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COMMUNICATION

Star Block-Copolymers: Enzyme-Inspired Catalysts for Oxidation of Alcohols in Water

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Clément Mugemana, Ba-Tian Chen, Konstantin V. Bukhryakov and Valentin Rodionov*^aReceived 00th December 2013,
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A number of fluoruous amphiphilic star block-copolymers containing a tris(benzyltriazolylmethyl)amine motif have been prepared. These polymers assembled into well-defined nanostructures in water, and their mode of assembly could be controlled by changing the composition of the polymer. The polymers were used for enzyme-inspired catalysis of alcohol oxidation.

Nature's enzymes are complex polymer catalysts that are capable of facilitating thousands of challenging reactions with perfect fidelity and selectivity. This exquisite level of functionality is achieved through precise, programmed folding into intricate tertiary structures¹ and close participation of cofactors, prosthetic groups and metal ions. Often, the active sites and cofactor binding pockets are separated from the bulk aqueous phase and buried in the hydrophobic interior of the protein.

Recent publications explored the use of chemist-made macromolecules, either branched^{2,3} or single-chain,⁴ as enzyme-inspired catalysts. Rational design of linear polymers with protein-like tertiary or quaternary structures and catalytic function remains an elusive (but tantalizing) goal.⁵ Materials with branched topologies are amenable to structural engineering, at the cost of greater synthetic complexity (dendrimers) or increased heterogeneity (star polymers).

In this study, we present a pathway to enzyme-inspired catalytic materials based on star block-copolymers with limited branching. These polymers incorporate hydrophilic, superhydrophobic, and polydentate metal-binding characteristics. The interplay of these structural characteristics determines the mode of self-assembly and the catalytic competence of the macromolecules.

The Cu/TEMPO (2,2,6,6-tetramethyl-1-piperidine-N-oxyl) system, introduced by Semmelhack⁶ in 1984 and further developed by Sheldon,⁷ Stahl⁸ and others,⁹ has emerged as one of the most

attractive catalysts for selective aerobic oxidation of primary alcohols.¹⁰ The established protocols for Cu/TEMPO catalyzed alcohol oxidation strongly favor organic solvents, especially acetonitrile.⁸ We aimed to design an enzyme-inspired functional macromolecular architecture that could enable the transfer of this catalytic system to pure water. Such a transfer could enable large-scale applications of Cu/TEMPO, while circumventing the usual safety concerns associated with combining oxygen and organic solvents.

We envisioned that amphipolar, globular assemblies, with metal-binding sites buried inside hydrophobic cores (Figure 1a), could provide the necessary site isolation of the catalytic metal centers.¹¹ However, the accumulation of hydrophobic reaction products inside such assemblies would be undesirable, as the transfer of additional alcohol substrate to the active site would be hindered. To avoid this potential problem, we chose "everything-phobic" fluoruous monomers as building blocks for the cores of our prospective catalysts.^{12,13} Understanding that perfluorocarbons and their emulsions in water are capable of dissolving substantial amounts of O₂,^{14,15} we reasoned that a fluoruous core of a polymer globule could pre-concentrate oxygen in the vicinity of the active metal site.

We selected the tris(benzyltriazolylmethyl)amine (TBTA) motif⁶ as a metal-binding site, due to its ability to stabilize the Cu^I oxidation state, its versatile coordination chemistry¹⁷ (Figure 1b), and its easy synthetic accessibility. Starting with the TBTA-based polymerization initiator **1** (Figure 1c), we proceeded to synthesize a number of superhydrophobic three-arm polymers via nitroxide-mediated polymerization (NMP).¹⁸ We chose this mode of polymerization over synthetically simpler atom-transfer radical polymerization,¹⁹ as the latter can be affected by the presence of Cu^I binding sites in the target polymers.

Pentafluorostyrene (PFS), 2,2,3,3,4,4,4-heptafluorobutyl acrylate (PFBA) and 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate (PFDA) were

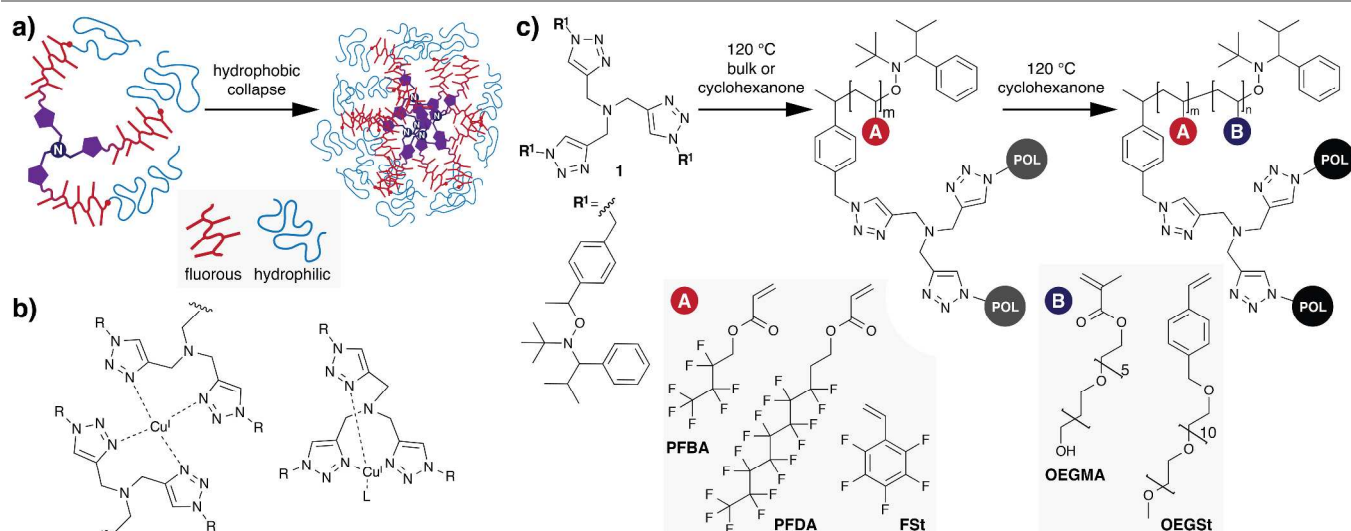


Figure 1. a) Design for an amphiphilic block copolymer micelle with metal binding sites at the core. b) Some of the modes of coordination possible for a TBTA-type ligand. c) Synthesis of amphiphilic star block copolymers.

Table 1. Characterization of amphiphilic star block copolymers

Entry	Polymer ^a	M _n ^b	M _w ^b	PDI _{SEC}	DLS (nm) ^c	PDI _{DLS}	AFM (nm) ^d	TEM (nm)
1	(PFS ₇ - <i>b</i> -OEGSt ₃) ₃	5900	6600	1.12	20(90%) / 160(10%)	0.23	76 ± 10	20 ± 2 ^f
2	(PFS ₁₀ - <i>b</i> -OEGSt ₄) ₃	11200	13216	1.18	28(30%) / 135(70%)	0.22	44 ± 6	26 ± 2 ^f
3	(PFS ₁₆ - <i>b</i> -OEGSt ₄) ₃	12400	15130	1.22	70(70%) / 130(30%)	0.24	46 ± 4	42 ± 4 ^e
4	(PFBA ₂₀ - <i>b</i> -OEGSt ₄) ₃	12800	16400	1.28	70	0.36	100 ± 14	120-350 ^f
5	(PFDA ₄ - <i>b</i> -OEGSt ₄) ₃	11500	14720	1.28	20(90%) / 140(10%)	0.54	74 ± 4	22 ± 1 ^f
6	(PFS ₁₆ - <i>b</i> -OEGMA ₃₀) ₃	13500	16470	1.22	120(42%) / 200(58%)	0.22	70 ± 6	44 ± 8 ^f
7	(PFBA ₇ - <i>b</i> -OEGMA ₁₈) ₃	11230	13360	1.19	30(48%) / 300(52%)	0.28	70 ± 8	58 ± 10 ^e
8	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	13200	15970	1.21	30(89%) / 250(11%)	0.29	88 ± 4	52 ± 10 ^e
9	(PFDA ₄ - <i>b</i> -OEGMA ₃₀) ₃	11000	12320	1.12	40(86%) / 255(14%)	0.44	76 ± 10	24 ± 4 ^f

^a Degree of polymerization determined by ¹H NMR. ^b Determined by SEC (calibration against linear polystyrene). ^c Hydrodynamic diameters determined by dynamic light scattering (DLS) in water at 1 g·L⁻¹. For multimodal distributions, diameters are estimated based on intensity distribution, and relative ratios based on volume distribution. ^d Diameters of aggregates determined from AFM height images. ^e Diameter of aggregates determined from TEM images. ^f Diameter of aggregates determined from cryo-TEM images.

polymerized with initiator **1**, either in the bulk or in cyclohexanone at 120 °C. For each fluorinated monomer, we aimed to create at least two macroinitiators with different degrees of polymerization (DP) to evaluate the effects of the hydrophobic core size on catalytic competency (Table S₃, ESI). A DP higher than 4 could not be reached for PFDA due to the anomalously low solubility of resulting polymers.

The hydrophobic macroinitiators were used for the polymerization of two hydrophilic monomers, *p*-oligo(ethylene glycol) styrene (OEGSt) and oligo(ethylene glycol) methacrylate (OEGMA). OEGSt was polymerized in cyclohexanone, leading to a range of amphiphilic star copolymers (Table 1, Entries 1-5). Although NMP is rarely a polymerization of choice for methacrylates,²⁰ we obtained a higher DP for the copolymerization of OEGMA than we did for styrenic OEGSt (Table 1, Entries 6-9). Size exclusion chromatography (SEC) on all the copolymerization reactions indicated a clean shift of population towards a higher number-average molecular weight (M_n), with little to no tailing (although limited aggregation was observed for (PFDA₄-*b*-OEGSt₄)₃ and (PFBA₂₀-*b*-OEGSt₄)₃).

We investigated the self-assembly modes of the copolymers by obtaining cryogenic transmission electron microscopy (cryo-TEM) and atomic force microscopy (AFM) images of their aggregates. Spherical aggregates with diameters between 20 and 50 nm were the main type

of assemblies for (PFS₇-*b*-OEGSt₃)₃, (PFS₁₀-*b*-OEGSt₄)₃, (PFBA₇-*b*-OEGMA₁₈)₃, (PFBA₁₄-*b*-OEGMA₃₀)₃, (PFDA₄-*b*-OEGMA₃₀)₃, and (PFS₁₆-*b*-OEGMA₃₀)₃ (Figure 2 a-c, and Sections 4.6-7, ESI). AFM phase images (Figure 2 b and Section 4.6, ESI) revealed the separation between the hydrophobic aggregate cores and hydrophilic coronas. The size of the aggregates observed was consistent between cryo-TEM and AFM, taking into account the flattening/spreading of soft material on the substrate (Table 1 and Table S₂, ESI).

We found that by increasing the weight fraction of the fluorinated block in the copolymer, more complex morphologies could be triggered. (PFBA₂₀-*b*-OEGSt₄)₃ copolymer, which contains 67 wt % of the fluorinated monomer, assembled into well-defined vesicles, unilamellar (Figure 2 f), as well as multilamellar (Figure 2 g). The thickness of the vesicle boundaries was ca. 9 nm, which suggests that they were formed by a single layer of macromolecules. The AFM image of (PFBA₂₀-*b*-OEGSt₄)₃ showed that some vesicles remain intact even in the partially dry state. Objects with diameters ranging from ca. 60 to 120 nm and with heights from 30 to 40 nm were observed. In addition to the aggregates with pronounced height, flat structures of similar lateral dimensions could be seen (Figure 2 d-e). We presume that some of the vesicles retain their interior water when deposited on the substrate, while others “deflate” and spread. Unlike

Table 2. Catalytic oxidation of benzyl alcohol in the presence of block-copolymer micellar aggregates.

Entry	Block Copolymer	Time [h]	TEMPO [mol %] ^a	DMAP [mol %] ^a	CuSO ₄ [mol %] ^a	Polymer [wt %]	Conversion [%] ^b
1	-	36	1	5	0.2	-	<1
2	-	44	2.5	50	2	-	5
3	(PFS ₁₀ - <i>b</i> -OEGSt ₄) ₃	36	1	5	0.2	0.04	6
4	(PFBA ₂₀ - <i>b</i> -OEGSt ₄) ₃	36	1	5	0.2	0.04	28
5	(PFS ₁₆ - <i>b</i> -OEGMA ₃₀) ₃	36	1	5	0.2	0.04	5
6	(PFBA ₇ - <i>b</i> -OEGMA ₁₈) ₃	36	1	5	0.2	0.04	25
7	(PFDA ₄ - <i>b</i> -OEGMA ₃₀) ₃	36	1	5	0.2	0.04	6
8	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	36	1	5	0.2	0.04	22
9	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	37	2.5	25	4	3.11	46
10	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	31	2.5	25	2	1.56	53
11	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	21	5	25	2	1.27	61
12	(PFBA ₁₄ - <i>b</i> -OEGMA ₃₀) ₃	44	2.5	50	2	1.56	90

^a Relative to benzyl alcohol. ^b Determined by ¹H NMR.

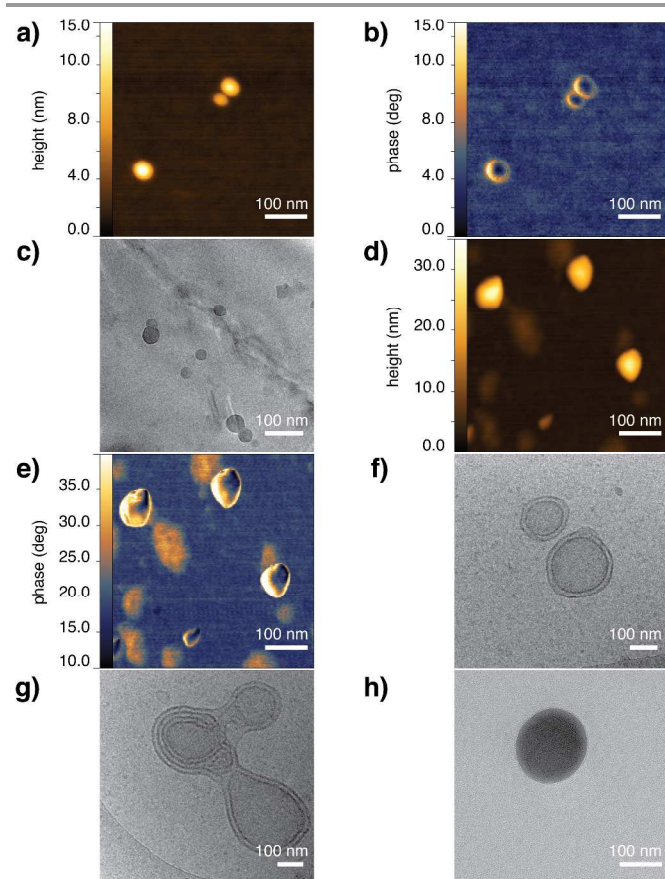


Figure 2. a) and b) AFM height and phase images of (PFS₁₆-*b*-OEGMA₃₀)₃ block copolymer micelles spin-coated onto Si substrate. c) Cryo-TEM image of (PFS₁₆-*b*-OEGMA₃₀)₃ block copolymer micelles in water. d) and e) AFM height and phase images of (PFBA₂₀-*b*-OEGSt₄)₃ vesicular structures. f) and g) Cryo-TEM images of (PFBA₂₀-*b*-OEGSt₄)₃ vesicular structures, unilamellar and multilamellar. h) Cryo-TEM image of a (PFBA₂₀-*b*-OEGSt₄)₃ vesicle in the presence of CuSO₄.

spherical aggregates, the “deflated” vesicles show no core-corona contrast in the AFM phase image. The vesicular structures persisted after addition of CuSO₄. A significant amount of Cu was sequestered in the vesicle’s boundary, as is evidenced by the increased contrast in the cryo-TEM image (Figure 2 h).

Examination of aqueous polymer solutions by DLS (Section 4.5, ESI) revealed 20-70 nm aggregates in agreement with AFM and TEM images, as well as larger species with hydrodynamic diameters varying from ca. 100 to 300 nm. It is likely that the larger species are not abundant enough to feature prominently in TEM images, and unravel/disassemble when spread on AFM substrates. Much smaller, 5-20 nm species were observed in the polymer solutions prepared in good organic solvents, such as DMF and THF (Figures S41-S42, ESI).

The catalytic competency of the star polymers was evaluated for a Cu/TEMPO-catalyzed alcohol oxidation reaction, using a modification of the protocol originally reported by Stahl.⁸ Polymers were dispersed in water, the “cofactors” TEMPO and 4-dimethylaminopyridine (DMAP) were added, and the solutions were treated with ultrasound. CuSO₄ and benzyl alcohol were added to start the reaction. The rate of oxidation was negligible in the absence of the star polymers (Table 2, Entries 1 and 2). Addition of PFS and PFDA copolymers led to a marginal improvement of reaction yields (Table 2, Entries 3, 5 and 7). To our delight, the TEMPO/Cu system became catalytically competent in the presence of star polymers with PFBA hydrophobic cores (Table 2, Entries 4, 6 and 8). The nature of the hydrophilic monomer, the degree of polymerization, or the weight fraction of the fluorinated monomer had little influence on the catalytic competency: (PFBA₂₀-*b*-OEGSt₄)₃, (PFBA₇-*b*-OEGMA₁₈)₃, and (PFBA₁₄-*b*-OEGMA₃₀)₃ were similar in their capacity for catalyzing alcohol oxidation. Upon further optimization of reaction conditions (Table 2, Entries 9-12), an almost quantitative yield of benzaldehyde was obtained in the presence of (PFBA₁₄-*b*-OEGMA₃₀)₃.

The capacity of the polymers to pre-concentrate molecular oxygen was assessed next. Polymer solutions (2 wt %) were saturated with O₂ by vigorous shaking them in vials in an atmosphere of pure oxygen. Following this, the vial headspace was vented, and the concentration of O₂ in solution was measured in 5 min intervals using an Inlab 605 probe (Mettler Toledo). For both pure water and (PFS₁₆-*b*-OEGSt₄)₃ solution, the dissolved O₂ concentration dropped to its air-saturated value of ~9 mg·L⁻¹ in ~25 min (Figure S69, ESI). Similar equilibration kinetics was observed for the 2 wt % solution of Pluronic P123. Since Pluronic solutions are prone to foaming, the slightly slower O₂ release in this case compared to pure water can be attributed to gas retention

in foam bubbles. The behavior of the (PFBA₁₄-*b*-OEGMA₃₀)₃ solution was markedly different. After 30 min, the dissolved O₂ concentration was still ~20 mg·L⁻¹, which is approximately 200% of air-saturated concentration in pure water. This suggests that the catalytic competency of amphiphilic PFBA copolymers is due to their capacity to attract and pre-concentrate O₂ in the hydrophobic environment surrounding the metal-binding site.

In conclusion, we prepared a library of well-defined star block-copolymers from a trifunctional nitroxide initiator based on the TBTA motif. In water, the copolymers self-assemble into micelles or vesicles, depending on the specific polymer composition. Copolymers containing PFBA monomer show evidence of molecular oxygen pre-concentration in the fluorinated cores of their micellar aggregates. In combination with DMAP and TEMPO "cofactors" and in the presence of CuSO₄, these copolymers act as competent catalysts for oxidation of alcohols to aldehydes in water.

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Notes and References

^a KAUST Catalysis Center and Division of Physical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal, 23955-6900, Kingdom of Saudi Arabia. E-mail: valentin.rodionov@kaust.edu.sa; Tel: +966 (12) 8084592

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