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Arm-Cleavable Microgel Star Polymers: A Versatile Strategy for Direct Core Analysis and Functionalization

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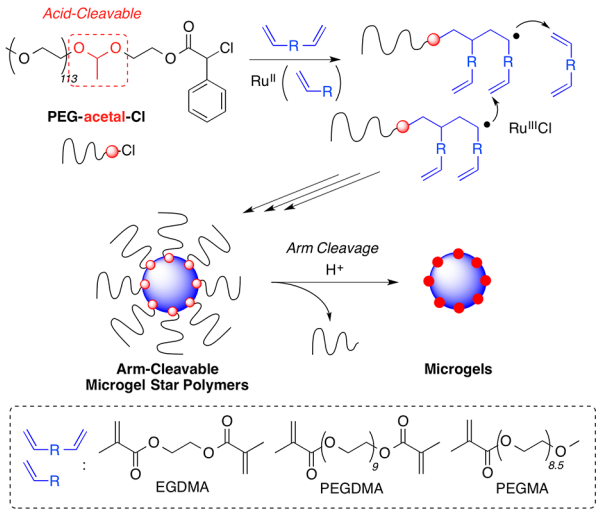
Supporting Information

ABSTRACT: Arm-cleavable microgel star polymers were developed, where the arm chains can readily be cleaved by acidolysis after the synthesis, allowing isolation of the core, direct analysis of its structure, and also the creation of functional nanometer-sized microgels. The key is to employ a macroinitiator (PEG−acetal−Cl) that carries an acetal linkage between a poly(ethylene glycol) arm chain and a chloride initiating site. From this, star polymers were synthesized via the linking reaction with a divinyl monomer and a ruthenium catalyst in living radical polymerization. The arms were subsequently cleaved by acidolysis of the acetal linker to give soluble microgels (cores free from arms). Full characterization revealed that the microgel cores are spherical, nano-sized (<20 nm), and of relatively low density. Amphiphilic, water-soluble, and thermosensitive arm-free microgels can be obtained by additionally employing functional methacrylate upon arm linking.

Scheme 1. Arm-Cleavable Microgel Star Polymers for Core Isolation and Functional Microgel Formation



Microgel-core star polymers[1−16] are core−shell-type microgels in which a core is covered by 10−100 linear polymers (arms) and thus is isolated from the outer environment and solubilized, despite a cross-linked network therein. After the first discovery in living anionic polymerization in the 1960−70s,[5−7] microgel star polymers have been synthesized by the arm-linking method, in which living linear polymers or macroinitiators (or macromonomers) are locally cross-linked with multifunctional linking agents (e.g., divinylbenzene) to form microgel cores. More recently, microgel star polymers[10−15] have been revisited in living radical polymerization[17,18] to create functional compartments for efficient and selective molecular recognition[11−13,15] and unique catalysis for organic synthesis and polymerization.[10,13,14]

These results are important in that, despite the cross-linked network structure, microgel cores have a void spacious enough for the diffusion and/or encapsulation of substrates, guest molecules, and polymers. Rather surprisingly, however, direct characterization of the microgels in terms of structure, size, density, and solubility has hardly been examined over 40 years after the first discovery,[16] except for some examples of star polymer characterization with scattering techniques.[1,9] This is primarily because the cores always have arms and are difficult to separate for detailed characterization.

In this work, we designed "arm-cleavable" microgel star polymers via living radical polymerization to isolate and directly analyze the microgel cores (Scheme 1). The new approach involves arm chains, prepared and isolated in advance, that carry a readily cleavable unit in addition to an initiating site (an alkyl halide) for metal-catalyzed living radical polymerization or the arm-linking step for star polymer synthesis in the presence of a bifunctional linking agent. The cleavable unit herein is an acetal,[19,20] which is readily cleaved after the core formation by acidolysis without affecting the arm chains and their pendant groups (esters for methacrylates).

Beyond our anticipation and previous consideration, it has turned out that the microgel cores separated from their arms are fully soluble in common organic solvents and water, which allows detailed characterization in regard to the molecular weight, size, density, and viscosity as with soluble non-cross-linked polymers, for the first time to our best knowledge.

The arm-cleavable microgel star polymers were further applicable as versatile templates to create well-defined and functionalized soluble microgels with nanometer size (<20 nm), whereas the synthesis of such microgels by other means is generally difficult, as direct polymerization of divinyl monomers often induces gelation even under dilute conditions and/or provides microgels with a broad molecular weight distribution.[21]

As illustrated in Scheme 1, we first designed an "acid-cleavable" macroinitiator (PEG−acetal−Cl) that carries an acetal linkage between poly(ethylene glycol) methyl ether (PEG−OH) ($M_n \approx$

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5000) for arm chains and a chlorine-based initiating group for microgelation. The acetal unit is stable under the relatively basic conditions for star polymer synthesis via ruthenium-catalyzed polymerization, while it should be easily cleaved under acidic conditions. The macroinitiator was prepared in high yield (93%) by the treatment of PEG−OH with 2-(vinyloxy)ethyl 2-chloro-2-phenylacetate in the presence of pyridinium *p*-toluenesulfonate in CH_2Cl_2 at 0 °C. The quantitative introduction of a chlorine-based initiating group was confirmed by ^{1}H NMR spectroscopy (Figure S1 in the Supporting Information), where PEG−acetal−Cl shows the methyne (4.7 ppm) and methyl (1.2 ppm) protons of the acetal unit, and also by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Figure S2).

Microgel star polymers were then synthesized by the linking reaction of PEG−acetal−Cl (M_n = 4600; M_w/M_n = 1.04) with ethylene glycol dimethacrylate (EGDMA) and a ruthenium catalytic system [Ru(Ind)Cl(PPh_3)$_2$/*n*-Bu_3N] in toluene 80 °C ([PEG−acetal−Cl]$_0$ = 20 mM, r = [EGDMA]$_0$/[PEG−acetal−Cl]$_0$ = 10/1) (Figure 1a). EGDMA was smoothly consumed up

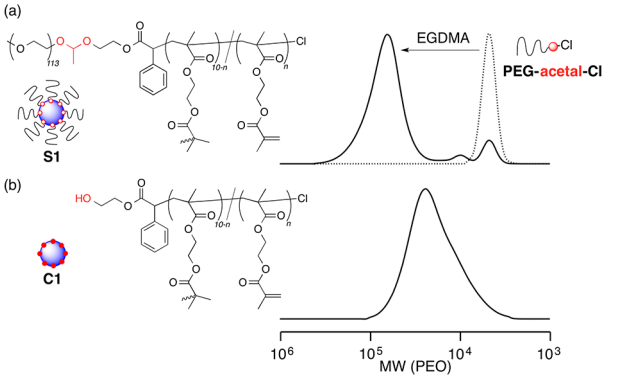

Figure 1. SEC curves of (a) arm-cleavable microgel star polymer **S1** prepared by the linking reaction of PEG−acetal−Cl with EGDMA and (b) EGDMA microgel **C1** obtained by arm cleavage of **S1** with trifluoroacetic acid.

to 94% in 49 h, giving star polymer **S1** with a high molecular weight and a narrow molecular weight distribution in high yield [88% by size-exclusion chromatography (SEC)].

After the removal of the residue of unreacted arms and intermediates (two peaks in the low-molecular-weight region), **S1** was characterized by SEC coupled with multiangle laser light scattering SEC (SEC-MALLS) and found to have an absolute weight-average molecular weight (M_w) of 340 000, an arm number (N_{arm}) of 51, and a radius of gyration (R_g) of 10 nm (Table 1, entry 1). ^{1}H NMR analysis supported the formation of EGDMA microgels by the broad signals originating from unreacted pendant olefin (5.6 and 6.1 ppm) and methacrylate backbones (0.8−2.2 ppm) (Figure S3). Importantly, the in-arm acetal units remained intact during the core formation, as the methyne (4.6 ppm) and methyl (1.2 ppm) protons were observed.

The arms were cleaved with trifluoroacetic acid, and the free PEG chains were separated by washing the reaction mixture with water and/or by preparative SEC to give microgel core **C1**. The quantitative cleavage of the acetal linkage of **S1** was confirmed by ^{1}H NMR analysis (Figure S3). The isolated core was soluble in common organic solvents (DMF, THF, CH_2Cl_2, etc.) even without linear arms, which allowed its full characterization by analytical techniques generally employed for soluble polymers such as star polymer **S1**.

The overall molecular weight of **C1** by SEC was smaller than that of **S1** (Figure 1b), and importantly, the absolute M_w was 96 000 by SEC-MALLS (Table 1, entry 2), in reasonable agreement with the calculated value of 120 000 [$M_{w,calcd} = F_w \times r \times$ (conv./100) $\times N_{arm} \times M_w/M_n$, where F_w is the formula weight of EGDMA, r = [EGDMA]$_0$/[PEG−acetal−Cl]$_0$ (10/1), conv. is the conversion of EGDMA, N_{arm} = 51, and M_w/M_n is the dispersity ratio as determined by SEC (1.4)].

The concentration of unreacted pendent olefins in the in-core EGDMA units of **C1** was 13 mol %, as estimated by ^{1}H NMR analysis (in CD_2Cl_2 at 25 °C) on the basis of the olefin (5.6 and 6.1 ppm) to aromatic (7.1−7.4 ppm) signal intensity ratio (Figure S3); a similar olefin content was found in **S1**, from which **C1** was obtained. Despite their same origin, the methacrylate signals of the isolated core appeared stronger than in the star, indicating that in **S1** the arm chains somehow reduce the mobility of the cross-linking chains but not the pendant olefins, which rather freely dangle at the end of the spacer.

With 10 EGDMA fed per arm, a 94% EGDMA conversion upon linking, and 51 arms per molecule (Table 1, entries 1 and 2), the microgel core of **S1** and **C1** obtained therefrom contain an average of ∼480 EGDMA units (=10 × 0.94 × 51), among which at least 50 units (or ∼10%) were employed for intermolecular linking (i.e., one unit for attaching an additional arm). With 13% of the pendant olefins remaining unreacted in

Table 1. Characterization of Arm-Cleavable Microgel Star Polymers and Microgels[a]

entry	code	core monomer (r)	[Arm]$_0$ (mM)	conv. (%)[b]	time (h)	olefin (%)[c]	M_w (SEC)[d]	M_w/M_n (SEC)[d]	M_w (MALLS)[e]	N_{arm}[f]	M_w (calcd)[g]	R_g (nm)[e]	[η] (mL/g)[e]	a[h]
1	**S1**	EGDMA (10)	20	94	49	13	84900	1.22	340000	51	–	10	21	0.27
2	**C1**	–	–	–	–	13	23500	1.40	96000	–	120000	n.d.[i]	8.5	0.56
3	**S2**	EGDMA (10)	40	89	20	16	170000	1.58	765000	116	–	18	23	0.30
4	**C2**	–	–	–	–	17	39000	1.69	309000	–	345000	8.4	6.0	0.44
5	**S3**	EGDMA/PEGMA (10/10)	20	92	146	7	49000	1.46	200000	19	–	9.7	22	0.27
6	**C3**	–	–	–	–	7	31700	1.37	136000	–	150000	n.d.[i]	7.5	0.52
7	**S4**	PEGDMA (10)	20	82	34	8	87100	1.66	410000	45	–	17	30	0.28
8	**C4**	–	–	–	–	8	47000	1.38	240000	–	280000	11	14	0.41

[a]Conditions: In toluene at 80 °C. [(P)EGDMA]$_0$/[PEGMA]$_0$/[PEG−acetal−Cl]$_0$/[Ru(Ind)Cl(PPh_3)$_2$]$_0$/[*n*-Bu_3N]$_0$ (mM): **S1** and **S4**, 200/0/20/2.0/20; **S2**, 400/0/40/2.0/20; **S3**, 200/200/20/2.0/20. [b]Monomer(s) conversion by ^{1}H NMR analysis. [c]Olefin content per core EGDMA unit by ^{1}H NMR analysis. [d]By SEC in DMF (10 mM LiBr) with a PEO calibration. [e]By SEC-MALLS viscometry in DMF (10 mM LiBr). [f]Number of arms per star: N_{arm} = (weight fraction of arms) × M_w (MALLS)/$M_{w,arm}$ [g]Molecular weight of microgels calculated as M_w (calcd) = F_w (core monomers) × conv. × N_{arm} × r × M_w/M_n (SEC). [h]Obtained from the Mark−Houwink−Sakurada equation ([η] = KM^a). [i]Not determined because of the size limit.

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the core, this means that ~77% of the pendant olefins (=100 − 10 − 13) were consumed by the intramolecular cross-linking and/or ladderlike polymerization in the core region upon core formation. It should be noted that such a detailed analysis of the core's chemical structure was made possible by the core separation and isolation in this work.

The arm cleavage also enabled for the first time the characterization of the physical properties of the core compared with its parent star polymer. Generally, globular macromolecules show solution viscosities smaller than those of their linear counterparts.[22,23] Analysis by SEC-MALLS with a viscosity detector (Figure 2 and Table 1, entries 1 and 2) showed that **S1**

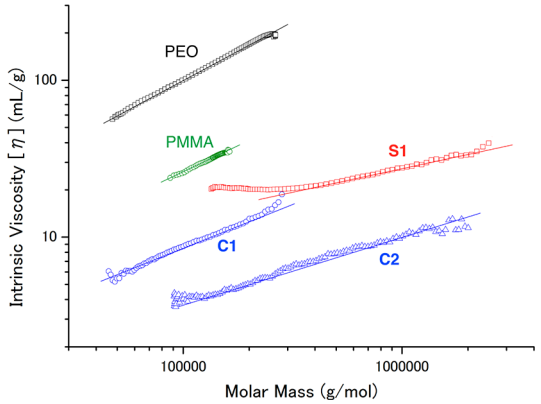


Figure 2. Molecular weight dependence of the intrinsic viscosity for **S1** (M_w = 340 000), **C1** (M_w = 96 000), **C2** (M_w = 309 000), PEO (M_w = 187 000), and PMMA (M_w = 146 000) in DMF.

and **C1** actually had intrinsic viscosities ($[\eta]$) smaller than those of their linear counterparts poly(ethylene oxide) (PEO) (M_w = 187 000) and poly(methyl methacrylate) (PMMA) (M_w = 146 000), respectively, with similar molecular weights ($[\eta]$ = 21, 8.5, 160, and 33 mL/g for **S1**, **C1**, PEO, and PMMA, respectively, in DMF at room temperature).

The double logarithmic plots of $[\eta]$ versus molar mass (M_w by MALLS) were fitted using the Mark−Houwink−Sakurada equation ($[\eta] = KM^a$), where the index a (the slope) depends on the polymer conformation (a < 0.5, spherical; 0.5 < a < 1.0, random coil of a linear chain) (Figure 2). For **S1**, the slope a over the SEC peak molecular weight ($M_p \approx$ 230 000) was 0.27, indicating that it is globular and different from the linear polymers (PEO, a = 0.72; PMMA, a = 0.69). In addition, $[\eta]$ slightly decreased with increasing M_w to reach a minimum around M_p (Figure S6). This suggests that the conformation of the star gradually changes from branched to globular with increasing M_w or arm number, and this conformational shift, in turn, offsets an increase in $[\eta]$ expected for star polymers with more arms.

For **C1**, a was 0.56, close to the upper limit of 0.5 for a spherical shape but small for a random coil. The fact that the shape index was clearly larger than that of the star suggests that the core would be a swelled, nearly spherical gel and more flexible in shape than the parent star polymer surrounded by linear arms.

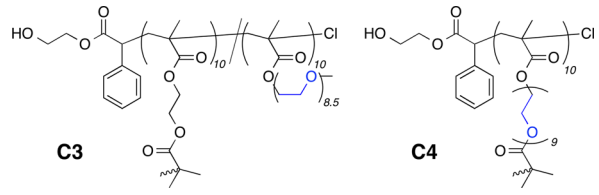
The core−shell structure of **S1** and the nearly spherical structure of **C1** were further supported by small-angle X-ray scattering (SAXS) analysis in DMF (Figure S7). The radii of gyration (R_g) as determined by the Guinier plot were 7.1 nm for **S1** and 4.4 nm for **C1**. With the assumption of a spherical shape, the EGDMA density in the core microgel was thus 0.44 g/mL, meaning that **C1** is occupied by solvent about 55% in volume.

From these results, the microgel core is of a swelled and spherical network structure with a relatively low density. The R_g data for **C1** also revealed that the arm chain density over the core surface of **S1** was 0.21 chain/nm^2, indicating a high-density polymer brush.[24]

The primary structure and the physical properties of the arm-cleaved microgels could be tuned by changing the synthetic conditions of their parent star polymers (Table 1 and Figure S4). For example, increasing the initial concentration of PEG−acetal−Cl from 20 to 40 mM while applying the same feed ratio of EGDMA (r = 10) led to star polymer **S2** and arm-free microgel **C2** (~1030 EGDMA units) with an increased molecular weight [M_w (MALLS)] and a larger size (R_g) (Table 1, entries 3 and 4) relative to **S1** and **C1**, respectively. The enhanced core formation is most likely due to a more efficient intermolecular arm linking. In spite of the larger M_w, both the viscosity $[\eta]$ and shape index a of **C2** were smaller than those of **C1** (Figure 2), indicating a higher network density in the former.

As illustrated in Chart 1, an amphiphilic and thermosensitive microgel, **C3** (M_w = 136 000 with 175 short pendent PEG

Chart 1. Amphiphilic and Thermosensitive PEG Microgels



chains), was obtained from star polymer **S3**, for which PEG methyl ether methacrylate (PEGMA) (M_n = 475) was additionally employed with EGDMA on arm linking. A similar microgel, **C4** (M_w = 240 000 with 370 short PEG spacers) was also obtained from star polymer **S4** with PEG dimethacrylate (PEGDMA) (M_n = 550) as a linking agent in place of EGDMA (Table 1 and Figures S4 and S5). While **S4** and **S1** carried nearly the same numbers of arms, M_w and R_g of the former were larger as expected from a longer spacer in the linking agent. As a result, **C4** had a larger M_w than **C1**.

C3 and **C4** were amphiphilic and soluble not only in organic solvents but also in alcohols and water. With either pendant or spacer PEG units, these microgels were thermosensitive with lower critical solution temperature-type phase separation in water[25,26] at 60 °C (**C3**) and 40 °C (**C4**) (Figure S8). In spite of the smaller hydrophobic contents [hydrophobic methacrylate/hydrophilic PEG = 3/1 (**C3**), 2/1 (**C4**)], **C4** had a cloud point lower than that for **C3**. This would be due to the restricted mobility and conformation of the PEG spacers bridging the methacrylate units, promoting dehydration of PEG units.

In conclusion, we successfully isolated and directly analyzed microgel cores in star polymers with an acid-cleavable macroinitiator (PEG−acetal−Cl). To our knowledge, the structures and some physical properties of microgel cores were precisely characterized for the first time in over 40 years since the initial synthesis of microgel-core star polymers. Despite the absence of surrounding arm layers, the isolated cores are soluble in various solvents, in contrast to a previous premise that microgel cores are solubilized by their linear arms. The cores are spherical, have a nanoscale network structure (<20 nm) with a relatively large void space (~50%), and can be amphiphilic and thermosensitive with designed linking agents. As a result of their tunable properties and precise characterization, arm-cleavable microgel star

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polymers and the resulting isolated microgels would lead to tailor-made functional microgels (nanogels), capsules, and delivery vessels, among others.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, SEC curves, ^{1}H NMR spectra, Mark–Houwink–Sakurada plots, and SAXS profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Blencowe, A.; Tan, J. F.; Goh, T. K.; Qiao, G. G. *Polymer* **2009**, *50*, 5.
(2) Gao, H.; Matyjaszewski, K. *Prog. Polym. Sci.* **2009**, *34*, 317.
(3) Gao, H. *Macromol. Rapid Commun.* **2012**, *33*, 722.
(4) Terashima, T.; Sawamoto, M. *ACS Symp. Ser.* **2012**, *1101*, 65.
(5) Zilliox, J.-G.; Rempp, P.; Parrod, J. *J. Polym. Sci., Part C: Polym. Symp.* **1968**, *22*, 145.
(6) Bauer, B. J.; Fetters, L. J. *J. Rubber Chem. Technol.* **1978**, *51*, 406.
(7) Bywater, S. *Adv. Polym. Sci.* **1979**, *30*, 90.
(8) Kanaoka, S.; Yagi, N.; Fukuyama, Y.; Aoshima, S.; Tsunoyama, H.; Tsukuda, T.; Sakurai, H. *J. Am. Chem. Soc.* **2007**, *129*, 12060.
(9) Terashima, T.; Motokawa, R.; Koizumi, S.; Sawamoto, M.; Kamigaito, M.; Ando, T.; Hashimoto, T. *Macromolecules* **2010**, *43*, 8218.
(10) Terashima, T.; Nomura, A.; Ito, M.; Ouchi, M.; Sawamoto, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7892.
(11) Koda, Y.; Terashima, T.; Nomura, A.; Ouchi, M.; Sawamoto, M. *Macromolecules* **2011**, *44*, 4574.
(12) Fukae, K.; Terashima, T.; Sawamoto, M. *Macromolecules* **2012**, *45*, 3377.
(13) Bosman, A. W.; Vestberg, R.; Heumann, A.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715.
(14) Chi, Y.; Scroggins, S. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6322.
(15) Cho, H. Y.; Srinivasan, A.; Hong, J.; Hsu, E.; Liu, S.; Shrivats, A.; Kwak, D.; Bohaty, A. K.; Paik, H.-J.; Hollinger, J. O.; Matyjaszewski, K. *Biomacromolecules* **2011**, *12*, 3478.
(16) Wiltshire, J. T.; Qiao, G. G. *Macromolecules* **2006**, *39*, 9018.
(17) Ouchi, M.; Terashima, T.; Sawamoto, M. *Chem. Rev.* **2009**, *109*, 4963.
(18) Matyjaszewski, K. *Macromolecules* **2012**, *45*, 4015.
(19) Rikkou, M. D.; Patrickios, C. S. *Prog. Polym. Sci.* **2011**, *36*, 1079.
(20) Satoh, K.; Poelma, J. E.; Campos, L. M.; Stahl, B.; Hawker, C. J. *Polym. Chem.* **2012**, *3*, 1890.
(21) Funke, W.; Okay, O.; Joos-Müller, B. *Adv. Polym. Sci.* **1998**, *136*, 139.
(22) Higashihara, T.; Segawa, Y.; Sinananwanich, W.; Ueda, M. *Polym. J.* **2012**, *44*, 14.
(23) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401.
(24) Tsujii, Y.; Ohno, K.; Yamamoto, S.; Goto, A.; Fukuda, T. *Adv. Polym. Sci.* **2006**, *197*, 1.
(25) Lutz, J.-F. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 3459.
(26) Terashima, T.; Kawabe, M.; Miyabara, Y.; Yoda, H.; Sawamoto, M. *Nat. Commun.* **2013**, *4*, 2321.