Synthesis of Conjugates Combining Macromolecular Brushes and Rigid Macrocycles

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Dedicated to Professor *Krzysztof Matyjaszewski* on the occasion of his 65th birthday

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Abstract: A synthesis route towards conjugates comprised of two macromolecular brushes and a central shape persistent macrocycle utilizing atom transfer radical polymerization techniques is presented. The extended brush conformation could be visualized by atomic force microscopy on mica substrates, which allows for the observation of the position of the macrocycle within individual brush-cycle-brush conjugates. As a result of the architecture and the properties of the combined structure elements a functional macromolecule is obtained that might regulate accessibility to a central shape persistent macrocycle via reversible brush-coil transitions.

Introduction

Proteins combine simple secondary structure elements such as α -helices, β -sheets or γ -turns into functional nano objects with hierarchical internal structure.[1] From this simple concept with a restricted number of structural building blocks a large functional space is generated, leading to bioorganic macromolecules that constitute catalysts, receptors, transporters, channels, or high performance construction materials.[2]

In synthetic macromolecular chemistry the diversity of discrete molecular objects that can be generated is rather restricted. Despite a few other more rare objects, macrocycles, molecular discs, globular dendrimers as well as molecular rods or helical foldamers constitute the most investigated, shape persistent molecular structures.[3-7] The combination of such objects to integrated molecular structures, with potential functions, however, remains difficult.

During the last decades, densely grafted macromolecules, referred to as “macromolecular brushes”, developed to an intensively studied class of macromolecules.[8-14] Macromolecular brushes exhibit a defined, three dimensional conformation and can thus be described as cylindrical nano-objects.[15] These macromolecules can be accessed via diverse synthesis routes.[16-19] In particular, the atom transfer radical polymerization (ATRP[20-23]),

combined with the “grafting from” approach, allows for precise synthesis and the control of a variety of molecular parameters.[8, 9, 15, 24-29] Macromolecular brushes offer a remarkable structural transition from a cylindrical to a globular brush conformation.[30-32] The transition, which can be induced by several stimuli such as lateral surface pressure, solvent quality, temperature, ionic strength or light, is fully reversible and leads to dramatic structural changes.[30, 33-36]

Shape-persistent macrocycles appear to be highly suited as a complementary nano-object to the cylindrical molecular brush structures.[37, 38] Macrocycles with distinct shape exhibit an interior cavity that is on average equal to the contour length of the ring-backbone divided by π . The relatively rigid ring structure prevents a collapse of the interior lumen and allows the precise positioning of functional groups. It was demonstrated in previous studies that the groups present in the internal cavity of a macrocycle, which can interact using hydrophobic effects and other non-covalent intermolecular interactions, such as electrostatic, charge-transfer, and hydrogen-bonding modes are adjustable, allowing for geometry and chemistry selective substrate binding.[39] Hence, shape-persistent macrocycles might have the potential to act as simple models for receptors or enzymatic centers.

Here, we present a straightforward synthesis route to combine macromolecular brushes with shape persistent macrocycles by using ATRP methodologies. While we focus on the analysis of the molecular species here, the brush-cycle conjugate might provide a potential mechanism to control accessibility to a precise functional center (cf. Figure 1), which might be developed further to a substrate specific host. The functional property of a macromolecular brush to perform a reversible structure transition might be utilized to control accessibility to the central structure element by burying it in a globular brush structure. The access restriction might be reversible as the extended cylindrical brush conformation enables potential accessibility to the central cycle.

Figure 1. Idealized structure and function of the brush-macrocycle-brush conjugate (for illustrative reasons macrocycle is drawn out of scale); extended cylindrical brush conformation with accessible cycle (left) and collapsed, globular brush conformation restricting the access to the cyclic structure (right).

Experimental Section

Materials: The initiator functionalized macro cycle (**In-MC-In I**) was synthesized from the corresponding macrocyclic diol that was described previously.[37, 40, 41] 2-(Trimethylsilyloxy)ethyl methacrylate (HEMA-TMS, 97.4% (GC)) and 4,4'-di(5-nonyl)-2,2'-bipyridyne (dNbpy) were prepared as described previously.[8] *n*-Butyl acrylate (*n*BuA, Aldrich, 98%) and copper(I) bromide (Aldrich, 98%) were purified according to standard procedures.[8] Copper(II) bromide (Aldrich, 99+%), all solvents and internal standards were used as received without further purification

Measurements: Weight average molecular weights and dispersities were determined by gel permeation chromatography (GPC) equipped with Waters microstyragel columns (pore size 10^5 , 10^4 , 10^3 Å), a differential refractometer (Waters Model 410) and GPC Win software. Measurements were conducted in THF (35 °C), at a flow rate of 1 mL/min. The setup was calibrated against low dispersity poly(methyl methacrylate) (pMMA) standards (PSS, Germany) with toluene as internal standard. Absolute molecular weights were determined on a GPC setup with a multi detection system combining a differential refractometer (Waters model 410), a multiangle laser light-scattering (MALLS) detector (DAWN model F) and a

differential viscometer (Viscotek model H502). Measurements were conducted in THF (35 °C) at flow rates of 1 mL/min. In addition to the GPC characterization, degrees of polymerization (DP) were estimated from monomer conversion data by assuming quantitative initiation for both macroinitiator and brush synthesis, $DP_{\text{conv}} = \Delta[M]/[I]_0$.

¹H-NMR characterization was performed on a Bruker 400 MHz spectrometer operating at 400.1 MHz. The measurements were carried out in chloroform-d₁ or methylenechloride-d₂.

Atomic force micrographs were recorded with a Nanoscope IIIa instrument (Digital Instruments, St. Barbara, USA) operating in the tapping mode. The measurements were performed at ambient conditions (in air, 56% relative humidity, 27 °C) using Si cantilevers with a spring constant of ca. 50 N/m, a tip radius of 10 nm, and a resonance frequency of about 300 kHz. The set-point amplitude ratio was maintained at 0.9 to minimize the sample deformation induced by the tip. The samples for tapping mode SFM measurements were prepared by spin casting on rotating substrate at 2000 rpm of dilute solutions of brush molecules in chloroform.

Synthesis: Synthesis of In-MC-In (**1**): 2-Bromoisobutyryl bromide (240 mg, 1.063 mmol) was added to a solution of the macrocyclic diol [41]) (80 mg, 0.053 mmol) and NEt₃ (110 mg, 1.063 mmol) in dry THF (20 mL). The mixture was stirred under argon at room temperature for 3 h and the product precipitated by adding cold methanol (100 mL). After filtration and drying under vacuum, **1** was obtained as a slightly yellow powder (75 mg, 79 %) mp > 200 °C dec; ¹H NMR (300 MHz, CDCl₃), δ: 1.32 (s, 36 H), 1.43-1.60 (m, 8 H), 1.66-1.78 (m, 8 H), 1.92 (s, 12 H), 3.99 (t, *J* = 6.15 Hz, 4 H), 4.19 (t, *J* = 6.48 Hz, 4 H), 7.02 (d, *J* = 1.57 Hz, 4 H), 7.34 (t, *J* = 1.43 Hz, 2 H), 7.48-7.57 (m, 28 H); GPC (THF) single peak at *M*_{peak} = 2400 g mol⁻¹ (vs. PS); MS (FD) *m/z* = 1803.2 [*M*⁺]. Synthesis of the 2-(trimethylsilyloxy)ethyl methacrylate (pHEMA-TMS) precursor ((pHEMA-TMS)-MC-(pHEMA-TMS); **II**): In a 25 mL Schlenk flask **I** (0.03 g; 0.033 mmol initiator groups), dNbpy (0.02 g, 0.05 mmol), toluene (15 mL) and HEMA-TMS (3.37 g, 0.017 mol) were added and stirred for 30 min. at

35 °C. The homogeneous reaction mixture was degassed by three freeze-pump-thaw cycles. After stirring for 1 h at r.t., CuCl (0.0025 g, 0.025 mmol) was added and the flask was placed in a thermostated oil bath at 90 °C. The polymerization was stopped after 46 h by cooling to r.t. and opening the flask to air. Relative monomer conversion was determined by GC (66% monomer consumption; $DP_{n,conv.} = 2 \times 170$). GPC-analysis was used to analyze molecular weight and dispersity ($M_{n,app.} = 6.3 \times 10^4$ g/mol and $\bar{D} = 1.22$). The GPC samples were not precipitated; rather they were diluted with THF, passed through a short alumina column to remove the copper catalyst and analyzed directly in THF against pMMA standards. The reaction mixture was diluted with 50 mL chloroform and filtered through an alumina column (10×2 cm). The solvent was removed under vacuum at 30 °C and the polymer / monomer mixture was dried under vacuum (2×10^{-2} mbar) for 24 h.

Synthesis of the poly(2-(2-bromopropionyloxy)ethyl methacrylate (pBPEM) macroinitiator (pBPEM-MC-pBPEM; **III**): The crude reaction mixture of **II** (assumed 17 mmol) was dissolved in 80 mL dry THF under nitrogen. Potassium fluoride (1.0 g; 17 mmol) was added followed by slow addition of 0.17 mL tetrabutylammonium fluoride (TBAF, 1 M in THF; 0.17 mmol) and 2.72 mL of 2-bromopropionyl bromide (25.7 mmol) over the course of 15 min. The reaction mixture was stirred at room temperature for 4 h, was precipitated into methanol/ice (50/50 v/v), redissolved in 100 mL CHCl₃ and filtered through activated alumina column (basic). The polymer was reprecipitated three times in hexane and dried in vacuum at 25 °C for 24 h. 1.33 g **pBPEM-MC-pBPEM** was obtained (90% yield). Complete conversion was determined by ¹H-NMR spectroscopy (absence of TMS-resonance $\delta = 0.2$ ppm (9H, bs, (H₃C)₃Si-)). ¹H-NMR (400 MHz, CD₂Cl₂, δ in ppm): 7.63-7.60 (ring H, non-resolved m, Ar-H); 7.59-7.53 (ring H, non-resolved m, Ar-H); 7.52-7.51 (ring H, non-resolved m, Ar-H); 7.36-7.34 (ring H, non-resolved m, Ar-H); 7.09-7.05 (ring H, non-resolved m, Ar-H); 4.52 (1H, quart., J = 6.8 Hz, Br-CH-CH₃); 4.37 (2H, bs, -O-CH₂-CH₂-O-CO-CH-Br); 4.19 (2H, bs, -O-CH₂-CH₂-O-CO-CH-Br); 1.85 (overlapped, d, J = 6.8 Hz, Br-CH-CH₃); 2.21-1.44

(overlapped, m, $\text{CH}_2\text{-C-CH}_3$); 1.26, 1.07, 0.91 (3H, 3 $\times$ bs, $\text{CH}_2\text{-C-CH}_3$). Resonances of the aromatic protons assignable to the macrocycle could be detected. The integration of the aromatic region (δ = 7.65-7.00 ppm) yields an overall integral intensity of $2.6\times 10^{-3}/\text{H}$. This was compared to the intensities of the pBPEM (1/H) allowing the estimation of the $\text{DP}_{\text{n,NMR}} = 2\times 190\pm 25$. GPC-analysis: $\text{M}_{\text{n,app.}} = 7.2\times 10^4$ g/mol, $\text{Đ} = 1.27$.

Synthesis of macromolecular brushes pBPEM-graft-pnBuA (p(BPEM-g-nBA)-MC-p(BPEM-g-nBA); **IV**): In a 50 mL Schlenk flask **III** (0.1 g; 0.38 mmol initiator centers), CuBr_2 (0.0021 g, 0.009 mmol) and dNbpy (0.31 g, 0.76 mmol) were purged three times with inert gas. Deoxygenated nBuA (19.43 g, 21.6 mL, 0.15 mol) and MEK (3 mL, 12 vol%) were then added and the reaction mixture was degassed by three freeze-pump-thaw cycles. After stirring for 1 h at r.t., CuBr (0.027 g, 0.190 mmol) was added and the flask was placed in a thermostated oil bath at 70 °C. The polymerization was stopped after 67 h by cooling to r.t. and opening the flask to air. GPC was used to analyze the molecular weight and the dispersity of the final sample that has not been precipitated ($\text{M}_{\text{n,app.}} = 4.0\times 10^5$ g/mol and $\text{Đ} = 1.32$). The polymer was purified as described above. Yield: 2.2 g isolated polymer (11% monomer conversion; $\text{DP}_{\text{sc;grav.}} = 40$).

Results and Discussion

The macrocycle (**I**) utilized in this study has a backbone structure comprising out of phenylene-ethynylene units (Figure 2).[42] It exhibits an interior of 0.8×1.2 nm, which is larger than that of a β -cyclodextrin and provides the possibility to position diverse functional groups specifically in the interior (Figure 2, I, I') or at the exterior (Figure 2, E, E').[43] The macrocycle (**I**) was accessed via multi-step organic synthesis, by oxidative acetylene cross-coupling reactions in combination with an orthogonal protecting group strategy as it was described previously.[40, 41] **I** exhibits four extraannulare *tert*-butyl substituents (Figure 2, position E') to increase solubility and two extraannulare 6-(1-hexanole) ether functionalities

positioned at opposite ring corners (Figure 2, position E). The ATRP initiator functionalities were introduced by esterification of the free hydroxyl groups with α -bromo isobutyric acid. The chemical structure was confirmed by $^1\text{H-NMR}$, GPC and MS analysis, proving the structure of the bivalent macrocyclic ATRP initiator **I**.

Figure 2. Shape persistent macrocycle on the basis of phenylene-ethynylene with intraannula (I, I'), extraannular (E, E') and adaptable (A, A') substituents. The functionalities of the macrocyclic ATRP initiator (**I**): I, I', A, A' = H; E' = *tert.*-butyl and E = $-\text{O}-(\text{CH}_2)_6-\text{O}_2\text{C}-\text{C}(\text{CH}_3)_2\text{Br}$.

The synthesis of the brush-macrocycle-brush system (**IV**) is outlined in Scheme 1. In a first polymerization step the bifunctional, macrocyclic initiator (In-MC-In, **I**) was used to start a polymerization of HEMA-TMS yielding the p(HEMA-TMS)-MC-p(HEMA-TMS) (**III**). Due to the poor solubility of **I** in the polar HEMA-TMS, 79 vol.% of toluene was necessary to achieve a homogeneous solution. This and the applied halogen switch that was required to provide a fast initiation with respect to the propagation, result in a fairly slow polymerization reaction. However, samples taken during the polymerization revealed a continuous shift of the GPC-traces towards higher molecular weights (cf. supporting

information). The apparent $\bar{D}$ increased in the early stage of the polymerization from 1.03 of the macrocyclic initiator (**I**) to about 1.2 and then remains relatively constant. All GPC-traces appear monomodal and no remaining macroinitiator was detectable. This indicates high initiation efficiency and shows that the majority of the polymer chains grow in both directions. Due to the continuous and complete shift of the GPC-traces, and the constant $\bar{D}$, the ATRP reaction appears to proceed in a controlled manner. The polymerization was stopped after 45.3 h and the monomer consumption was determined via GC, relative to toluene as internal standard. Based on the determined 66% conversion a $DP_{n,conv.} = 2 \times 170$ was calculated assuming a quantitative initiation reaction. The final product exhibits an apparent molecular weight of $M_{n,app.} = 6.3 \times 10^4$ and a $\bar{D} = 1.22$.

The transformation of **II** to the pBPEM-MC-pBPEM brush macroinitiator (**III**) was conducted by fluoride mediated deprotection of the HEMA hydroxyl functionalities, followed by esterification with α -bromopropionyl bromide (Scheme 1).[8] The chemical structure was confirmed by $^1\text{H-NMR}$ spectroscopy showing the absence of the trimethylsiloxy resonances and the stoichiometric presence of the ester groups. **III** was further characterized by GPC-analysis providing an apparent molecular weight of $M_{n,app.} = 7.2 \times 10^4$ g/mol and a $\bar{D} = 1.27$ (cf. supporting information). The increased dispersity was due to the appearance of a slight shoulder at lower elution volumes, indicating a minor amount of intermolecular transesterification.

Scheme 1. Conjugation of the macromolecular bushes towards the rigid macrocycle.

(Conditions: ATRP *i*: [HEMA-TMS]₀/[In-MC-In (**I**)]₀/[CuCl]₀/[dNbpy]₀ = 500/0.50/0.75/1.50, toluene = 79 vol.-%, 90° C; ATRP *ii*: [*n*BA]₀/[pBPEM-MC-pBPEM (**III**)]₀/[CuBr]₀/[CuBr₂]₀/[dNbpy]₀ = 400/0.500/0.500/0.025/1.050, MEK = 12 vol.-%, 70° C).

Based on the ¹H-NMR-analysis an average DP_{n,NMR} was estimated to be ~ 2×(190±25). This was accessed by comparing the overall integral intensity of the aromatic proton resonances, belonging to the 34 protons of the macrocycle to those of the characteristic pBPEM signals. The calculated value agrees well with that determined from the monomer conversion during the synthesis of **II** (DP_{n,conv.} = 2×170). This confirms a relative high initiation efficiency of the macrocyclic ATRP initiator, a well-controlled polymerization reaction and a quantitative functionality transformation process.

The brush macroinitiator **III** exhibiting multiple initiation sides was used to initiate the ATRP process of *n*BA. As a result of this “grafting from” polymerization the symmetric conjugate comprising two macromolecular brushes and the rigid macrocycle (brush-MC-

brush) was obtained (Scheme 1). Due to the solubilizing properties of the pBPEM segments of **IV** the *n*BuA polymerization proceeds under standard conditions as it is summarized in (Scheme 1).[8] After 67 hours the polymerization was stopped and gravimetric analysis of the precipitated product reveals 11% monomer conversion. Based on this the average degree of polymerization of the side chains could be calculated to be $DP_{n,grav.} \sim 40$ assuming quantitative initiation. The GPC-analysis of the final polymer (**IV**) reveals a molecular weight of $M_{n,app.} = 4.0 \times 10^5$ g/mol and a $\bar{D} = 1.32$. The GPC-trace shifts completely towards higher molecular weights (cf. Supporting Information). In addition, no low molecular weight tailing or high molecular weight shoulder formation was obvious, indicating a controlled polymerization reaction.

AFM molecular imaging techniques have proved to be highly suitable for the analysis of dimensions of macromolecular brushes.[44, 45] To investigate the molecular structure of **IV**, polymer samples were cast onto Mica substrates. The adsorbed macromolecules can be imaged in high resolution (Figure 3). The AFM micrograph clearly shows the backbones and the poly(*n*-butyl acrylate) side chains as a visible corona of the brush, due to the strong interactions of the poly(*n*-butyl acrylate) side chains with the alumina silicate surface.

Figure 3. AFM micrograph of *IV* prepared by spin-coating of a 1 g/L solution in CHCl₃ on Mica substrate and inset showing the defects occurring in the homogeneous brush structure which are attributed to the central macrocycle (tapping mode; 100 nm scale).

Figure 3 shows that *IV* adopts an expanded, worm-like conformation, which is typical for molecular brushes with poly(*n*-butyl acrylate) side chains adsorbed on a substrate.[9] The center from which the brush arms originate is evident for many of the molecules. In several structures, the position of the macrocycle can be identified as an obvious interruption in the bottlebrush contour (cf. Figure 3, inset). This corroborates well-controlled synthesis of the 2-arm polymer bottlebrush by the ATRP polymerization. Moreover, the images suggest the ease of accessibility of the ring structure if the brushes adopt the extended conformation. Recently, it was demonstrated that the average molecular weight and the molecular weight distribution of macromolecular brushes can be accessed accurately by statistical evaluation of AFM micrographs.[45] The obtained values could be compared to those of a multi detection GPC analysis with online light scattering (MALLS) and to the values calculated based on monomer conversion. Table 1 summarizes the estimated values from monomer conversion, the GPC-MALLS analysis results and the statistical AFM data.

Table 1. Molecular weight characterization of *III* and *IV* from GPC and AFM Measurements

Sample	Monomer conversion	MALLS-GPC		RI-GPC		AFM	
	$M_n \cdot 10^6$ g/mol	$M_n \cdot 10^6$ g/mol	$\bar{D}$	$M_n \cdot 10^6$ g/mol	$\bar{D}$	$M_n \cdot 10^6$ g/mol	$\bar{D}^*$
<i>III</i>	0.09	0.15	1.6	0.07	1.27	n.d.	n.d.
<i>IV</i>	1.83	0.95	1.6	0.40	1.32	1.8	1.08

* $\bar{D}$ was determined from the length distribution as L_w/L_n

While the monomer conversion based on GC and gravimetry enables the prediction of brush structures with $DP_{n,bb,conv.} = 2 \times 170$ and $DP_{n,sc,conv.} = 40$, the GPC-MALLS analysis reveals substantially longer brushes with $DP_{n,bb,MALLS} = 2 \times 280$. The analysis of AFM micrographs of sample *IV* (Figure 3) allows for accurate determination of the number average molecular weight of the brushes as $M_{n,AFM} = 1.8 \times 10^6$, which is in excellent agreement with the value that could be calculated from monomer conversion. We also measured the number average length and length dispersity of the imaged bottlebrushes as $L_n = 137 \pm 3$ nm and $L_w/L_n = 1.1$, respectively. Furthermore, given the clear identification of the position of the macrocycle within the brush structures, we have separately analyzed the length distribution of the two brush “arms” and obtained $L_{n,arm} = 69 \pm 1$ nm and a remarkable low distribution of $L_{w,arm}/L_{n,arm} = 1.15$. This indicates a quite controlled positioning of the macrocycle within the brush structures and confirms that the synthesis of *III* proceeds in a controlled manner. From the total contour length $L_n = 137 \pm 3$ nm, a $DP_{n,bb,AFM} = 2 \times 274$ could be calculated assuming a fully extended all-trans backbone with 0.25 nm/repeat. Therefore, the AFM data of the backbone length are in very good agreement with the GPC-MALLS results. Besides the molecular weights also the polydispersity of *IV* was accessed by statistic evaluation of AFM micrographs (cf. supporting information). The average degree of polymerization of the side chains can be calculated as $DP_{n,sc,AFM} = M_{n,AFM} / (DP_{n,bb,AFM} \times M_{BA}) = 26$, which is below $DP_{n,sc,conv.} = 40$ calculated from monomer conversion.

In summary, a well-defined conjugate was prepared, combining a shape persistent macrocycle and two lateral macromolecular brushes, using a “grafting from” approach and atom transfer radical polymerization (ATRP). The four-step synthesis strategy comprises the synthesis of a difunctional, macrocyclic ATRP initiator (In-**MC**-In). This was used to start the polymerization of HEMA-TMS yielding the p(HEMA-TMS)-**MC**-p(HEMA-TMS) that was

transformed into the brush macroinitiator (p(BPEM)-**MC**-p(BPEM)). The final brush cycle conjugate (p(BPEM-*g-n*BA)-**MC**-p(BPEM-*g-n*BA)) was obtained in a well-defined manner by grafting *n*BA from poly(BPEM) segments using the ATRP process. The molecular structures of the brush segments could be visualized with atomic force microscopy (AFM). High-resolution AFM allows the indirect visualization of the macrocyclic segment, when a cylindrical brush conformation was adapted. This distinct irregularity in the brush structure might indicate the accessibility of the macrocyclic structure. This might pave the way to utilize the transition of molecular brushes from an extended cylindrical brush conformation to a collapsed globular structure to actively control the accessibility of the central macrocycle. Even if the macrocycle applied in this study does not exhibit specific recognition properties, it can potentially be functionalized with diverse, precisely positioned functionalities yielding a size and chemistry selective host moiety.

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