# Maleimidophenyl Isocyanates as Postpolymerization Modification Agents and their Applications in the Synthesis of Block Copolymers

**Rikito Takashima,[1] Jumpei Kida,[1] Daisuke Aoki ,[1,2] Hideyuki Otsuka [1]**

[1]Department of Chemical Science and Engineering, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro-ku, Tokyo 152-8550, Japan
[2]JST-PRESTO, 2-12-1 Ookayama, Meguro-ku, Tokyo 152-8550, Japan
Correspondence to: D. Aoki (E-mail: daoki@polymer.titech.ac.jp); H. Otsuka (E-mail: otsuka@polymer.titech.ac.jp)

Received 13 June 2019; Revised 13 July 2019; accepted 18 July 2019
**DOI: 10.1002/pola.29450**

**ABSTRACT**: The maleimide structure is highly reactive, exemplified by thiol–ene click reactions with thiols and Diels–Alder reactions with furans. Although postpolymerization modifications and macromolecular conjugations involving maleimide units have been widely studied, mostly due to their selectivity and high reactivity, little has been reported on the one-pot postpolymerization introduction of maleimides in polymer chains. Herein, we report *p*-maleimidophenyl isocyanate and its derivatives as modification agents to introduce maleimide moieties by reaction with hydroxy groups into polymer chains. The high reactivity of the resulting modification agents and of the corresponding maleimide structures once inserted in the polymer chains was examined by studying their reaction kinetics. Furthermore, these modification agents were successfully applied to the synthesis of macromonomers for graft polymerization and various block copolymers, with, for example, AB-type, star-shaped, and H-shaped architectures. © 2019 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2019**

**KEYWORDS**: block copolymers; click chemistry; maleimide; polymer modification; topological polymer

**INTRODUCTION** Functional polymers with reactive sites are widely used as components for smart materials. Maleimides are highly reactive, exemplified by their thiol–ene click reactions with thiol reagents,[1–7] reversible Diels–Alder reactions with furans,[8–10] alternating copolymerization reactions with vinyl monomers such as styrene,[11–13] and photoactivated reactions.[14,15] Due to their high and selective reactivity, maleimides have been extensively studied, whereby growing interest has been focused on the application of maleimides in polymer chemistry for the development of well-designed functional materials. For example, remendable crosslinked polymers have been prepared by exploiting the reaction of maleimides with dienophiles,[16–21] as well as biocompatible modifications using thiol-terminated reactive polymers facilitated by the advent of click chemistry.[22,23] These applications are based on the unique reactivity of maleimides, which includes the reversibility of its reaction with furan derivatives and high reactivity toward thiols in the absence of a metal catalyst, which is a clear advantage for bio-oriented applications and environmentally friendly syntheses.

Although postpolymerization modifications using maleimides as the scaffold have been widely studied,[24–27] little has been reported on the one-pot postpolymerization introduction of maleimides in polymer chains. The easy introduction of maleimide moieties in common polymer chains, that is, those easily synthesized or commercially available, would provide powerful scaffolds and building blocks for the rapid construction of macromonomers and block copolymers. For that purpose, we focused our attention on *p*-maleimidophenyl isocyanate (**PMPI**)[28–36] [Fig. 1(a)] as a modification agent, which can be used to directly transform the hydroxy groups in polymer chains into reactive maleimide groups via a one-pot reaction with the reactive isocyanate group.

It is well known that isocyanates are highly reactive toward hydroxy groups, which are the most common functional groups in organic chemistry, to afford a urethane structure.[37–40] However, to the best of our knowledge, a comprehensive study of the reactivity of the isocyanate group in **PMPI** and its derivatives toward hydroxy moieties has not been reported so far. In this study, we have explored the potential of **PMPI** derivatives as hydroxy-modification agents to easily endow conventional polymers with new functionality. The prominent feature of isocyanate groups is the high reactivity toward hydroxy groups, which is much faster than other reactions such as esterification and amidation under facile conditions. We describe the synthesis and kinetic studies of **PMPI** derivatives, which were

Additional supporting information may be found in the online version of this article.

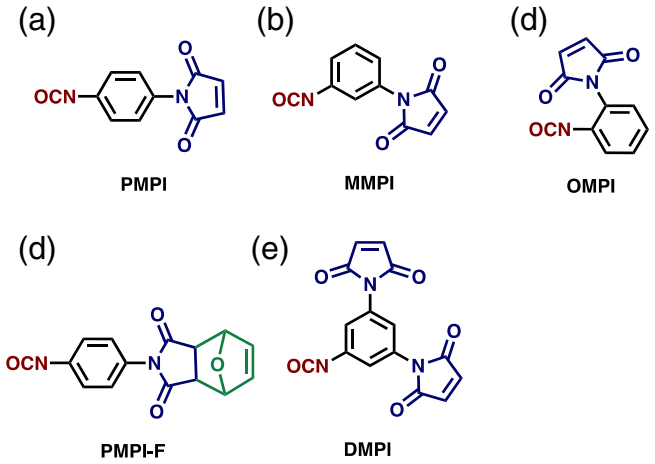


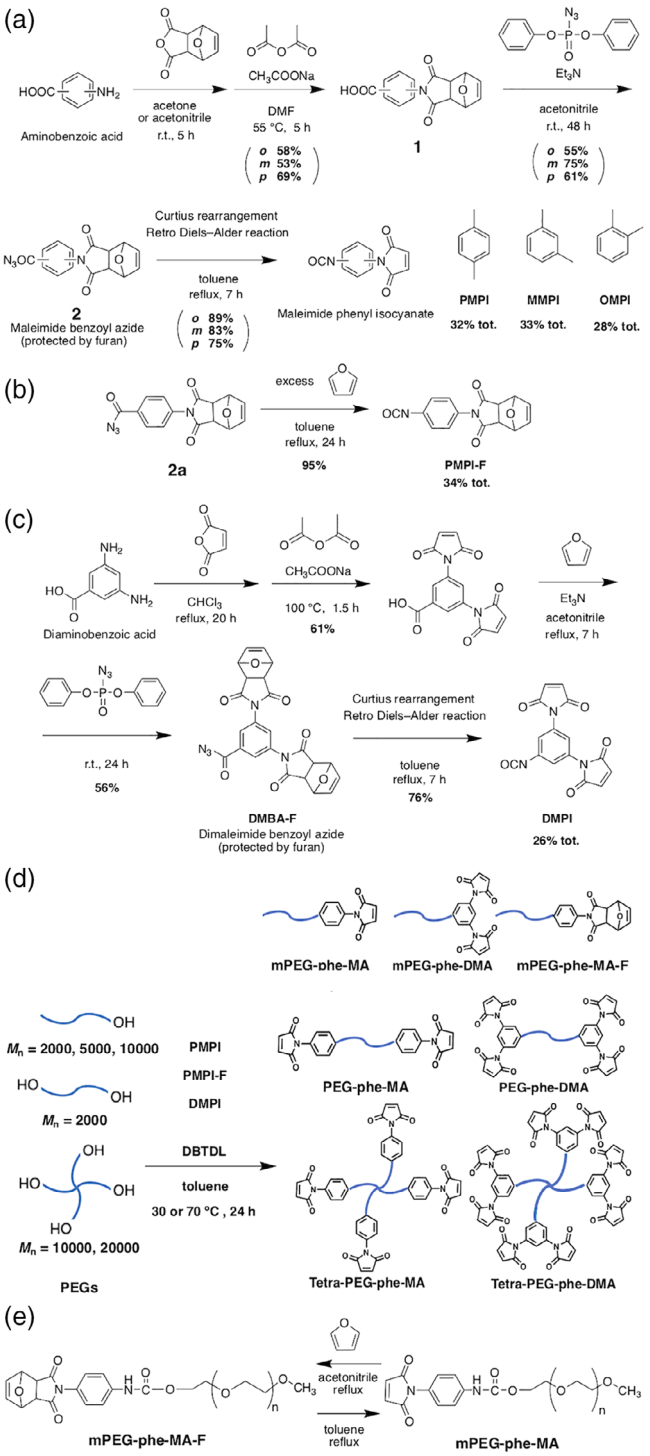

**FIGURE 1** (a) **PMPI**; (b) **MMPI**; (c) **OMPI**; (d) the corresponding Diels–Alder adduct of **PMPI** (**PMPI-F**); and (e) disubstituted derivative **DMPI**. [Color figure can be viewed at wileyonlinelibrary.com]

subsequently applied in postpolymerization modification reactions of hydroxy-terminated polymers, to demonstrate their promising potential for the development of functional polymers.

## RESULTs AND DISCUSSION

### Synthesis of Maleimidophenyl Isocyanates

**PMPI** and its derivatives, that is, its positional isomers, Diels–Alder adduct, and disubstituted derivative prepared as modification agents in this study, are shown in Figure 1. These compounds were synthesized starting from commercially available aminobenzoic acids (Scheme 1). The amino groups of these starting materials were reacted with a furan-maleic anhydride adduct, that is, exo-oxabicyclo[2.2.1] hept-5-ene-2,-3-dicarboxylic anhydride, followed by a dehydrative cyclization to give furan–maleimide Diels–Alder-adduct-based benzoic acids **1** [Scheme 1(a)]. It should be noted here that the Diels–Alder adducts of these compounds are easily generated by simple mixing with furan, and as easily reverted by heating in solution. Furan is thus an easy-to-remove protecting group for maleimide derivatives, endowing the resulting compounds with good solubility in common organic solvents and desirable crystallinity for purification. The corresponding acyl azides (**2**) were obtained from **1** using diphenylphosphoryl azide (DPPA) in the presence of a base catalyst under mild condition. A solution of **2** in toluene was heated to reflux in order to induce the simultaneous Curtius rearrangement and deprotection of furan, affording **PMPI** and its isomers [*m*-maleimidophenyl isocyanate (**MMPI**) and *o*-maleimidophenyl isocyanate (**OMPI**)]. Importantly, the Diels–Alder-adduct-based phenyl isocyanate **PMPI-F** was synthesized by refluxing a toluene solution of **2a** (*para*) in the presence of excess furan to induce a Curtius rearrangement under retention of the structure of the Diels–Alder adduct (Scheme 1b). 3,5-(Dimaleimido)phenyl isocyanate (**DMPI**), a di-maleimidation agent that provides further divergence, was synthesized from 3,5-diaminobenzoic acid in a similar manner [Scheme 1(c)]. The products were fully characterized by nuclear magnetic resonance (NMR) spectroscopy (Figs. S1–S14),




**SCHEME 1** Synthesis of (a) **PMPI** and its isomers; (b) Diels–Alder adduct **PMPI-F**; (c) disubstituted derivative **DMPI**; and (d) phenyl maleimide-terminated PEG polymers. (e) Reversible Diels–Alder reaction of monofunctional phenyl maleimide-terminated PEG. [Color figure can be viewed at wileyonlinelibrary.com]

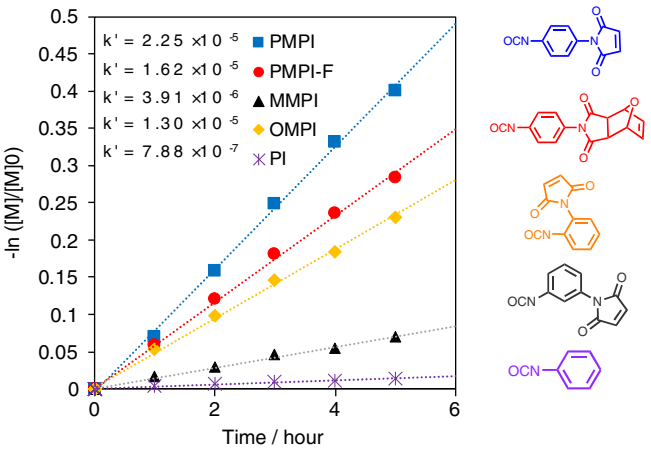



**FIGURE 2** Kinetic analysis of the reactions between 3-phenyl-1-propanol and a 10-fold excess of the corresponding isocyanate reagents (blue: **PMPI**, red: **PMPI-F**, yellow: **OMPI**, black: **MMPI**, and purple: **PI**) in $CDCl_3$ at 30°C. [Color figure can be viewed at wileyonlinelibrary.com]

infrared (IR) spectroscopy, and fast atom bombardment mass spectrometry (FAB-MS) or electron ionization MS (EI-MS) (see Supporting Information for details). Although handling the acyl azide derivatives needs a careful eye, the present protocol for the preparation of **PMPI** derivatives via Diels–Alder adducts is amenable to large-scale syntheses without the need for elaborate purification procedures such as a column chromatography.

### Reactivities of Maleimidophenyl Isocyanates

The reactivity of the isocyanate groups in the resulting derivatives was studied. The prepared compounds were treated with 3-phenyl-1-propanol as a model alcohol to quantitatively afford the corresponding urethane derivatives that bear maleimide units. The reactivity of each mono-maleimidophenyl isocyanate (**PMPI**, **PMPI-F**, **MMPI**, and **OMPI**) was evaluated in detail in the reaction between 3-phenyl-1-propanol and a 10-fold excess of the isocyanate in $CDCl_3$ at 30°C in the absence of a catalyst, and was monitored by $^1$H NMR spectroscopy (Figs. S15–S19). As shown in Figure 2, the pseudo-first-order kinetics revealed larger rate constants ($k'$) for the maleimide-substituted phenyl isocyanates than for unsubstituted phenyl isocyanate (**PI**). The reactivity of the isocyanate probably increases in the mono-maleimidophenyl derivatives as the maleimide unit acts as an electron-withdrawing group. In turn, the reactivity of the *ortho*- and *para*-substituted phenyl isocyanates is greater than that of the *meta*-substituted derivative, which is consistent with the general theory. The $k'$ values of the *para*-substituted phenyl isocyanates (**PMPI** and **PMPI-F**) were 20–30 times larger than that of unsubstituted **PI**, and thus the largest of all derivatives.

### Postpolymerization Modification

Based on this model reaction, **PMPI** and **PMPI-F** were applied in further polymer-modification reactions, along with **DMPI** as a di-maleimidation agent. Poly(ethylene glycol) (PEG) with hydroxy groups at the polymer ends was used as the model hydroxy-containing polymer to demonstrate the reactivity of the present modification agents. The postpolymerization modification of a variety of hydroxy-terminated PEG polymers with different molecular weights and topology was carried out with **PMPI**, **PMPI-F**, and **DMPI** in the presence of dibutyltin dilaurate (DBTDL) as the catalyst [Scheme 1(d)]. It should be noted that the modification reaction of hydroxy-terminated PEG proceeded without catalyst, but it was not as fast as that of model alcohol (Fig. S20). To achieve quick and

**TABLE 1** Characterization of Phenyl-Maleimide-Terminated PEG Polymers

| Sample[a] | $M_n$[b] (NMR) | $M_n$[c] (SEC) | $M_w/M_n$[c] (SEC) | Conv.[d] (%) | Yield (%) |
|---|---|---|---|---|---|
| **mPEG$_{2000}$-phe-MA** | 2300 | 2800 | 1,03 | quant. | 70 |
| **mPEG$_{5000}$-phe-MA** | 5200 | 6800 | 1.08 | quant. | 77 |
| **mPEG$_{10000}$-phe-MA** | 9500 | 14,000 | 1.03 | quant. | 74 |
| **mPEG$_{2000}$-phe-DMA** | 2400 | 2900 | 1.03 | quant. | 65 |
| **mPEG$_{5000}$-phe-DMA** | 5300 | 6800 | 1.07 | quant. | 81 |
| **mPEG$_{10000}$-phe-DMA** | 9600 | 14,000 | 1.03 | quant. | 71 |
| **mPEG$_{2000}$-phe-MA-F** | 2400 | 2800 | 1.03 | quant. | 94 |
| **mPEG$_{2000}$-phe-MA-F** | 5200 | 6900 | 1.08 | quant. | 89 |
| **mPEG$_{2000}$–phe-MA-F** | 9600 | 14,000 | 1.03 | quant. | 79 |
| **PEG$_{2000}$-phe-MA** | 2500 | 2700 | 1.02 | quant. | 67 |
| **PEG$_{2000}$-phe-DMA** | 2700 | 2800 | 1.02 | quant. | 74 |
| **Tetra-PEG$_{10000}$-phe-MA** | 12,000 | 11,000 | 1.03 | quant. | 71 |
| **Tetra-PEG$_{20000}$-phe-MA** | 23,000 | 22,000 | 1.03 | quant. | 54 |
| **Tetra-PEG$_{10000}$-phe-DMA** | 12,000 | 11,000 | 1.04 | quant. | 72 |
| **Tetra-PEG$_{20000}$-phe-DMA** | 24,000 | 20,000 | 1.04 | quant. | 44 |

[a] The subscript numbers indicate the molecular weight of the original PEG with the chemical structures shown in Scheme 1(d).
[b] Estimated by $^1$H NMR analysis.
[c] Estimated by SEC using THF as the eluent.
[d] Estimated by $^1$H NMR analysis.

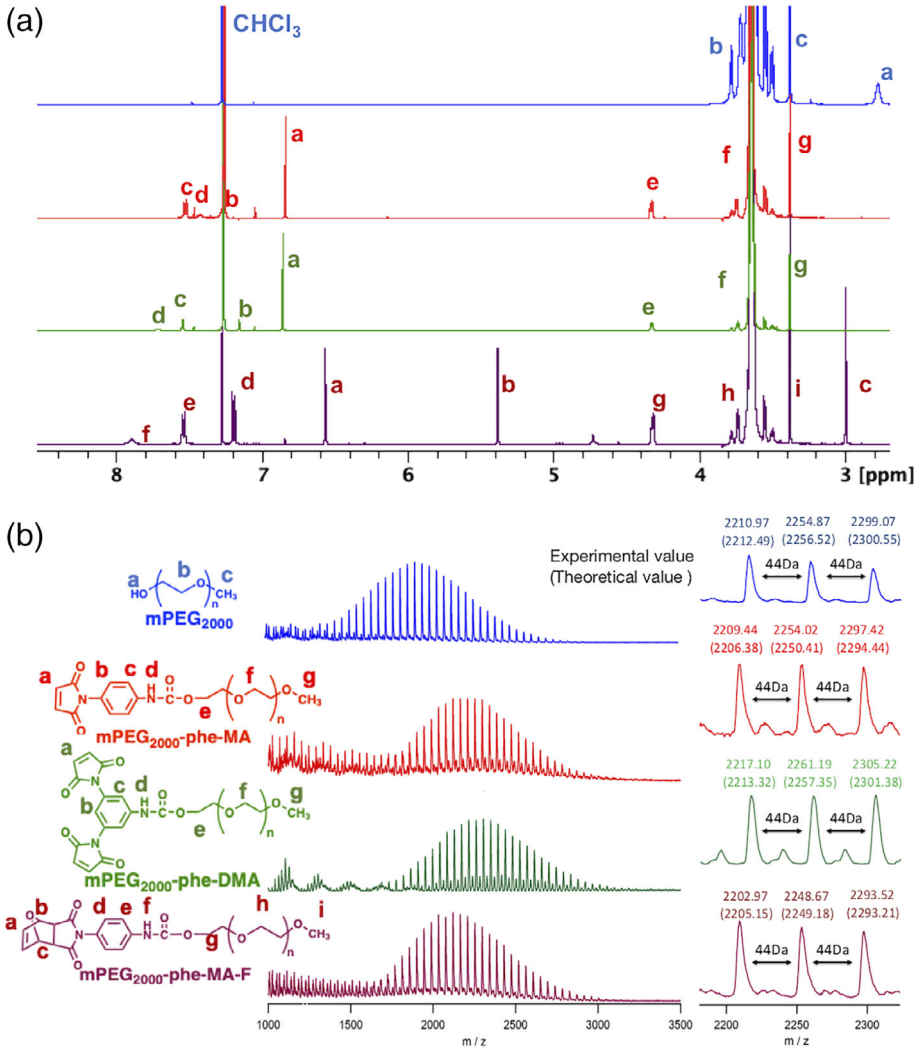



**FIGURE 3** (a) $^{1}$H NMR spectra (500 MHz, 25°C, $CDCl_3$) and (b) MALDI–TOF MS spectra (matrix: DHBA) of precursor **mPEG$_{2000}$** (blue) and maleimide-terminated **mPEG$_{2000}$** polymers (red: **mPEG$_{2000}$-phe-MA**; green: **mPEG$_{2000}$-phe-DMA**; purple: **mPEG$_{2000}$-phe-MA-F**). [Color figure can be viewed at wileyonlinelibrary.com]

quantitative conversion of polymer end, the catalyst was added into the following modification reaction in polymer chains.

Maleimide-terminated PEGs were obtained from one-pot reactions, and these polymers were characterized by $^{1}$H NMR spectroscopy, size exclusion chromatography (SEC), and matrix-assisted laser desorption ionization–time-of-flight (MALDI–TOF) MS. Their conversion, as estimated by $^{1}$H NMR spectroscopy, is summarized in Table 1. In the $^{1}$H NMR spectra, the complete disappearance of the resonances associated with the hydroxy groups and the consistency of the signal integrals with the theoretical values confirmed the quantitative progress of the modification reactions [Figs. 3(a) and S21–S27].

The SEC profiles and MALDI–TOF MS clearly show the complete progress of the reaction without any side reactions [Figs. 3(b) and S28–S37]. Although purification process to remove excess amount of isocyanate reagents decreased the isolated yield, modified polymers were easily obtained in moderate to good yield. Concurrently, the Diels–Alder adduct at the terminal structure of the polymer chain, that is, that obtained using **PMPI-F**, was easily removed by heating and introduced again under heating in the presence of excess furan [Scheme 1(e), Fig. S38].

As the undesired dimerization of maleimide units sometimes leads to storage instability, mono-maleimide-terminated PEG was irradiated with ultraviolet (UV) light in solution, that is, **mPEG$_{2000}$-phe-MA** dissolved in acetonitrile was exposed to strong UV light in quartz glass for 7 h at room temperature. The $^{1}$H NMR and SEC analyses revealed no reaction, supporting the high stability of phenyl maleimide against dimerization reactions (Figs. S39 and S40).[41]

As the postmodification reactions with **PMPI**, **PMPI-F**, and **DMPI** proceeded successfully, we subsequently explored the

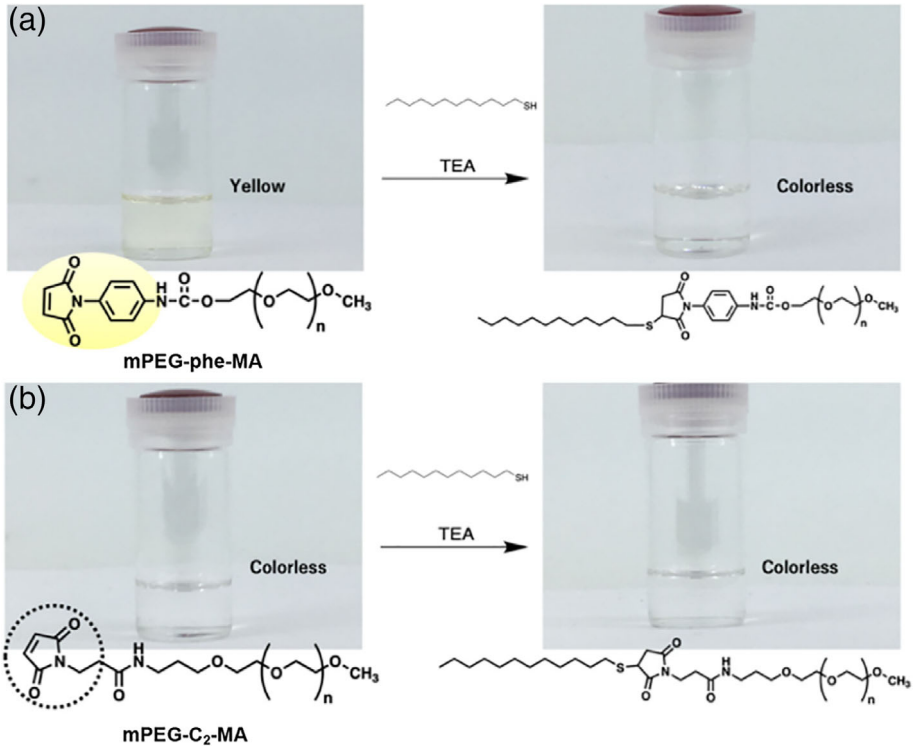



**FIGURE 4** Color changes in the reactions between maleimide-terminated PEG polymers and dodecanethiol. (a) *N*-aryl maleimide (**mPEG$_{2000}$-phe-MA**) and (b) *N*-alkyl maleimide (**mPEG$_{2000}$-C$_2$-MA**). [Color figure can be viewed at wileyonlinelibrary.com]

reactivity of the maleimide-modified polymers toward dodecanethiol. It should be noted here that the maleimide units are connected to an aromatic ring that is in turn attached to the polymer chain via a urethane moiety. Therefore, the reactivity of a general maleimide unit connected to an aliphatic alkyl group was also studied for comparison. To evaluate the reactivity of maleimide at the polymer ends, the pseudo-first-order kinetic rate constant $k'$ was determined for the reaction with a 10-fold excess of dodecanethiol as a primary thiol reagent and with modified PEGs that exhibit different maleimide structures (alkyl or aryl) and molecular weights (in $CDCl_3$; $T$ = 30°C; catalytic triethylamine). All obtained rate constants $k'$ were similar, regardless of the chemical structures or molecular weights, demonstrating the high reactivity of the modified maleimide moieties from **PMPI** (Figs. S41–S46). The progress of the reaction between the maleimide units directly connected to aromatic rings and thiols could also be confirmed by the change in color from yellow (derived from the maleimide-substituted aromatic ring) to colorless, indicating one further advantage of the use of these modification agents compared to the case of a maleimide unit connected to an aliphatic alkyl chain (Fig. 4).

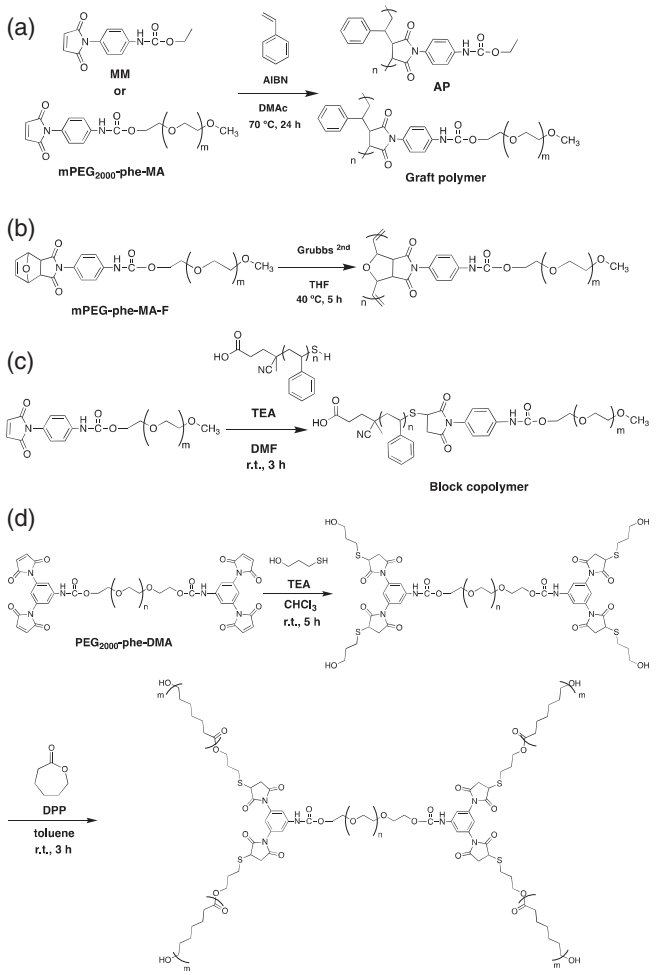
### Applications of Phenyl Maleimide-Terminated PEG Polymers

The modification agents were further applied to the synthesis of (a) graft polymers by alternating copolymerization of **mPEG-phe-MA** with styrene [Scheme 2(a)] or ring-opening metathesis polymerizations (ROMP) of **mPEG-phe-MA-F** [Scheme 2(b)], as well as (b) a variety of block copolymers, with, for example, AB-type, star-shaped, and H-shaped architectures [Scheme 2(c,d)].

The alternating copolymerization of **mPEG-phe-MA** with styrene was carried out by free-radical polymerization. Prior to the polymerization with the macromonomer, a model monomer (**MM**) was synthesized and subjected to alternating copolymerization with styrene [Scheme 2(a)]. The progress of the free-radical polymerization of **MM** to give the corresponding alternating copolymer (**AP**) was only observed when styrene was added (Figs. S47 and S48). In the $^1$H NMR spectrum of **AP**, the calculated composition ratios were consistent with the feed ratio (1:1), and the differential scanning calorimetry (DSC) analysis of **AP** revealed its excellent thermal properties ($T_g$ = 240°C), thus demonstrating the successful synthesis of an alternating polymer (Table S1, Figs. S49–S52). Then, maleimide-terminated PEG (**mPEG-phe-MA**) was used as a macromonomer and subjected to alternating copolymerization with styrene in a similar manner, affording a graft polymer [Figs. 5(a) and S53].

As it is well known that Diels–Alder adducts with furan can be subjected to ROMP due to their ring strain, we carried out a ROMP of **mPEG-phe-MA-F** using Grubbs second generation catalyst [Scheme 2(b), Figs. 5(b) and S54]. The polymerization of **mPEG-phe-MA-F** proceeded to furnish a different type of graft polymer.

As for the synthesis of block copolymers, the reaction between maleimide-terminated PEGs and thiol-terminated polymers synthesized by reversible addition–fragmentation chain transfer




**SCHEME 2** Application of maleimide-terminated PEG polymers: (a) alternating copolymerization with styrene; (b) ROMP of **mPEG-phe-MA-F**; (c) synthesis of a block copolymer by reaction with thiol-terminated PS; and (d) end-group functionalization with a thiol reagent and synthesis of an H-shaped copolymer by subsequent ring-opening polymerization.

polymerization was conducted in the presence of a base catalyst [Scheme 2(c)]. The characterization of the obtained polymers was performed by $^{1}$H NMR analysis and diffusion ordered spectroscopy (DOSY) experiments as well as SEC [Figs. 5 (c) and S55–S64]. AB-type, three-arm star-shaped, and ABA-type block copolymers composed of PEG and polystyrene (PS) chains were successfully prepared (Table S2). The macromolecular conjugation reactions proceeded very quickly and reached saturation within 1 h, demonstrating the excellent applicability of the modification agents in this study. Since PEG is known as biocompatible polymer and soluble in water, further application such as biomedical gel and drug delivery system could be achieved by using present phenyl maleimide-terminated PEG.

Finally, topological block copolymers, such as H-shaped, three-arm star, and five-arm star polymers were also synthesized by combination with thiol–ene click reactions, used here to introduce an initiator moiety for subsequent living polymerization of such macroinitiators [Scheme 2(d)]. Modification with 1-mercapto-3-propanol and subsequent ring-opening polymerization of ε-caprolactone successfully proceeded to give topological block copolymers with well-defined structures [Figs. 5(d) and S65–S76, Table S3].

## CONCLUSIONS

We have synthesized maleimidophenyl isocyanate derivatives as modification agents that are able to transform the hydroxy groups in polymer chains into reactive maleimide groups via a one-pot reaction. The high reactivity of the modification agents was demonstrated by the kinetics of the addition reactions between a model alcohol and the isocyanates as well as by coupling of the obtained maleimide-terminated polymers with thiol-terminated polymers, enabling further applications as building blocks for a variety of topological polymers, such as graft, star-shaped, and H-shaped polymers. The present protocol for the preparation of modification agents via Diels–Alder adducts is attractive and suitable for large-scale syntheses without the need for elaborate purification procedures such as column chromatography, since the Diels–Alder adducts of these compounds work as an easy-to-remove protecting group for maleimide derivatives and endow the resulting compounds with good solubility in common organic solvent and excellent crystallinity for the purification process. The present work thus represents a major contribution to polymer chemistry and materials science, which is supported by the convenience of the employed synthetic methodology that can be employed to transform commercially available materials, the wide availability and applicability of the present modification agents, and the access to functional materials as one further application of these modification agents.

## EXPERIMENTAL

### Materials

All reagents and solvents were purchased from Sigma-Aldrich (MO, USA), FUJIFILM Wako Pure Chemical Corporation (Tokyo, Japan), Tokyo Chemical Industry (Tokyo, Japan), and Kanto Chemical (Tokyo, Japan) and used as received, unless otherwise noted. Commercially available maleimide-terminated PEG polymers (SUNBRIGHT) were purchased from NOF Group (Tokyo, Japan). Four-arm PEGs were purchased from Biochempeg Scientific Inc. (MA, USA) and SINOPEG (Xiamen, China). Vinyl monomers were purified by basic alumina column (Merck KGaA) (Darmstadt, Germany) to remove the stabilizer and ε-caprolactone was purified by distillation prior to use.

### Measurements

$^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE III HD500 spectrometer. The LED method for DOSY measurement was used. Pulse program: ledbpgp2s, diffusion time: 40 ms, diffusion gradient length: 2000 μs, maximum gradient strength: 51 g cm$^{-1}$.[42] IR spectra were recorded on a JEOL FT/IR-4100 Fourier transform infrared (FTIR) spectrometer as thin films with KBr. Analytical SEC (SEC) measurements were carried out at 40°C on TOSOH HLC-8320 SEC system

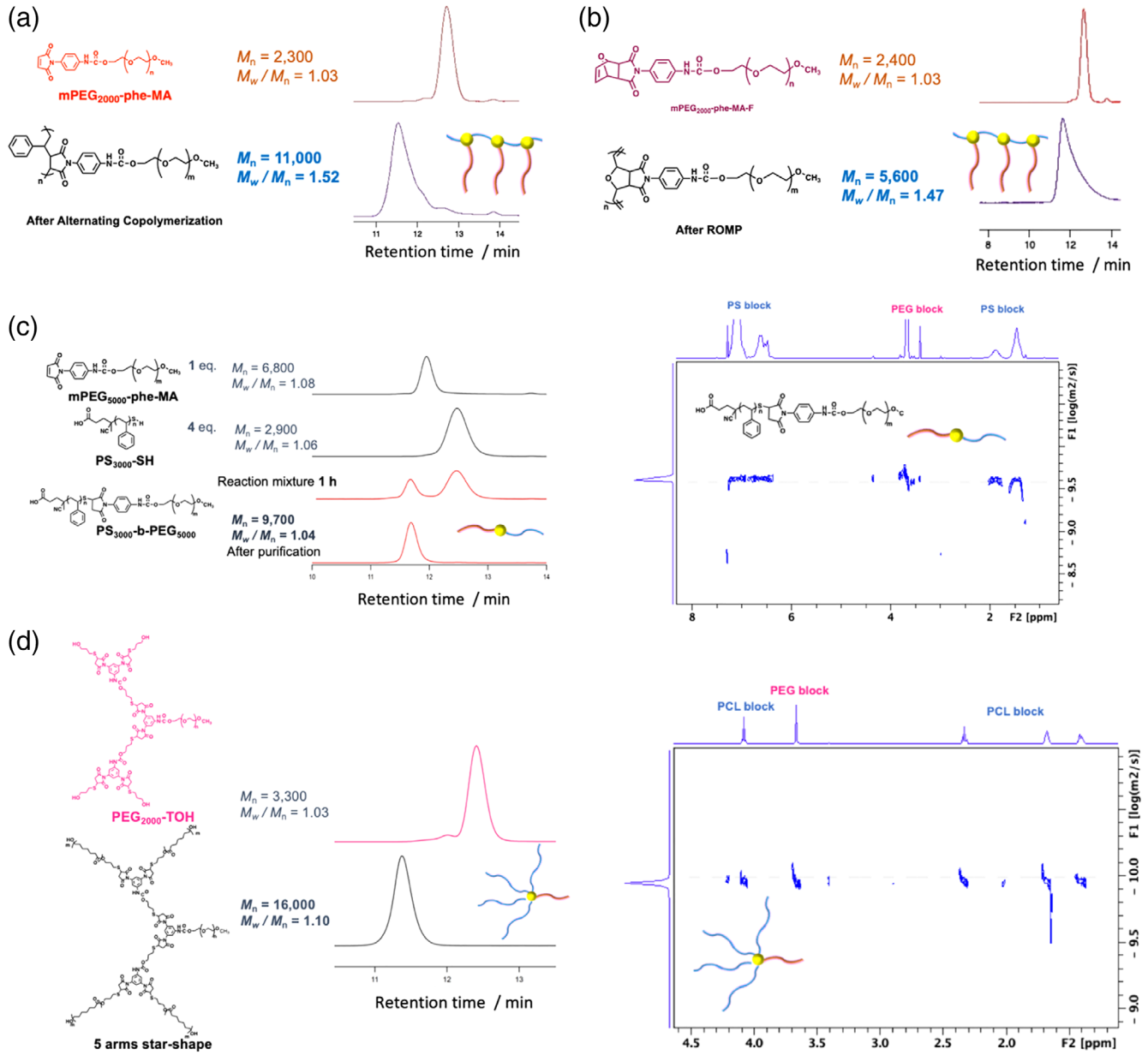



**FIGURE 5** (a) SEC charts in polymerization of **mPEG$_{2000}$-phe-MA** and styrene at 70°C (red: original **mPEG$_{2000}$-phe-MA**, purple after purification) (PS standard, eluent, THF; flow rate, 0.6 mL min$^{-1}$, detected by RI). (b) SEC charts of ROMP experiment (red: **PEG$_{2000}$-phe-MA-F**, purple: after ROMP) (PS standard, eluent, THF; flow rate, 0.6 mL min$^{-1}$, detected by RI). (c) SEC charts of PS-PEG block copolymer **PS$_{3000}$-b-PEG$_{5000}$** and its precursors (black: **mPEG$_{5000}$-phe-MA** and thiol-terminated PS **PS$_{3000}$-SH**, red: reaction mixture 1 h and after purification) (PS standard, eluent, THF; flow rate, 0.6 mL min$^{-1}$, detected by RI) and DOSY spectrum of **PS$_{3000}$-b-PEG$_{5000}$** (500 MHz, 25°C, $CDCl_3$). (d) SEC charts of **five-arm star-shaped block copolymer** and its precursor (pink: tetra-functional macroinitiator **PEG-TOH**, black: **five-arm star-shaped block copolymer**) (PS standard, eluent, THF; flow rate, 0.6 mL min$^{-1}$, detected by RI) and DOSY spectrum of **five-arm star-shaped block copolymer** (500 MHz, 25°C, $CDCl_3$). [Color figure can be viewed at wileyonlinelibrary.com]

equipped with a guard column (TOSOH TSK guard column Super H-L), three columns (TOSOH TSK gel SuperH 6000, 4000, and 2500), a differential refractive index detector, and a UV–visible detector. Tetrahydrofuran (THF) was used as the eluent at a flow rate of 0.6 mL min$^{-1}$. PS standards ($M_n$ = 4430–3,142,000; $M_w/M_n$ = 1.03–1.08) were used to calibrate the SEC system. MALDI–TOF MS spectra were determined on a Shimadzu AXIMA-CFR mass spectrometer. The spectrometer was equipped with a nitrogen laser (λ = 337 nm) and with pulsed ion extraction. The operation was performed at an accelerating potential of 20,000 V by a linear-positive ion mode. The sample polymer solution (1 mg mL$^{-1}$)

was prepared in THF, and 2,5-dihydroxybenzoic acid (DHBA) as a matrix reagent and sodium trifluoroacetate as a cationizing agent were dissolved in THF (20 and 1 mg $mL^{-1}$, respectively), and 50 μL of each solution was mixed prior to MALDI analysis. DSC was carried out using a Shimadzu DSC-60A DSC at a heating rate of 10°C $min^{-1}$ under $N_2$ flow.

### Synthesis of 3-(Carboxyphenylcarbamoyl)-7-oxabicyclo [2.2.1]hept-5-ene-2-carboxylic acid (Precursor of Compounds 1-a, b, c) (a; *para*-, b; *meta*-, c; *ortho*-)

Precursor of Compounds **1a–1c** was synthesized by the reaction of acid anhydride and amino benzoic acids. A typical procedure is presented below. Exo-oxabicylco[2.2.1] hept-5-ene-2,3-dicarboxylic anhydride (11.4 g, 68.6 mmol) was dissolved in acetone (210 mL). To this solution, *p*-amino benzoic acid (9.66 g, 70.5 mmol) was added. After stirring for 5 h at room temperature, a white solid precipitated from the solution. The solid was filtered and dried under vacuum (16.8 g, 81%).[43]

Precursor of **1a**, yield 81%. $^1$H NMR [dimethyl sulfoxide (DMSO-$d_6$)], δ (ppm): 10.15 (s, 1H, COOH), 7.89–7.87 (d, 2H, *J* = 8.8 Hz, aromatic protons), 7.67–7.65 (d, 2H, *J* = 8.8 Hz, aromatic protons), 6.52–6.48 (m, 2H, —CH—CH═CH—CH—), 5.14 (br, 1H, —CH—CH═CH—CH—), 5.07 (br, 1H, —CH—CH═CH—CH—), 2.83–2.81 (d, 2H, *J* = 9.2 Hz, HOOC—CH—CH—CONH), 2.71–2.69 (d, 2H, *J* = 9.2 Hz, HOOC—CH—CH—CONH).

Precursor of **1b**, yield 83%. $^1$H NMR (DMSO-$d_6$), δ (ppm): 9.99 (s, 1H, COOH), 8.22 (t, 1H, *J* = 1.5, 1.5 Hz, aromatic proton), 7.74–7.73 (m, 1H, aromatic proton), 7.62–7.60 (m, 1H, aromatic proton), 7.43–7.40 (t, 1H, *J* = 7.9, 7.9 Hz, aromatic proton), 6.52–6.49 (m, 2H, —CH—CH═CH—CH—), 5.14 (br, 1H, —CH—CH═CH—CH—), 5.06 (br, 1H, —CH—CH═CH—CH—), 2.85–2.83 (d, 2H, *J* = 9.2 Hz, HOOC—CH—CH—CONH), 2.72–2.70 (d, 2H, *J* = 9.2 Hz, HOOC—CH—CH—CONH).

Precursor of **1c**, reaction solvent; $CH_3CN$, yield 87%. $^1$H NMR (DMSO-$d_6$), δ (ppm): 11.03 (s, 1H, COOH), 8.47–8.45 (d, 1H, *J* = 8.4 Hz, aromatic proton), 7.95–7.93 (d, 1H, *J* = 7.9 Hz, aromatic proton), 7.58–7.54 (m, 1H, aromatic proton), 7.14–7.11 (t, 1H, *J* = 7.0, 7.1 Hz, aromatic proton), 6.53–6.47 (m, 2H, —CH—CH═CH—CH—), 5.19 (br, 2H, —CH—CH═CH—CH—), 2.84–2.82 (d, 2H, *J* = 9.3 Hz, HOOC—CH—CH—COONH), 2.76–2.74 (d, 2H, *J* = 9.3 Hz, HOOC—CH—CH—COONH).

### Synthesis of 1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl benzoic acid (Compounds 1-a, b, c)

Compounds **1a–1c** were synthesized by the dehydration cyclization reaction of precursor of **1a–1c**. A typical procedure is presented below. Precursor of Compound **1a** (16.8 g, 55.4 mmol) was dissolved in dimethylformamide (60.0 mL) at 55°C. To this solution, acetic anhydride (60.0 mL, 635 mmol) and sodium acetate (4.00 g, 122 mmol) were added under stirring. After stirring for 5 h at 55°C, the reaction mixture was poured into 1 L of a 0.6 M aqueous hydrochloric acid solution in an ice bath. The precipitated brown color solid was filtered and dried under vacuum (11.4 g, 72%).[43]

**1a**, yield 72%. $^1$H NMR (DMSO-$d_6$), δ (ppm): 8.05–8.03 (d, 2H, *J* = 8.6 Hz, aromatic protons), 7.36–7.34 (d, 2H, *J* = 8.4 Hz, aromatic protons), 6.62 (br, 2H, —CH—CH═CH—CH—), 5.27 (br, 2H, —CH—CH═CH—CH—), 3.11 (s, 2H, OC—CH—CH—CO).

**1b**, yield 64%.$^1$H NMR (DMSO-$d_6$), δ (ppm): 8.00–7.98 (m, 1H, aromatic proton), 7.79–7.78 (t, 1H, *J* = 1.8, 1.8 Hz, aromatic proton), 7.66–7.62 (t, 1H, *J* = 7.9, 7.9 Hz, aromatic proton), 7.50–7.48 (m, 1H, aromatic proton), 6.62 (br, 2H, —CH—CH═CH—CH—), 5.28 (br, 2H, —CH—CH═CH—CH—), 3.11 (s, 2H, OC—CH—CH—CO).

**1c**, yield 79%.$^1$H NMR (DMSO-$d_6$), δ (ppm): 8.04–8.02 (d, 1H, *J* = 7.5 Hz, aromatic proton), 7.72–7.69 (t, 1H, *J* = 7.5, 7.2 aromatic proton), 7.61–7.58 (t, 1H, *J* = 7.5, 7.2 Hz, aromatic proton), 7.14–7.13 (d, 1H, *J* = 7.8 Hz, aromatic proton), 6.62 (br, 2H, —CH—CH═CH—CH—), 5.29 (br, 2H, —CH—CH═CH—CH—), 3.13 (s, 2H, OC—CH—CH—CO).

### Synthesis of 1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl benzoyl azide (Compounds 2-a, b, c)

The conversion of benzoic acid to benzoyl azide was carried out by using DPPA as an azidation agent in the presence of a base catalyst. A typical procedure is presented below. Compound **1a** (11.4 g, 40.0 mmol) was dissolved in acetonitrile (50 mL) and triethylamine (11.0 mL, 78.9 mmol). To this solution, DPPA (11.0 mL, 51.0 mol) was added under stirring and the reaction mixture was stirred for 48 h at room temperature.

Compound **2a**: Precipitated solid was filtered and dried under vacuum (7.56 g, 61%). $^1$H NMR [$CDCl_3$, tetramethylsilane (TMS)], δ (ppm): 8.14–8.11 (d, 2H, *J* = 8.6 Hz, aromatic protons), 7.47–7.44 (d, 2H, *J* = 8.6 Hz, aromatic protons), 6.59 (br, 2H, —CH—CH═CH—CH—), 5.41 (br, 2H, —CH—CH═CH—CH—), 3.05 (s, 2H, OC—CH—CH—CO), $^{13}$C NMR ($CDCl_3$), δ (ppm): 174.80 (C═O imide ring), 171.62 (C═O acyl azide), 136.78 (—CH—CH═CH—CH—), 136.82, 130.44, 130.28, and 126.51 (aromatic carbons), 81.54 (—CH—CH═CH—CH—), 47.65 (OC—CH—CH—CO), FTIR (KBr, $cm^{-1}$): 2140 ($CON_3$), 1720, 1680, 1600, 1500, 1380, 1250, 1180, 1000, 870, and 720, high-resolution mass spectrometry (HRMS) (FAB): 311.0780 $[M + H]^+$, calculated for $C_{15}H_{11}N_4O_4$ $[M + H]^+$: 311.0780.

Compound **2b**: Reaction mixture was chromatographed over activated silica using acetone as an eluent. Except for **2b**, column chromatography technique was not required. The elute was evaporated *in vacuo* to give **2b** (75%) as a white solid. $^1$H NMR (DMSO-$d_6$), δ (ppm): 8.03–8.01 (m, 1H, aromatic proton), 7.83–7.82 (t, 1H, *J* = 1.8, 1.8 Hz, aromatic proton), 7.73–7.70 (t, 1H, *J* = 7.8, 7.9 Hz, aromatic proton), 7.62–7.60 (m, 1H, aromatic proton), 6.62 (br, 2H, —CH—CH═CH—CH—), 5.28 (br, 2H, —CH—CH═CH—CH—), 3.12 (s, 2H, OC—CH—CH—CO), $^{13}$C NMR (DMSO-$d_6$), δ (ppm): 176.00 (C═O imide ring), 171.65 (C═O acyl azide), 137.13 (—CH—CH═CH—CH—), 133.30, 133.09, 131.44, 130.49, 129.33, and 127.52 (aromatic carbons), 81.29 (—CH—CH═CH—CH—), 48.12 (OC—CH—CH—CO),

FTIR (KBr, $cm^{-1}$): 2150 ($CON_3$), 1710, 1690, 1590, 1490, 1450, 1380, 1180, 1030, 880, and 710, HRMS (FAB): 311.0782 $[M + H]^+$, calculated for $C_{15}H_{11}N_4O_4$ $[M + H]^+$: 311.0780.

Compound **2c**: Precipitated solid was filtered and dried under vacuum (55%). $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 8.12–8.11 (d, 1H, *J* = 8.0 Hz, aromatic proton), 7.72–7.70 (t, 1H, *J* = 7.5, 7.4 Hz, aromatic proton), 7.55–7.52 (t, 1H, *J* = 7.5, 7.7 Hz, aromatic proton), 7.31–7.29 (d, 1H, *J* = 7.8 Hz, aromatic proton), 6.58 (br, 2H, —CH—CH═CH—CH—), 5.41 (br, 2H, —CH—CH═CH—CH—), 3.11 (s, 2H, OC—CH—CH—CO), $^{13}C$ NMR ($CDCl_3$), δ (ppm): 175.43 (C═O imide ring), 170.80 (C═O acyl azide), 136.71 (—CH—CH═CH—CH—), 134.90, 132.12, 131.77, 130.23, 129.75, and 127.25 (aromatic carbons), 81.23 (—CH—CH═CH—CH—), 48.11 (OC—CH—CH—CO), FTIR (KBr, $cm^{-1}$): 2140 ($CON_3$), 1715, 1680, 1600, 1490, 1450, 1380, 1180, 1000, and 870, HRMS (FAB): 311.0781 $[M + H]^+$, calculated for $C_{15}H_{11}N_4O_4$ $[M + H]^+$: 311.0780.

### Synthesis of Maleimidophenyl Isocyanate (PMPI, MMPI, OMPI)

Maleimidophenyl isocyanates were synthesized by the Curtius rearrangement reaction and deprotection from furan of benzoyl azide. A typical procedure is presented below. **2a** (3.00 g, 9.67 mmol) and toluene (120 mL) were added to a round-bottom flask and the mixture was heated at reflux condition for 7 h. Then the solution was filtered to remove by-products and the filtrate was evaporated *in vacuo* to give **PMPI** (1.83 g, 89%) as a yellow solid.

**PMPI,**[35] yield 89%. $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 7.28–7.26 (d, 2H, *J* = 8.9 Hz, aromatic protons), 7.20–7.18 (d, 2H, *J* = 8.9 Hz, aromatic protons), 6.87 (s, 2H, —CH═CH—).

**MMPI,**[35] yield 83%. $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 7.44–7.40 (t, 1H, *J* = 8.1, 8.1 Hz, aromatic proton), 7.24–7.22 (m, 1H, aromatic proton), 7.15–7.14 (t, 1H, *J* = 2.0, 2.0 Hz, aromatic proton), 7.12–7.10 (m, 1H, aromatic proton), 6.88 (s, 2H, —CH═CH—).

**OMPI**, yield 75%. $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 7.44–7.40 (m, 1H, aromatic proton), 7.33–7.29 (m, 1H, aromatic proton), 7.28–7.26 (m, 1H, aromatic proton), 7.23–7.21 (m, 1H, aromatic proton), 6.92 (s, 2H, —CH═CH—), $^{13}C$ NMR ($CDCl_3$), δ (ppm): 168.98 (C═O imide ring), 134.72 (—CH═CH—), 132.10, 130.51, 129.83, 126.60, 126.43, and 125.67 (aromatic carbons), FTIR (KBr, $cm^{-1}$): 2260 (NCO), 1710, 1600, 1530, 1460, 1390, 1270, 1150, 1100, 1060, 950, and 830, HRMS (FAB): 215.0451 $[M + H]^+$, calculated for $C_{11}H_7N_2O_3$ $[M + H]^+$: 215.0457.

### Synthesis of 2-(4-Isocyanatophenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (PMPI-F)

**PMPI-F** was synthesized by the Curtius rearrangement reaction of **2a** under an excess amount of furan. **2a** (6.00 g, 19.3 mmol), toluene (160 mL) and furan (40.0 mL, 550 mmol) were added to a round-bottom flask and the mixture was heated at reflux condition for 24 h. Then, the solution was filtered and the filtrate was evaporated *in vacuo* to give **PMPI-F** (5.19 g, 95%) as an orange color solid. $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 7.28–7.26 (d, 2H, *J* = 8.8 Hz, aromatic protons), 7.19–7.17 (d, 2H, *J* = 8.9 Hz, aromatic protons), 6.58 (br, 2H, —CH—CH═CH—CH—), 5.40 (br, 2H, —CH—CH═CH—CH—), 3.02 (s, 2H, CO—CH—CH—CO), $^{13}C$ NMR ($CDCl_3$), δ (ppm): 175.18 (C═O imide ring), 136.73 (—CH—CH═CH—CH—), 133.79, 129.12, 127.79, and 125.40 (aromatic carbons), 81.45 (—CH—CH═CH—CH—), 47.56 (OC—CH—CH—CO), FTIR (KBr, $cm^{-1}$): 2280 (NCO), 1710, 1600, 1530, 1380, 1190, 1100, 940, and 870, HRMS (FAB): 283.0721 $[M + H]^+$, calculated for $C_{15}H_{11}N_2O_4$ $[M + H]^+$: 283.0719.

### Synthesis of 3,5-Dimaleimide Benzoic Acid

Precursor of 3,5-dimaleimide benzoic acid was synthesized by the reaction of acid anhydride and 3,5-diaminobenzoic acid. Maleic anhydride (2.94 g, 30.0 mmol) was dissolved in chloroform (100 mL). To this solution, 3,5-diaminobenzoic acid (1.52 g, 1.00 mmol) was added. After stirring for 20 h at reflux, a yellow solid precipitated from the solution. The solid was filtered and dried under vacuum (3.34 g, 96%). $^1H$ NMR (DMSO-$d_6$), δ (ppm): 10.58 (s, 1H, COOH), 8.33–8.32 (t, 1H, *J* = 1.9, 1.9 Hz, aromatic proton), 7.98–7.97 (d, 2H, *J* = 2.0 Hz, aromatic protons), 6.48–6.45 (d, 2H, *J* = 12 Hz, HNOC—CH═CH—)COOH), 6.35–6.32 (d, 2H, *J* = 12 Hz, HNOC—CH═CH—)COOH).[14]

The obtained solid (3.34 g, 9.59 mmol), acetic anhydride (75.0 mL, 793 mmol), and sodium acetate (250 mg, 30.5 mmol) were added to a round-bottom flask. After stirring for 1.5 h at 100°C, the reaction mixture was poured into 1 L of 0.6 M aqueous hydrochloric acid solution in an ice bath twice. Then beige color solid was precipitated from solution. The solid[14] was filtered and dried under vacuum (2.01 g, 64%).$^1H$ NMR (DMSO-$d_6$), δ (ppm): 7.98–7.97 (d, 1H, *J* = 2.0 Hz, aromatic proton), 7.65–7.64 (t, 2H, *J* = 1.9 Hz, aromatic protons), 7.21 (s, 4H, —CH═CH—).

### Synthesis of 3,5-Bis(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)benzoyl azide (DMBA-F)

The conversion of benzoic acid to benzoyl azide was carried out by using DPPA as an azidation agent in the presence of a base catalyst after the protection of 3,5-dimaleimide benzoic acid by furan. 3,5-Dimaleimide benzoic acid (2.01 g, 6.44 mmol) was dissolved in acetonitrile (80 mL) and triethylamine (1.50 mL, 10.8 mmol). To this solution, furan (30.0 mL, 413 mmol) was added and stirring for 7 h under reflux condition. After cooling to room temperature, DPPA (1.53 mL, 7.10 mmol) was added to the reaction solution under stirring and the mixture was stirring for 24 h at room temperature. After the reaction mixture was concentrated by evaporation *in vacuo*, a white solid precipitated from the solution. The solid was filtered and dried under vacuum (1.62 g, 56%). $^1H$ NMR ($CDCl_3$, TMS), δ (ppm): 8.05 (d, 2H, *J* = 1.9 Hz, aromatic protons), 7.67–7.66 (t, 1H, *J* = 1.9 Hz, aromatic proton), 6.59 (br, 4H, —CH—CH═CH—CH—), 5.42 (br, 4H, —CH—CH═CH—CH—), 3.04 (s, 4H, OC—CH—CH—CO), $^{13}C$ NMR ($CDCl_3$), δ (ppm): 174.52 (C═O imide ring), 170.65 (C═O acyl azide), 136.77 (—CH—CH═CH—CH—), 132.74, 132.22, 129.43 and 127.01 (aromatic carbons), 81.46 (—CH—CH═CH—CH—), 47.63

(CO—CH—CH—CO), FTIR (KBr, $cm^{-1}$): 2145 ($CON_3$), 1715, 1600, 1450, 1370, and 1190, HRMS (FAB): 474.1061 $[M + H]^+$, calculated for $C_{23}H_{16}N_5O_7$ $[M + H]^+$: 474.1050.

**Synthesis of DMPI**

**DMBA-F** (1.00 g, 2.11 mmol) and toluene (120 mL) were added to a round-bottom flask and the mixture was heated at reflux condition for 7 h. Then, the solution was filtered to remove by-products and the filtrate was evaporated *in vacuo* to give **DMPI** (499 mg, 76%) as a yellow solid. $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.41–7.40 (t, 1H, $J$ = 1.9, 1.9 Hz, aromatic proton), 7.20 (d, 2H, $J$ = 1.9 Hz, aromatic protons), 6.89 (s, 4H, —C—CH=CH—)C—), $^{13}$C NMR ($CDCl_3$), δ (ppm): 167.76 (C=O imide ring), 133.36 (—C—CH=CH—)C—), 131.81, 127.60, 119.74, and 118.49 (aromatic carbons), FTIR (KBr, $cm^{-1}$): 2280 (NCO), 1710, 1600, 1530, 1380, and 1190, HRMS (EI): 309.0382 $[M]^+$, calculated for $C_{15}H_7N_3O_5$ $[M]^+$: 309.0386.

**Kinetics Experiment**

To estimate the reactivities of isocyanate reagents with alcohol, $^1$H NMR analysis was carried out. Pseudo-first-order kinetics rate constant $k'$ was measured in reaction between excess amount of isocyanate reagents and 3-phenyl-1-propanol or **mPEG$_{2000}$** as a primary alcohol reagent in $CDCl_3$ at 30°C. A typical measurement is presented below. **PMPI** (43.0 mg, 200 μmol) was dissolved in $CDCl_3$ including 0.03% of trimethoxy silane (2.00 mL). Then, 10 vol % of benzene propanol solution (27.2 μL, 20.0 μmol) was added and stirred. A total volume of 1 mL of this solution was taken to an NMR tube as a sample and heated at 30°C. Measuring its $^1$H NMR spectrum every hour, —OH group conversion rate $x$ was determined by the ratio of original signal (t, 2H, —CH$_2$—OH) at 3.6 ppm to appearing signal [t, 2H, —CH$_2$—O—(C=O)—NH—] at 4.2 ppm. Rate constant $k'$ was calculated from the following equation:

$$k't = -\ln(1-x)$$

Same experiment was carried out to estimate reactivities of polymer terminated-maleimide to thiol reagents (see Supporting Information for details).

**Synthesis of Phenyl Maleimide-Terminated PEG Polymers**

Maleimide-terminated PEG polymers were synthesized by the one-pot reaction of hydroxy groups and each phenyl maleimide isocyanate (**PMPI**, **PMPI-F**, and **DMPI)**. A typical procedure is presented below. **PMPI** (172 mg, 800 μmol) and PEG monomethyl ether ($M_n$ 2000 g mol$^{-1}$) (400 mg, 200 μmol) were added to a round-bottom flask. Dehydrated toluene (24.0 mL) and four drops of 10 vol % DBTDL in toluene were added under inert atmosphere. After stirring for 24 h at 70°C, the reaction mixture was poured into 200 mL of a poor solvent (diethyl ether/ethanol, 30/1, v/v) in an ice bath. The precipitate was separated by filtration and dried under vacuum to obtain **mPEG$_{2000}$-phe-MA** as a yellow solid (70%). The reaction was carried out at 30°C only when modifying with **PMPI-F**. Yields of all other maleimide-terminated PEG polymers are shown in Table 1.

**mPEG-phe-MA**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.54–7.52 (d, 2H, $J$ = 8.8 Hz, aromatic protons), 7.27–7.25 (d, 2H, $J$ = 8.8 Hz, aromatic protons), 7.05 (s, 2H, —CH—CH=CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × n, (—OCH$_2$CH$_2$O—)$_n$), 3.38 (s, 3H, CH$_3$O—].

**mPEG-phe-MA-F**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.55–7.53 (d, 2H, $J$ = 8.8 Hz, aromatic protons), 7.20–7.19 (d, 2H, $J$ = 8.8 Hz, aromatic protons), 6.57 (br, 2H, —CH—CH=CH—CH—), 5.38 (br, 2H, —CH—CH=CH—CH—), 4.33–4.31 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × n, (—OCH$_2$CH$_2$O—)$_n$], 3.38 (s, 3H, CH$_3$O—), 3.00 (s, 2H, OC—CH—CH—CO).

**mPEG-phe-**dimethylacetamide (**DMA**), $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.55 (br, 2H, aromatic protons), 7.16 (t, 1H, $J$ = 1.8 Hz, aromatic proton), 6.86 (s, 4H, —CH—CH=CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × n, (—OCH$_2$CH$_2$O—)$_n$], 3.38 (s, 3H, CH$_3$O—).

**PEG-phe-MA**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.54–7.52 (d, $J$ = 8.8 Hz, 2H, aromatic protons), 7.27–7.25 (d, $J$ = 8.8 Hz, 2H, aromatic protons), 7.05 (s, 2H, —CH—CH=CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × n, (—OCH$_2$CH$_2$O—)$_n$].

**PEG-phe-DMA**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.55 (br, 2H, aromatic protons), 7.16 (t, 1H, $J$ = 1.8 Hz, aromatic proton), 6.86 (s, 4H, —CH—CH=CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × n, (—OCH$_2$CH$_2$O—)$_n$].

Maleimide-terminated four-arm PEG polymers (**Tetra-PEG-phe-MA** and **Tetra-PEG-phe-DMA**) were synthesized by the one-pot reactions of hydroxy groups in four-arm PEGs and **PMPI** or **DMPI**. The products were purified by preparative high-performance liquid chromatography (HPLC). Although precipitation technique gave the modified four-arm PEG polymers, it has been difficult to efficiently remove small molecular byproducts originated from isocyanate. This tendency was remarkable for PEG with number of branches. It should be noted that conversion of hydroxy groups is quantitative and HPLC preparation is not required if purity is not emphasized. A typical procedure is presented below. **PMPI** (344 mg, 1.60 mmol) and four-arm PEG [$M_{n(SEC)}$ 10000 g mol$^{-1}$, PDI 1.03] (200 mg, 20.0 μmol) were added to a round-bottom flask. Dichloromethane (48 mL) and eight drops of 10 vol % DBTDL in dichloromethane were added under inert atmosphere. After stirring for 72 h at 30°C, the reaction mixture was evaporated *in vacuo*. An oily residue was purified by preparative HPLC using chloroform as an eluent and dried under vacuum to obtain **Tetra-PEG$_{10000}$-phe-MA** as a yellow solid (71%). Yields of all other maleimide-terminated PEG polymers are shown in Table 1 in the main text.

**Tetra-PEG-phe-MA**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.54–7.52 (d, 2H, $J$ = 8.8 Hz, aromatic protons), 7.27–7.25 (d, 2H, aromatic protons), 7.05 (s, 2H, —CH—CH=CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —CH$_2$—CH$_2$—O—(C=O)—], 3.66–3.58 [m, 4H × 4n, (—OCH$_2$CH$_2$O—)$_n$].

**Tetra-PEG-phe-DMA**, $^1$H NMR ($CDCl_3$, TMS), δ (ppm): 7.55 (br, 2H, aromatic protons), 7.16 (t, 1H, $J$ = 1.9, 1.9 Hz, aromatic proton), 6.86 (s, 4H, —CH—CH═CH—CH—), 4.34–4.32 [t, 2H, $J$ = 4.6 Hz, —$CH_2$—$CH_2$—O—(C═O)—], 3.66–3.58 [m, 4H × n, (—O$CH_2CH_2$O—)$_n$].

### Reversible Diels–Alder Reaction of Monofunctional Phenyl Maleimide-Terminated PEG

**mPEG$_{2000}$-phe-MA** was synthesized by the deprotection of furan from **mPEG$_{2000}$-phe-MA-F**. **mPEG$_{2000}$-phe-MA-F** (200 mg, 83.3 μmol) and toluene (10 mL) were added to a round-bottom flask and the mixture was refluxed overnight. The solution was evaporated *in vacuo* to give **mPEG$_{2000}$-phe-MA** (quant.) as a yellow solid. Then, **mPEG$_{2000}$-phe-MA-F** was synthesized by protecting **mPEG$_{2000}$-phe-MA** with furan. **mPEG$_{2000}$-phe-MA**, acetonitrile (3 mL), and furan (2.0 mL, 23 mmol) were added to a round-bottom flask and the mixture was refluxed overnight. The solution was evaporated *in vacuo* to give **mPEG$_{2000}$-phe-MA-F** (quant.) as a brown solid.

### Applications of Phenyl Maleimide-Terminated PEG Polymers

Maleimide-terminated PEG polymers we synthesized were successfully applied to the macromonomers for graft polymerization and various block copolymers, with, for example, AB-type, star-shaped, and H-shaped architectures. The detailed information about syntheses of them are present in the Supporting Information.

## ACKNOWLEDGMENTS

This work was supported by KAKENHI grant 18K14272 (D. Aoki) from the Japan Society for the Promotion of Science (JSPS), as well as by JST, PRESTO grant JPMJPR18L1 (Japan).

## REFERENCES AND NOTES

**1** D. H. Marrian, *J. Chem. Soc.* **1949**, *0*, 1515.

**2** T. Matsumoto, Y. Urano, T. Shoda, H. Kojima, T. Nagano, *Org. Lett.* **2007**, *9*, 3375.

**3** S. H. Frayne, R. R. Murthy, B. H. Northrop, *J. Org. Chem.* **2017**, *82*, 7946.

**4** J. Bai, J. Ou, H. Zhang, S. Ma, Y. Shen, M. Ye, *J. Chromatogr. A* **2017**, *1514*, 72.

**5** Z. Huang, Q. Shi, J. Guo, F. Meng, Y. Zhang, Y. Lu, Z. Qian, X. Li, N. Zhou, Z. Zhang, X. Zhu, *Nat. Commun.* **2019**, *10*, 1918.

**6** O. Gok, I. Kosif, T. Dispinar, T. N. Gevrek, R. Sanyal, A. Sanyal, *Bioconjug. Chem.* **2015**, *26*, 1550.

**7** T. N. Gevrek, T. Bilgic, H. A. Klok, A. Sanyal, *Macromolecules* **2014**, *47*, 7842.

**8** H. Kwart, K. King, *Chem. Rev.* **1968**, *68*, 415.

**9** M. A. Tasdelen, *Polym. Chem.* **2011**, *2*, 2133.

**10** S. C. Harvey, *J. Am. Chem. Soc.* **1949**, *71*, 1121.

**11** G. Van Paesschen, D. Tilmmerman, *Makromol. Chem.* **1964**, *78*, 112.

**12** B. Saha, K. Bauri, A. Bag, P. K. Ghorai, P. De, *Polym. Chem.* **2016**, *7*, 6895.

**13** M. G. Mohamed, K. Hsu, J. Hong, S. Kuo, *Polym. Chem.* **2016**, *7*, 135.

**14** J. Guy, K. Caron, S. Dufresne, S. W. Michnick, W. G. Skene, J. W. Keillor, *J. Am. Chem. Soc.* **2007**, *129*, 11969.

**15** B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558.

**16** X. Chen, M. A. Dam, K. Ono, A. Mal, H. Shen, S. R. Nutt, K. Sheran, F. Wudl, *Science* **2002**, *295*, 1698.

**17** M. Watanabe, N. Yoshie, *Polymer* **2006**, *47*, 4946.

**18** B. T. Houseman, E. S. Gawalt, M. Mrksich, *Langmuir* **2003**, *19*, 1522.

**19** C. Zeng, H. Seino, J. Ren, K. Hatanaka, N. Yoshie, *Macromolecules* **2013**, *46*, 1794.

**20** T. Ikeda, D. Oikawa, T. Shimasaki, N. Teramoto, M. Shibata, *Polymer* **2013**, *54*, 3206.

**21** K. Sugane, R. Takagi, M. Shibata, *React. Funct. Polym.* **2018**, *131*, 211.

**22** S.-J. Xiao, M. Textor, N. D. Spencer, H. Sigrist, *Langmuir* **1998**, *14*, 5507.

**23** J. Huwyler, D. Wu, W. M. Pardridge, *Proc. Natl. Acad. Sci.* **1996**, *93*, 14164.

**24** D. J. Hall, H. M. Van Den Berghe, A. P. Dove, *Polym. Int.* **2011**, *60*, 1149.

**25** M. Arslan, O. Gok, R. Sanyal, A. Sanyal, *Macromol. Chem. Phys.* **2014**, *215*, 2237.

**26** A. Sanyal, *Macromol. Chem. Phys.* **2010**, *211*, 1417.

**27** Y. Oz, A. Sanyal, *Chem. Rec.* **2018**, *18*, 570.

**28** M. E. Annunziato, U. S. Patel, M. Ranade, P. S. Palumbo, *Bioconjug. Chem.* **1993**, *4*, 212.

**29** M. S. Shoichet, A. Chemistry, *Bioconjug. Chem.* **2007**, *16*, 874.

**30** T. Haoyu, Y. Lichen, H. K. Kyung, C. Jianjun, *Chem. Sci.* **2013**, *4*, 3839.

**31** B. N. Manjula, A. Malavalli, P. K. Smith, N. Chan, A. Arnone, J. M. Friedman, A. S. Acharya, *J. Biol. Chem.* **2000**, *275*, 5527.

**32** C. R. Zamecnik, M. M. Lowe, D. M. Patterson, M. D. Rosenblum, T. A. Desai, *ACS Nano* **2017**, *11*, 11433.

**33** K. Ananda, P. Nacharaju, P. K. Smith, S. A. Acharya, B. N. Manjula, *Anal. Biochem.* **2008**, *374*, 231.

**34** T. Cha, V. Boiadjiev, J. Lozano, H. Yang, X. Zhu, *Anal. Biochem.* **2002**, *311*, 27.

**35** C. Gaina, V. Gaina, *Des. Monomers Polym.* **2008**, *11*, 319.

**36** S. G. Lévesque, M. S. Shoichet, *Bioconjug. Chem.* **2007**, *18*, 874.

**37** J. L. Han, C. H. Yu, Y. H. Lin, K. H. Hsieh, *J. Appl. Polym. Sci.* **2007**, *107*, 3891.

**38** J. Park, J. F. Hershberger, *Chem. Phys. Lett.* **1994**, *218*, 537.

**39** T. Iwamura, I. Tomita, M. Suzuki, T. Endo, *J. Polym. Sci. Part A: Polym. Chem.* **2000**, *38*, 3440.

**40** Y. Itagaki, A. Sudo, T. Endo, *J. Polym. Sci. Part A: Polym. Chem.* **2006**, *44*, 681.

**41** H. Aida, S. Noma, H. Yoneda, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **1974**, *23*, 143.

**42** D. Wu, A. Chen, C. S. Johnson, *J. Magn. Reson. A* **1995**, *11*, 260.

**43** S. R. Mane, H. Dinda, A. Sathyan, J. Das Sarma, R. Shunmugam, *ACS Appl. Mater. Interfaces* **2014**, *6*, 16895.