. Therefore, we have used GC to obtain more accurate conversion values. $^1$H NMR spectrum was used to identify the obtained copolymer qualitatively after purification (Fig. 1d).
Adamantyl-functionalized thermo-responsive triblock copolymer (P1) provided supramolecular host-guest interactions with sugar decorated and non-decorated β-CD derivatives. Dynamic light scattering (DLS) is a versatile tool to investigate the complex formation in solution. We employed DLS to obtain the hydrodynamic diameter ($D_h$) of both β-CD complexed thermo-responsive triblock copolymer coils in solution. Heating of the CD-complexed and non-complexed thermo-responsive triblock copolymers show reversible temperature-induced transition from solution to micelle. That is, under cloud point ($T_c$), the PNIPAM chain of the polymer kept water soluble, and no micelle was formed. As temperature increased, the PNIPAM chains dehydrated and aggregated through hydrophilic-hydrophobic interactions, thus acting as a hydrophobic core for the micelle formation. Firstly, $D_h$ of around 6 nm for P1, after heating above the $T_c$, aggregates are formed with $D_h$ around 240 nm (Fig. 1b, 2a).

Strong host-guest interaction above the LCST causes the formation of smaller particles. All β-CD complexed thermo-responsive triblock copolymers show similar $D_h$ above the LCST (Supplementary Fig. S11). For DLS measurements, the LCST is identified by a sudden change in particle size. Cloud points of all β-CD complexed thermo-responsive triblock copolymers were determined by DLS. DLS measurements show in almost all cases an increased cloud point of the β-CD complexed copolymers compared to the adamantyl-functionalized copolymer; P1 (Fig. 2a), which is an expected behavior of supramolecular block copolymers with a thermo-responsive block. A possible explanation for such a behavior might be the shielding of the hydrophobic end groups by the CD moiety, increasing water solubility of adamantyl-functionalized copolymers. One other possible explanation of low $D_h$ values can be the steric hindrance that reduce the micelle formation on the β-CD complexed thermo-responsive triblock.
copolymers. As it is noted, in general, incorporating β-CD derivatives causes host-guest interaction and alters micelle sizes. Furthermore, this affect was also confirmed by SEC chromatograms, upon complexation polymers shifted to against obtained Dₜ (Fig. 2b and Table S3). Moreover, to investigate the supramolecular complex formation and its effect on micelle size the host:guest ratio was monitored by DLS (Supplementary Fig. S12). It was observed that, less β-CD molecules increase the micelle size that allows the penetration of more polymer chains for micelle formation.

2D NOESY NMR was utilized to prove the molecular nature of the complex formation, which is a well-suited tool to study host/guest complex formation. While DLS experiments probe the molecular nature of the triblock copolymers, 2D NOESY NMR was performed to demonstrate the formation of the inclusion complex between adamantyl moieties and β-CD molecules. The 2D NOESY NMR spectrum shows cross-correlation peaks that can be assigned to the signals of the adamantyl moiety at 1.5, 1.7, and 2.1 ppm and the inner protons of β-CD between 3.7 and 3.8 ppm thus proving that a supramolecular complex between β-CD and adamantyl- is present. The inclusion complexation was shown to be reversible, as heating to 70 °C leads to an expulsion of the adamantanyl- and β-CD and cooling to 25 °C to reformation of the complex (Fig. 2c,d).

Lectin binding assays of the all three β-CD and α-D-mannose decorated β-CD complexed thermo-responsive triblock copolymers (P1-CDₐ, P1-CDₐ, and P1-CDₐ) with Concanavalin A (ConA), a lectin which has a good affinity for α-D-mannose, were then carried out to fully assess and compare binding efficiencies based on their structures and sugar densities. UV-Vis spectrophotometer is a simple and valuable tool for analyzing protein-carbohydrate complex formation. Kiessling and coworkers investigated ConA to the glucose-containing glycopolymer binding rate by a turbidimetric assay and measured absorbance changes at 420 nm in HEPES buffer. In this study, the rate of binding of ConA to P1-CDₐ, P1-CDₐ, and P1-CDₐ glycopolymers was assessed by a turbidimetric assay, measuring changes of the absorbance at 420 nm of appropriate solutions of the lectin and polymer in HEPES buffer at pH 7.4, using a UV-vis spectrophotometer both below (12 °C) and above (40 °C) the cloud point (Fig. 3a, 3b). In the preliminary turbidity assay, we found that the temperature had an influence on the interaction of ConA and mannosylated polymer residues. As shown in Fig. 4a, at low temperature, below LCST, glycopolymers P1-CDₐ, P1-CDₐ, and P1-CDₐ do not show a sharp increase in activity with increasing sugar functionalization, nor would such an increase be expected because these unassembled mannosylated triblock copolymers, the unimers, are not large enough to span multiple binding sites of ConA. Above LCST, micelles formed from the assembly of mannosylated triblock copolymers were encouraging. With the interaction between ConA and glycopolymer micelles increase in size causing significant scattering, thus leading to a turbid solution, which is an indication of the presence of binding events. When glycopolymers P1-CDₐ and P1-CDₐ were mixed with Con A in a buffer solution, the turbidity of the solution increased over time. This result is consistent with the formation of higher order, cross-linked complexes in the presence of ligands, and soon a precipitate was deposited. Precipitation can be rationalized on the basis of cross-linkage between the tetrameric ConA molecule and multivalent polymer molecule carrying α-D-mannose residues in each repeating unit. It was clearly seen that, elevated temperature accelerated the reaction significantly, where the non-active DMA groups were hidden inside and the affinity to ConA enhanced by the micellar structure. In addition, we believe glycopolymers in the micelle has a brush-like conformation, while unimeric chains in contrast are expected to have a coil structure. Rigid scaffolds for sugars are entropically favorable to enhance binding. Our understanding was that the binding ability of ConA with a α-D-mannose corona was greatly enhanced due to the stronger multivalent effect displayed by the sufficient numbers of α-D-mannose groups on the triblock copolymers, which is similar to the observation of Stenzel and coworkers whose experiments show that the micellar system has a high sugar density arranged in a spherical shape, where multivalency theories are deemed to be favourable. Fig. 3a-b also shows the relationship between sugar density on binding efficiency. When glycopolymers mixed at 40 °C with ConA, P1-CDₐ showed a higher increase in absorbance than P1-CDₐ. Polymer P1 ((PDMAₐ-PAdac)₋b-PNIPAM₋b- (PDMAₐ-PAdac)) contains four adamantyl moieties. When P1 formed a supramolecular complex with four equivalence of CDₐ molecule, obtained P1-CDₐ glycopolymer contains almost 28 α-D-mannose units, whereas P1-CDₐ glycopolymer contains only 4 α-D-mannose units. The results reveal that glycopolymer P1-CDₐ has initiated the clustering of ConA more rapidly relative to P1-CDₐ glycopolymer due to differences in the number of α-D-mannose units per chain. It is observed that P1-CDₐ interacts with ConA more efficiently. Since single sugar units only bind weakly to the lectin receptors, only multivalent binding will lead to lectin clustering and precipitation. As expected, the activities of supramolecular glycopolymers increase as the number of carbohydrates per macromolecule increases. A control experiment was carried out with the non-sugar decorated triblock copolymer (P1-CDₐ) with ConA. Results did not show any change in turbidity even at 40 °C, there was probably no appreciable interaction between P1-CDₐ and ConA since it carries no binding site for α-D-mannose. This proves the specific interaction between α-D-mannose and ConA and no hydrophobic force involved between P1-CDₐ and ConA (Fig 3b). To investigate the stability of the glycopolymer-ConA complexes, reversal aggregation assays were employed. Following the turbidity measurement methyl-α-D-mannopyranoside was therefore added to the turbid solution of glycopolymers P1-CDₐ, P1-CDₐ and ConA mixture, and a clear solution was restored as turbidity almost disappears after 10 min. When α-D-mannose was added, which acts as a competitive ligand, the more sensitive monovalent receptor expelled the α-D-mannose resides from the binding sites resulting in dissociation of the multivalent interaction. An immediate decline in turbidity was observed confirming that
binding between polymer and ConA was specifically caused by the presence of mannopyranoside. On the other hand, the action of α-D-mannose was rapid, requiring less than 30 min for complete dissolution of the precipitate (Fig 3c).

Quantitative precipitation (QP) experiments were carried out to gain insight into the stoichiometry between the α-D-mannose units available in the glycopolymers for binding to each ConA lectin. Controlling the amount of α-D-mannose on the glycopolymer surface controls the relative activity of the glycopolymers for the lectin. Measurement of the polymer concentration necessary to quantitatively precipitate the lectin from a solution with a known concentration of ConA allowed the determination of the average number of ConA tetramers bound by each polymer chain. In QP assays were plotted as a function of ConA concentration. The results of the precipitation assay (for glycopolymers P1-CD1, P1-CD7) are summarized in Figure 3d. As the temperature has an effect on binding efficiency, the precipitation assays were performed at 40 °C, which is above the LCST. The precipitation assay suggests that the surface of the glycopolymer micelle is saturated with ConA. However, the precipitation assay was performed at a significantly higher concentration of ConA. In one α-D-mannose containing experiment (P1-CD1) the ratio of the α-D-mannose functionalized triblock copolymer in the precipitates to Con A quickly increased with increasing amount of the α-D-mannose functionalized triblock copolymer. Since the concentration of ConA was high enough, the glycopolymer caused the precipitation of the lectin. The ratio of glycopolymer to Con A at the point that maximum precipitation of Con A is observed is considered to be the maximum stoichiometry of Con A to glycopolymer. In seven α-D-mannose containing experiment (P1-CD7) a maximum was reached, and then the ratio steadily decreased. This decreasing behavior was likely to be caused due to the ionic strength of the solution. The salt content influences sugar binding to ConA. High salt content in the assay buffer can lower the affinity of the protein to α-D-mannose, which might disrupt

Figure 3. Turbidity and quantitative assay results of the β-CD complexed triblock copolymer. (a) Turbidity measurements to monitor the sugar lectin interaction of supramolecular copolymers; P1-CD derivatives at 40 °C. (b) Turbidity measurements to monitor the cluster formation of α-D-mannose containing CD derivatives with equimolar adamantyl functionalized building block; P1 and ConA at different temperatures. (c) Turbidity measurement to monitor the cluster formation of α-D-mannose containing CD derivatives with equimolar adamantyl functionalized building block; P1 and ConA at 40 °C (straight line, before). Reduction of turbidity in the presence of 1-methyl-D-mannopyranoside (dashed line, after). (d) Quantitative precipitation results for sugar lectin binding of α-D-mannose containing CD derivatives with equimolar adamantyl functionalized building block; P1.
the sugar-polymer cross-links and reduce the amount of precipitate observed in the precipitation assays. Con A concentration has not changed during the precipitation assays of both P1-CD1 and P1-CD7 glycopolymers, Con A concentration was high enough for binding with glycopolymer P1-CD1, whereas was insufficient for binding with high sugar amount of P1-CD7. When sugar concentration and ionic strength of the solution is high enough, soluble glycopolymer-protein complexes may occur and only small aggregates would form under these conditions. The precipitation assays suggest that we can independently attenuate lectin binding affinity and lectin clustering.

Conclusions

In summary, we discuss the synthesis and characterization of novel adamantane-containing ABA type triblock copolymer as well as its self-assembly properties in water. The triblock copolymer is composed of two similar arms of poly(N,N-Dimethylacrylamide) (PDMA) and hydrophobic poly(adamantane-acrylate) (PAdac) and mid block of poly(N-isopropylacrylamide) (PNIPAM). By carefully selecting the polymerization degree of PDMA and PAdac, and consequently the hydrophobic/hydrophilic ratio, a specific amphiphilic glycopolymer has been identified that forms stable micelles in water as is clearly revealed by DLS. In these polymers, two different carbohydrates are involved in establishing noncovalent interactions: β-Cyclodextrin operates as a receptor for adamantane whereas α-D-mannose is acting as a ligand for ConA. The addition of lectins induces agglutination of the micelles without disrupting the micelle bilayer. Lectin precipitation requires high carbohydrate density at the micelle surface. Furthermore, micelle agglutination is reversed by the addition of competing binders for either of the noncovalent binding sites (cyclodextrin and lectin). In conclusion, polymer chemistry provides a versatile toolbox to allow the creation of various bioactive glycopolymer structures, which enables the careful fine-tuning of the interaction between lectins and glycopolymers.

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Notes and references

Sugar-Lectin Interaction

(PDMA₉-PAdac₁₀₉)ₐ-P(NIPAM)₆₀ₐ-P(PDMA₉-PAdac₁₀₉)

/β-CD-(Mannose)₃

Con A

408x380mm (96 x 96 DPI)