Molecular Objects

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The Largest Synthetic Structure with Molecular Precision: Towards a Molecular Object**

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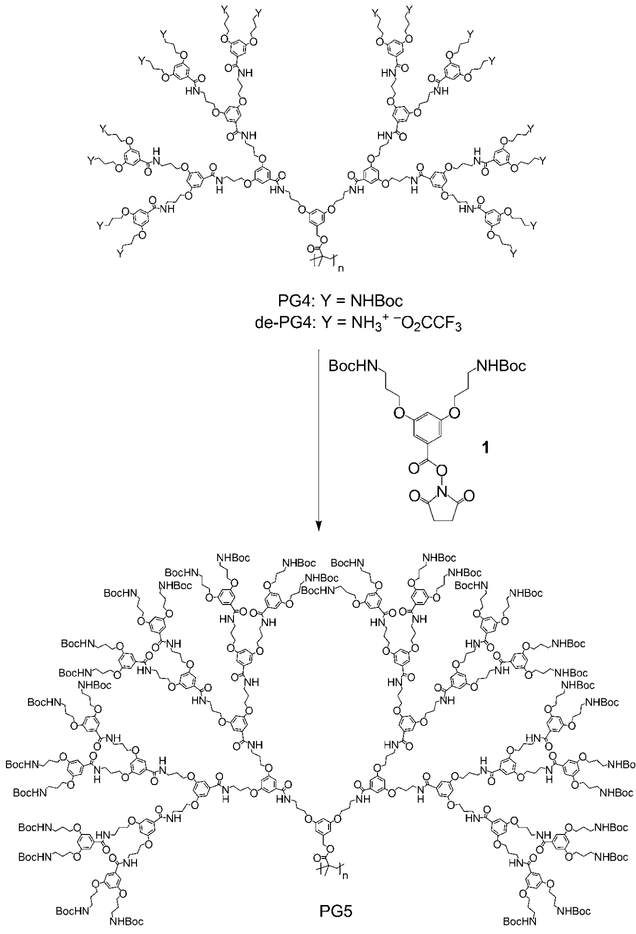
Since the advent of their discipline, organic chemists have sought to imitate biology through synthesis. This challenge combines four themes: chemical structure,[1] function,[2] size,[3] and molecular shape.[4] While structure and function are better understood, size and shape remain challenging. So far, chemists have not succeeded at making well-defined molecules as large as those found in biology—the highest-molecular-weight structurally precise synthetic polymer, a polystyrene, has a mass of only 40×10^6 Da,[5] a tiny fraction of the size of the largest DNA molecules. The control of shape in large synthetic molecules is even less advanced. This feat is routine for biology—even the simplest organisms have well-defined shapes, as exemplified by the rodlike tobacco mosaic virus (TMV). Indeed, to the chemist, the TMV is a paragon: a massive supramolecule with perfect control of chemical structure, function, size, and molecular shape. We report herein a dendronized polymer[6] that approximates the size and cylindrical shape of the TMV, thus advancing these chemical frontiers. Our synthesis relies on standard polymerization methods followed by radial expansion by using methods pioneered by Vögtle[7] and Tomalia.[8] First-generation dendrons were affixed to peripheral amino groups of the fourth-generation dendronized polymer, $PG4_{long}$,[9] by using



Scheme 1. Synthesis of PG5. Chemical structure of the starting polymers $PG4_{short}$ and $PG4_{long}$ and their conversion to the fifth generation by deprotection and reaction with the active ester dendron **1**.

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Merrifield-type active ester amidation[1] to give the fifth-generation macromolecule, PG5$_{long}$ (Scheme 1). This synthesis requires 170000 bond-forming reactions on a single molecule. From the known extent of conversion, the M_w of PG5$_{long}$ is estimated to be 200×10^6 Da. Proving the successful accomplishment of the synthesis was challenging. The extent of conversion in the Merrifield transformation that gave PG4$_{long}$ was demonstrated by multi-angle laser light scattering (MALLS) molar mass determination and by UV absorption measurements of labeled samples derivatized with chromophores at unreacted sites.[10,11] The shape of PG5 was investigated on solid substrates by AFM, TEM, and scanning electron microscopy (SEM), and in solution by cryo-TEM and small-angle neutron scattering (SANS). A shorter version of the compound (PG5$_{short}$) was used for the latter experiments. The shape of the macromolecules was also directly compared with TMV (Figure 1).

PG4$_{long}$ was obtained from PG1$_{long}$ through an iterative synthesis.[9] The polymer had a weight average of $M_w = 100 \times 10^6$ Da, a corresponding degree of polymerization $P_w = 17600$, a radius of gyration $R_g = 280$ nm, and a hydrodynamic radius $R_h = 158$ nm. The shorter analogue, PG4$_{short}$, had $M_w = 12 \times 10^6$ Da and $M_n = 7 \times 10^6$ Da, as determined by gel permeation chromatography. The integrated structural perfection from the respective PG1 amounted to 99.4% for PG4$_{short}$ and to 98.5% for PG4$_{long}$. MALLS and UV labeling showed that the starting material PG4$_{long}$ contained 170000 peripheral amine groups (for details, see the Supporting Information).

The synthesis of PG5$_{short}$ and PG5$_{long}$ involved the removal of Boc protecting groups to give the charged de-PG4$_{short}$ and de-PG4$_{long}$ followed by an exhaustive dendronization reaction with the active ester dendron **1** (Scheme 1). AFM analysis of hundreds of single de-PG4$_{long}$ chains on mica did not indicate main-chain scission, as was observed for bottlebrush polymers.[6,12,13] The conversion of the dendronization reaction was 97.1% for PG5$_{long}$ and 97.9% for PG5$_{short}$. This result leads to an average overall structural perfection of PG5 from PG1 of 94.3% (long) and 96.6% (short). From this extent of conversion and the known molecular weight of PG4$_{long}$, we calculate a M_w of 200×10^6 Da for PG5$_{long}$.

The shape of PG5$_{long}$ was first investigated by comparison of AFM tapping mode height images of air-dried, mixed samples of PG1$_{long}$–PG4$_{long}$[9] with PG5$_{long}$ on mica. Although tapping mode AFM heights (h_{app}) depend on the experimental conditions, their comparison is meaningful if the tip–object interaction is comparable for all substrates. We find: PG1$_{long}$: (0.4 ± 0.1) nm, PG2$_{long}$: (1.0 ± 0.1) nm, PG3$_{long}$: (2.2 ± 0.1) nm, PG4$_{long}$: (4.0 ± 0.4) nm, PG5$_{long}$: (6.2 ± 0.3) nm. For PG5$_{long}$ on highly oriented pyrolytic graphite (HOPG) $h_{app} = (6.5 \pm 0.3)$ nm was observed (not shown). All objects can be assigned to a particular generation (for large-scale images, see Figure S6 in the Supporting Information) and clear steps in size differentiate the generations.[14] The height increase from PG1$_{long}$ to PG5$_{long}$ is 6 nm, which suggests that PG5$_{long}$ does not flatten out as much as bottlebrush polymers on the mica substrate.[15,16] Next, absolute heights (h_{abs}) were determined by TEM for air-dried PG5$_{long}$ on mica to give $h_{abs} = (7.3 \pm 0.2)$ nm and absolute widths (w) were determined by SEM for freeze-dried PG5$_{long}$ on amorphous carbon to give $w = (9.4 \pm 0.3)$ nm. The h_{abs} (TEM) on mica is approximately 1 nm higher than h_{app} (AFM); this discrepancy is not unusual, as tapping mode AFM underestimates heights.[17,18] The h_{abs} and w values were compared to a simple cylinder model. The diameter of this cylinder is $d = 9.1$ nm, assuming 1) a projected length of the backbone repeat units of 2.38 Å instead of 2.50 Å for a backbone in the all-trans conformation and 2) an estimated density of $\rho = 1.2\ \mathrm{g\,cm^{-3}}$. Thus, PG5 on mica is flattened by 1.8 nm (20%) when air-dried. Visual comparison of PG5$_{long}$ and the TMV by AFM is striking (Figure 1d,e). Indeed, PG5$_{long}$ looks like TMV: its size, aspect ratio, and gross structure are similar. This suggests PG5 to be a molecular object, that is, a molecule the shape of which is

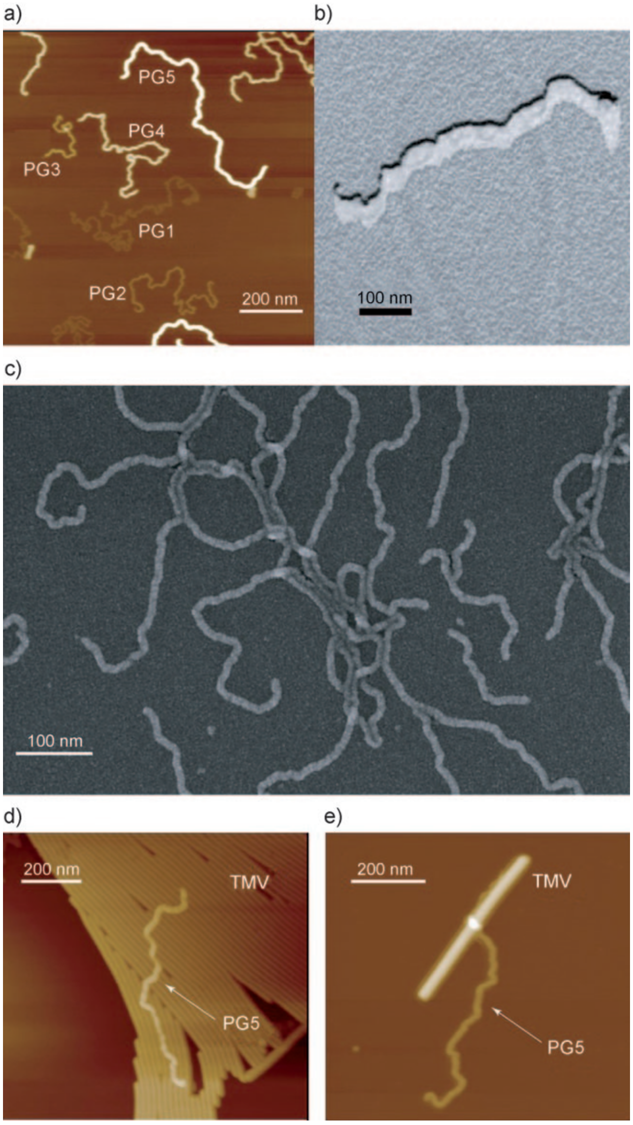

Figure 1. Thickness and width analysis of PG5$_{long}$. a) AFM tapping mode height images of coprepared PG1$_{long}$–PG5$_{long}$ on mica. b) TEM replica image of a unidirectional W-shadowed air-dried single chain. c) SEM image of a freeze-dried sample for width determination. d, e) AFM tapping mode height images of TMV and a single PG5$_{long}$ strand. The synthetic polymer is shown on an ordered monolayer array of TMV (d) and embracing a single TMV (e).

retained irrespective of its environment,[19] and to which an envelope can be assigned.

The diameter of $PG5_{short}$ in solution was determined by SANS and cryo-TEM. Analysis of the scattering (Figure 2 a), assuming a homogeneous density and a solvated, wormlike polymer,[20] gave a diameter of $d \approx 10$ nm. A more advanced cross-section analysis[21] gave the cross-section density distribution shown in Figure 2 b, which is consistent with the results from the simulations also shown in Figure 2 b. The diameter of $PG5_{short}$ in solution ($d = 10$ nm) is similar to the width of the macromolecule when freeze-dried (SEM, (9.4 ± 0.3) nm) and the diameter of the model cylinder ($d = 9.1$ nm). Together with the height of the air-dried macromolecules ($d = 7.3$ nm), it is concluded that the dimensions of PG5 both in solution and when dried on a solid substrate are comparable. We believe this to be a unique finding for synthetic polymers. This finding is qualitatively consistent with the cryo-TEM image (Figure 2 c), which shows a diameter of $PG5_{short}$ of at least $d = 7$ nm. Another SANS study (data not shown) confirms that chains of increasing generations are stiffer. In solution, the persistence length l_p of the thick chain ($PG5_{short}$, $l_p \approx 30$ nm) is eight times larger than that of a thin chain ($PG1_{short}$, $l_p \approx 4$ nm). Figure 2 d shows a snapshot of the simulation from which the profile in Figure 2 b was calculated.

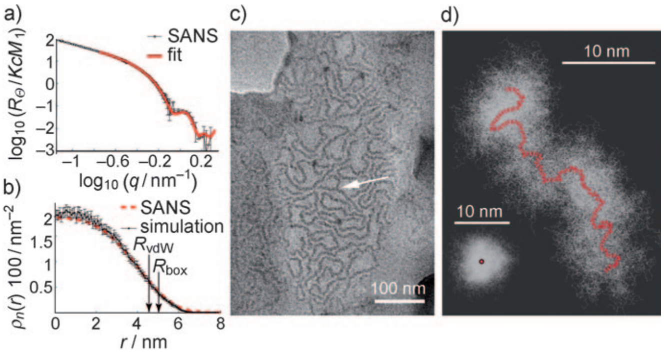

Figure 2. Characterization of $PG5_{short}$ in solution. a) SANS scattering curve in $[D_4]$MeOH (K = contrast factor, c = concentration, M_1 = monomer molecular mass). b) Density profile derived from (a) together with simulation results (see the Supporting Information for further details). c) Phase-contrast cryo-TEM image in dioxane that shows the cross-sectional diameter and the native solution conformation. The white arrow points towards a branching site. d) Snapshot of the simulated PG5 with 250 dendrons. Inset: cross-sections used to evaluate the density profile shown in (b).

$PG5_{long}$ is the largest covalent macromolecule with a precisely controlled structure that has ever been synthesized. This molecule is larger than amylopectin, which is amongst the largest biomacromolecules (ca. 160×10^6 Da), and the hyperbranched polymers (1×10^6 Da).[22] The related “graft-on-graft” polymers reach higher molecular weights (500×10^6 Da),[23,24] but as in the case of the hyperbranched polymers, their chemical structure and shape are less well defined. The mass increase associated with the post-polymerization dendronization is approximately 100×10^6 Da, which is larger than that of any polymerization leading to a structurally defined product.[5] Our synthesis is short and relies on established methods. Purification is simple: the huge weight difference between product and reagents allows for filtration through silica gel and renders any Merrifield-type solid-phase procedures unnecessary.

In contrast to biology and supramolecular chemistry of nano-objects, which both create shape involving self-assembly,[25,26] we create the shape of PG5 by using covalent bonds and steric congestion. Our approach is crude but nonetheless provides macromolecules with a persistent shape that is absent from other synthetic, macromolecular architectures when adsorbed as individual entities on solid substrates.[16] $PG5_{long}$ is the largest synthetic molecular object[19] with a defined shape.[27,28] The surface of these dendronized polymers can be modified for various applications.

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