# Temperature-selective dual radical generation from alkyl diiodide : applications to synthesis of asymmetric cabc multi-block copolymers and their unique assembly structures

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# Temperature-Selective Dual Radical Generation from Alkyl Diiodide: Applications to Synthesis of Asymmetric CABC Multi-Block Copolymers and Their Unique Assembly Structures

Jie Zheng,[‡] Chen-Gang Wang,[‡] Yu Yamaguchi, Michihiko Miyamoto, Atsushi Goto*

**Abstract:** Temperature-selective radical generation from a newly designed alkyl diiodide (I–$R_2$–$R_1$–I) was studied. $R_1$–I and I–$R_2$ had different reactivities for generating alkyl radicals in the presence of a tetraoctylammonium iodide (ONI) catalyst. Taking advantage of the temperature selectivity, we used the alkyl diiodide as a dual initiator in ONI-catalyzed living radical polymerization to uniquely synthesize CABC non-symmetric multi-block copolymers. Because of their non-symmetric structure, CABC multi-block copolymers form unique assemblies, i.e., Janus-type particles with hetero-segment coronas and flower-like particles with hetero-segment petals.
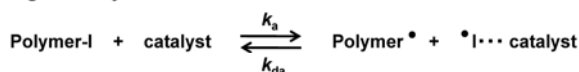
The generation of a carbon-centered radical (R•) from an alkyl halide (R–X) is a fundamental reaction in organic synthesis, and its reactivity significantly depends on the alkyl group (R). An alkyl di-halide (X–$R_2$–$R_1$–X) with largely different structures at $R_1$ and $R_2$ can selectively generate an alkyl radical from one site ($R_1$–X) at a given temperature and then another radical from the other site (X–$R_2$) at an elevated temperature. This temperature dependence enables each site to be independently transformed to a different functional group by simply altering the temperature.

Living radical polymerization (LRP) is a useful method for preparing block copolymers.[1-11] LRP is based on the reversible activation of a dormant species (Polymer−X) to a propagating radical (Polymer•) (Scheme 1a). We found that the iodide anion (I−) works as a catalyst for the reversible generation of R• from an alkyl iodide (R–I).[9] We used this reaction for the reversible activation of Polymer-I to Polymer• and developed a new class of LRP, i.e., organocatalyzed LRP (Scheme 1b).[9,10]



**Scheme 1.** Reversible activation: (a) General scheme and (b) Organocatalyzed LRP.

[*]     J. Zheng,[‡] Dr. C-G. Wang,[‡] Prof. Dr. A. Goto
        Division of Chemistry and Biological Chemistry, School of Physical
        and Mathematical Sciences, Nanyang Technological University, 21
        Nanyang Link, 637371 Singapore
        E-mail: agoto@ntu.edu.sg

        Y. Yamaguchi, M. Miyamoto
        Techno Research Center, Godo Shigeno Co., LTD., 1365 Nanaido,
        Chosei-Mura, Chosei-Gun, Chiba 299-4333, Japan

[‡]     These authors (JZ and CGW) contribute equally.

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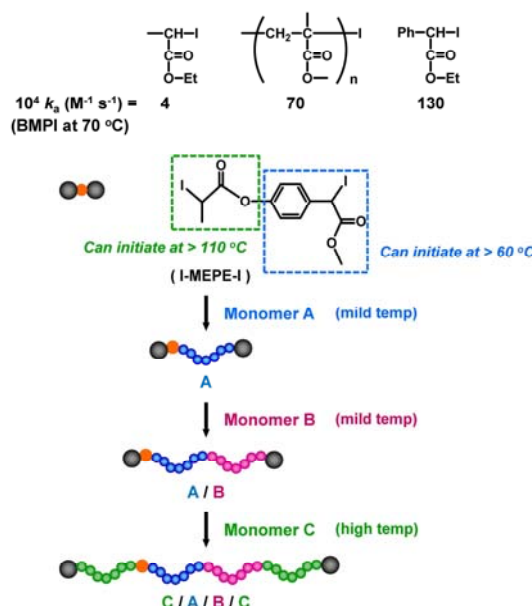


**Scheme 2.** Temperature-Selective Polymerization for Synthesis of CABC Multi-Block Copolymer.

In the present work, we propose a temperature-selective dual initiator as a conceptually new initiator in LRP. We designed an alkyl di-iodide (I–$R_2$–$R_1$–I) (Scheme 2) with considerably different reactivities of $R_1$–I and I–$R_2$; thus, it can initiate at a given temperature (from $R_1$–I) and an elevated temperature (from I–$R_2$) selectively. Interestingly, this initiator enables the synthesis of CABC non-symmetric multi-block copolymers (Scheme 2). At a mild temperature, two monomers A and B are successively polymerized from $R_1$–I, whereas I–$R_2$ remains unreacted. Another monomer C is subsequently polymerized at an elevated temperature, whereupon propagation occurs from both chain ends. CABC block copolymers are thus obtainable by simply altering the temperature.

Diblock, triblock, and multi-block copolymers have garnered increasing attention for their assembly structures. However, only several examples have been reported for the synthesis of CABC multi-block copolymers and experimental studies on their phase separation and vesicle and micelle formation.[12-15] Taking advantage of the non-symmetric structure of CABC block copolymer, we were motivated to for the first time synthesize a Janus-type particle with hetero-segment coronas and a flower-like particle with hetero-segment petals (Scheme 3) as unique applications. For the Janus-type particle, the B segment is crosslinked to form a particle with two distinguishable hetero-CA-segment and homo-C-segment coronas. For the flower-like particle, the C segment is crosslinked to form a particle with hetero-AB-segment petals. The temperature-selective synthesis of CABC block copolymers and the preparation of these two unprecedented particles are reported in the present paper.
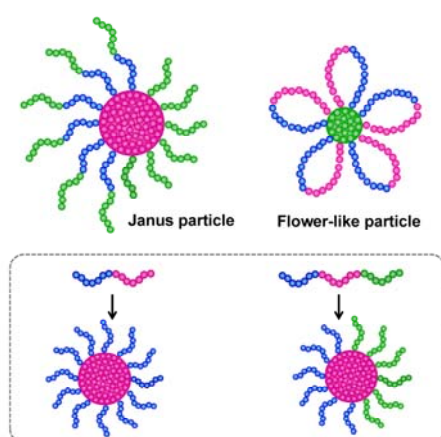
**Scheme 3.** Janus particles and flower-like particles synthesized in this work (top) and possible particles obtainable by AB diblock and ABC triblock copolymers (bottom).

We previously experimentally determined the activation rate constant $k_a$ (Scheme 1b) of several alkyl iodides catalyzed by tributylmethylphosphonium iodide (BMPI) at 70 °C.[16] The $k_a$ value ($M^{-1}$ $s^{-1}$) (Scheme 2) was more than 30 times different for R = propionate ($4\times10^{-4}$) and phenylacetate ($130\times10^{-4}$). Exploiting this large difference, we combined these two R groups and designed an alkyl diiodide dual initiator, methyl 2-iodo-2-(4'-(2"-iodopropionyloxy)phenylacetate) (I–MEPE–I) (Scheme 2). The phenylacetate site (PE–I) can initiate at a mild

temperature 60 °C, whereas the propionate site (I–ME) can initiate at only an elevated temperature 110 °C, thereby providing temperature selectivity. Importantly, the $k_a$ value was similar for R = poly(methyl methacrylate) (PMMA) ($70\times10^{-4}$) and phenylacetate ($130\times10^{-4}$). This means that PMMA–I generated from PE–I has a similar initiation ability to PE–I, ensuring that I–ME–PMMA–I (accessible after the first block polymerization) can also work as a temperature-selective dual macroinitiator. In the present work, the more soluble tetraoctylammonium iodide (ONI) was used as a catalyst instead of BMPI. We may reasonably assume a similar magnitude of the $k_a$ values for BMPI and ONI, because $I^-$ (not the counter cations) serves as the catalyst in both cases.

We synthesized a CABC block copolymer using methyl methacrylate (MMA), butyl methacrylate (BMA), and butyl acrylate (BA) as the A, B, and C monomers, respectively, as a proof of principle (Table 1 (entry 1) and Figures 1 and 2). We heated a mixture of MMA (8 M), I–MEPE–I (160 mM) (initiator), and ONI (80 mM) (catalyst) at 60 °C. To retain the high chain-end fidelity of iodide, the polymerization was intentionally stopped at a reasonably short time 3 h (monomer conversion = 68%). We obtained an I-ME-PMMA-I polymer with $M_n$ = 4100 and PDI = 1.13 before purification and $M_n$ = 4100 (36 monomer units of MMA) and PDI = 1.13 after purification by reprecipitation, where $M_n$ is the number-average molecular weight and PDI is the polydispersity index. Figures 2a and 2b show that 100% of PE-I initiated and that 96% of I-ME remained unreacted, demonstrating the high initiation-selectivity of the two sites.
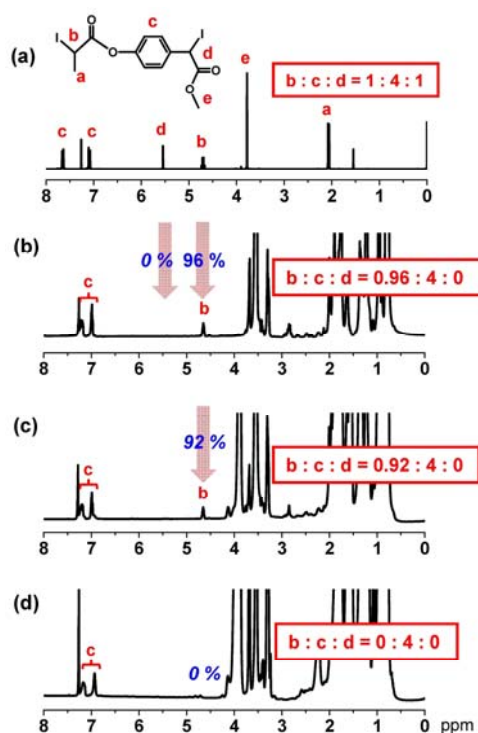
**Table 1.** Synthesis of CABC multi-block copolymers.

| Entry | Monomer | I−R−I | $[M]_0/[I-R-I]_0/[ONI]_0$ (mM)[a] | T (°C) | $t$ (h) | conv (%) | $M_n$ (GPC) ($M_{n,theo}$[b]) | DP ($^1$H NMR)[c] | PDI (GPC) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | MMA | I−MEPE−I | 8000/160/80 | 60 | 3 | 68 | 4100 (3900) | − | 1.13 |
| | | | | After purification | | | 4100 | 36 | 1.13 |
| | BMA | I−PMMA−I | 8000/160/80 | 60 | 6 | 47 | 7400 (7400) | − | 1.15 |
| | | | | After purification | | | 7800 | + 23 | 1.15 |
| | BA | I−PMMA−PBMA−I | 8000/160/320 | 110 | 24 | 59 | 11800 (11600) | − | 1.33 |
| | | | | After purification | | | 12800 | + 22 | 1.27 |
| 2 | MMA | I−MEPE−I | 8000/53/80 | 60 | 3 | 63 | 7900 (9900) | − | 1.12 |
| | | | | After purification | | | 8300 | 82 | 1.10 |
| | AMA | I−PMMA−I | 8000/27/13 | 60 | 1.3 | 12 | 13000 (13000) | − | 1.19 |
| | | | | After purification | | | 13000 | + 36 | 1.19 |
| | BA | I−PMMA−PAMA−I | 8000/8/32 | 110 | 5 | 7 | 22000 (20000) | − | 1.40 |
| | | | | After purification | | | 23000 | + 50 | 1.34 |
| | | | After reaction with $n$-hexylamine followed by purification | | | | 22000 | − | 1.36 |
| 3 | MMA | I−MEPE−I | 8000/20/20 | 60 | 3 | 30 | 12000 (12000) | − | 1.14 |
| | | | | After purification | | | 12000 | 105 | 1.12 |
| | BMA | I−PMMA−I | 8000/16/24 | 60 | 4 | 16 | 22000 (23000) | − | 1.16 |
| | | | | After purification | | | 22000 | + 90 | 1.16 |
| | DGDA | I−PMMA−PBMA−I | 8000/16/320 | 110 | 4 | 10 | 29000 | + 50 | 1.24 |
| | | | | | 16 | 14 | 59000 | + 70 | 2.33 |

[a] M = monomer. [b] Theoretical $M_n$ calculated with $M_n$ = ($[M]_0/[I−R−I]_0$) × conversion × (molecular weight of monomer) + (molecular weight of I-R-I). [c] DP obtained from the peak areas of the initiating PE unit (phenyl group) and the monomer units (with ±10% experimental error).
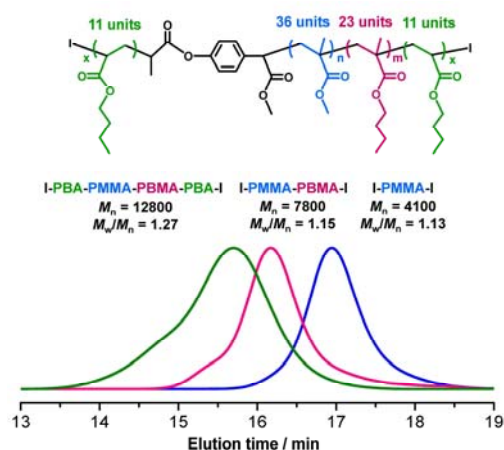
**Figure 1.** GPC curves for the synthesis of PBA-PMMA-PBMA-PBA (Table 1 (entry 1)).



**Figure 2.** $^1$H NMR spectra for the synthesis of PBA-PMMA-PBMA-PBA (Table 1 (entry 1)).

Using the purified I-ME-PMMA-I macroinitiator, we polymerized BMA at 60 $^o$C for 6 h and obtained an I-ME-PMMA-PBMA-I diblock copolymer with $M_n$ = 7400 and PDI = 1.15 before purification and $M_n$ = 7800 (23 monomer units of BMA) and PDI = 1.15 after purification, where PBMA is poly(butyl methacrylate). GPC traces (Figure 1) show that a large fraction of the I-ME-PMMA-I macroinitiator was extended to the I-ME-PMMA-PBMA-I block copolymer, confirming the high block-efficiency of the PMMA-I site. Moreover, 92% of I-ME remained unreacted after the two polymerizations (Figure 2c).

In the third step, we used an elevated temperature 110 $^o$C. Using the purified I-ME-PMMA-PBMA-I macroinitiator, we polymerized BA at 110 $^o$C, yielding an I-PBA-PBMA-PMMA-

PBA-I tetrablock copolymer with $M_n$ = 11800 and PDI = 1.33 before purification and $M_n$ = 12800 (11 monomer units in each BA segment) and PDI = 1.27 after purification, where PBA is poly(butyl acrylate). At this elevated temperature, 100% of I-ME initiated (Figure 2d), meaning that the polymer bears PBA segments on both sides of the polymer. Thus, a CABC block copolymer was successfully synthesized by simply changing the temperature. A slight shoulder on the higher molecular weight side in the GPC curve (Figure 1) is due to radical-termination products.

A Janus-type particle was synthesized by using a post-crosslinkable monomer, allyl methacrylate (AMA), in the B segment (36 units). The A segment was MMA (82 units), and the C segment was BA (25 units of each C segment). After the polymerization, the iodides at the chain ends were removed via a reaction with $n$-hexylamine.[17] The $M_n$ and PDI of the obtained CABC block copolymer were 23000 and 1.34, respectively (Table 1 (entry 2) and Figure 3a).
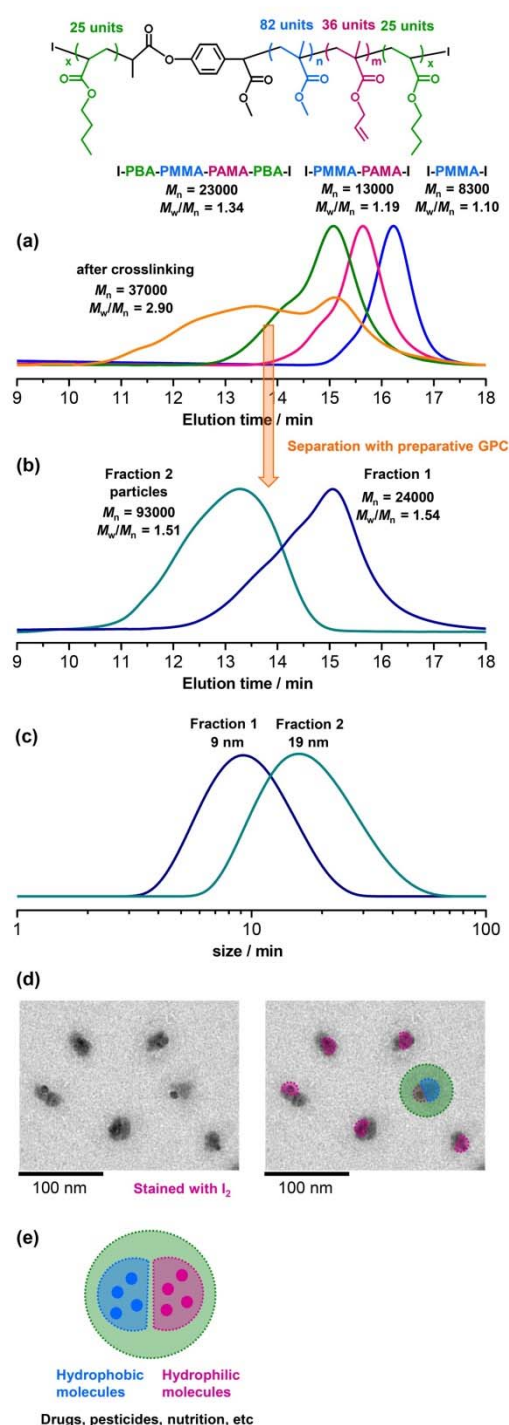
The obtained CABC block copolymer (30 wt%) was heated with benzoyl peroxide (BPO) as a radical source (3 wt%) in ethylbenzene (67 wt%) at 80 °C for 1 h. The B segment was crosslinked via the radical addition of the allyl groups (Figure 3a). A majority of the allyl groups remained unreacted during the polymerizations, because the methacrylic (B monomer) and acrylic (C monomer) C=C bonds are much more reactive than the allylic C=C bond (B monomer). We used a relatively large amount of BPO (0.2 equiv to the AMA units) and exploited the high reactivity of the generated oxygen-centered radical from BPO in the post-crosslinking to facilitate the radical addition of the allyl groups.

After crosslinking, the obtained polymer was fractionated with preparative GPC (Figure 3b). The lower-molecular-weight fraction (fraction 1) contains unreacted and intramolecularly crosslinked chains. The higher-molecular-weight fraction (fraction 2) contains intermolecularly crosslinked particles. The weight ratio was 35:65 (fraction 1: fraction 2).

Dynamic light scattering (DLS) analysis (Figure 3c) showed that the hydrodynamic size (DLS peak top) in THF increased from 9 nm (before crosslinking) to 19 nm (after crosslinking). The contour length of the CABC block copolymer (168 units) is 42 nm (= 0.25 nm x 168 units). The particle size (19 nm) was reasonably smaller than the contour length, indicating that the aggregation among the particles was negligible.

Figure 3d shows a TEM image of the particles (fraction 2). The particles were stained as follows. The particles (after crosslinking) still contained unreacted allyl groups (68% of the AMA units, as estimated with $^1$H NMR). The remaining allyl groups were reacted with $HSCH_2CH_2NH_2$ via the thiol-ene Michael addition to functionalize the B segment with the $NH_2$ groups. The particles were subsequently immersed in an $I_2$ solution (solvent = THF), and the B segment was stained through the $I_2/NH_2$ halogen bonding. The TEM image (Figure 3d) shows the stained B segment as the darkest dot in each particle. The A segment was observed as a gray domain neighboring the B domain. The C domain was observed as the lightest gray domain surrounding the A and B domains, because the C segment (butyl acrylate units) tended to spread on the grid due to the low glass transition temperature (below –50 $^o$C) of the butyl acrylate segment.

triblock copolymers can form Janus particles with one core (B) domain and two distinguishable shell (A and C) domains. Unlike ABC triblock copolymers, CABC tetrablock copolymers can provide Janus-type particles with two core (A and B) domains and one shell (C) domain. With this special structure, we may uniquely encapsulate two different types of molecules such as hydrophilic and hydrophobic molecules in the two core (A and B) domains and can release these molecules by a function of the shell (C) domain (Figure 3e). Such nano-containers can simultaneously carry two different molecules and may find unprecedented applications as co-delivery systems in, e.g., cancer therapy and agrochemical release.
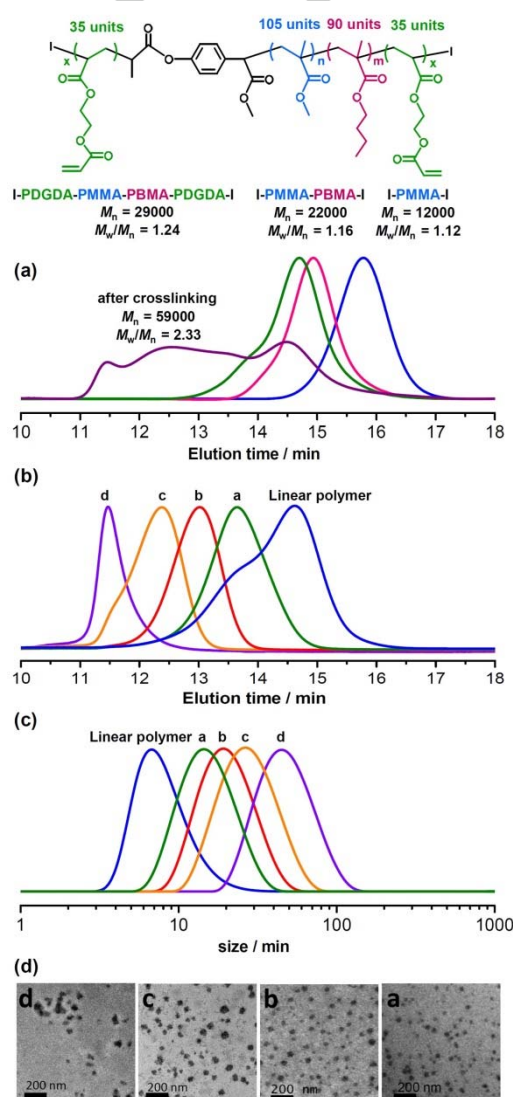


**Figure 3.** (a) GPC curves for the synthesis of PBA-PMMA-PAMA-PBA (Table 1 (entry 2)), (b) GPC curves after fractionation, (c) DLS curves after fractionation, (d) TEM image of generated particles, (e) possible future application as a co-delivery container.



**Figure 4.** (a) GPC curves for the synthesis of PDBA-PMMA-PAMA-PDBA (Table 1 (entry 3)), (b) GPC curves after fractionation, (c) DLS curves after fractionation, and (d) TEM image of generated particles.

Janus-type particles have gained widespread attention for their anisotropic properties and have been used as, e.g., solid surfactants, nano-probes, bio-sensors, electronic paper, micro-motors, and drug delivery vehicles. ABC triblock copolymers have been used in many cases.[18-20] As shown in Scheme 3, while AB diblock copolymers can form symmetric particles, ABC

A flower-like particle with hetero-petals was synthesized by using a crosslinkable monomer, diethylene glycol diacrylate (DGDA) in the C segment. The A segment was MMA (105 units), and the B segment was BMA (90 units). After the second

polymerization, the $M_n$ and PDI of the AB diblock copolymer were 22000 and 1.16, respectively (Table 1 (entry 3) and Figure 4a). The polymer chain was crosslinked during the third polymerization with DGDA (Figure 4a), and the resulting polymer was fractionated with preparative GPC (Figure 4b). The lowest-molecular-weight fraction contained non-crosslinked chains. The higher-molecular-weight fractions (fractions a-d) contained flower-like particles with different sizes. The weight ratio was 37:63 (fraction 1: fractions a-d).

Figure 4c shows the DLS curves with the peak tops at 8 nm (fraction 1), 16 nm (fraction a), 21 nm (fraction b), 29 nm (fraction c), and 50 nm (fraction d). Figure 4d shows the TEM images of the particles (fractions a-d). The particles in fractions a-c with different particle sizes were not aggregated. The particles in fraction d were interconnected. The contour length of the AB segment (totally 195 units) is 49 nm. Because the AB segment should be looped, the length of the petal is at most 24.5 nm. The sizes of particles a-c (16-29 nm) were reasonably smaller than the maximum particle size (two petals (49 nm) + core), confirming that the aggregation among the particles was negligible for these particles. The length of the petal segment was able to be made longer (242 A units and 137 B units) and shorter (53 A units and 30 B units) (Table S1 (entries 1 and 2) in Supporting Information). The core of the particle was made hydrophilic by using a hydrophilic monomer instead of DGDA (Table S1 (entry 3)). These results demonstrate accessibility to a range of particle design.

Flower-like particles have no chain ends in the petals and can exhibit properties between those of star-like particles and single-molecular macrocycles.[21-23] The lack of chain ends results in no entanglement with other polymers and particles and can exhibit lubrication. The diffusivity and biological recognition through the cell membranes can be tuned by the topological effects, and hence flower-like particles may serve as new vectors for drug delivery.[21] Our flower-like particle bears hetero-petals that can contain different functionalities in the A and B segments, thereby offering a new material design of flower-like particles.

In summary, the temperature-selective radical generation from a designed alkyl diiodide (I–MEPE–I) was utilized to synthesize CABC non-symmetric block copolymers. Exploiting the unique non-symmetric structure, we synthesized two new types of particles, i.e., a Janus-type particle with hetero-segment coronas and a flower-like particle with hetero-segment petals. Such particles may find promising applications as new co-delivery containers and dual-functional vectors.

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**Entry for the Table of Contents**

## COMMUNICATION

A newly designed alkyl diiodide (I–$R_2$–$R_1$–I) served as a temperature-selective dual initiator in organocatalyzed living radical polymerization to synthesize CABC non-symmetric multi-block copolymers. Taking advantage of the non-symmetric structure, a Janus-type particle with hetero-segment coronas and a flower-like particle with hetero-segment petals were synthesized as new types of nanoparticles.



≥ 110 °C    ≥ 60 °C

CABC Multi-Block Copolymer

Janus-type particle    Flower-like particle
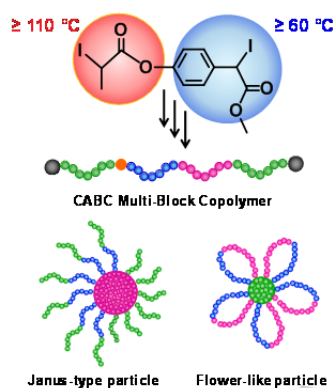
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