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Cationic Alternating Copolymerization of Vinyl Esters and 3-Alkoxyphthalides: Side Chain-Crosslinkable Polymers for Acid-Degradable Single-Chain Nanoparticles

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ABSTRACT: Cationic copolymerization of vinyl acetate and 3-alkoxyphthalides (ROPTs) was demonstrated to proceed using $GaCl_3$ as a Lewis acid catalyst. Both monomers did not undergo homopolymerization, while copolymerization smoothly occurred via the crossover reactions, resulting in alternating copolymers with molecular weights of over 10^4. The obtained copolymers could be degraded by acid due to the cleavage of the diacyloxymethine moieties, which were derived from the crossover reactions from vinyl acetate to ROPT, in the main chain. An advantage of not radical but cationic copolymerization of vinyl esters was exerted by copolymerizations of radically reactive group-containing vinyl esters with ROPTs. For example, vinyl cinnamate was successfully copolymerized with an ROPT by the cationic mechanism, while keeping the cinnamoyl groups intact. The obtained alternating copolymer was subjected to photodimerization reaction of the cinnamoyl groups in the side chains, resulting in an acid-degradable single-chain nanoparticle via the intramolecular crosslinking reactions.

Exploration of new comonomer pairs for copolymerization is a promising way to create copolymers with characteristic functions. The development of polymerization reactions has enabled synthesis of various copolymers by radical, anionic, cationic, coordination, and metathesis mechanisms. In particular, copolymerizations of monomers with different skeletons, such as vinyl monomers and cyclic monomers, potentially lead to polymers with features, such as degradability and regulated monomer sequences, arising from the structures derived from crossover reactions of different monomers.[1–6]

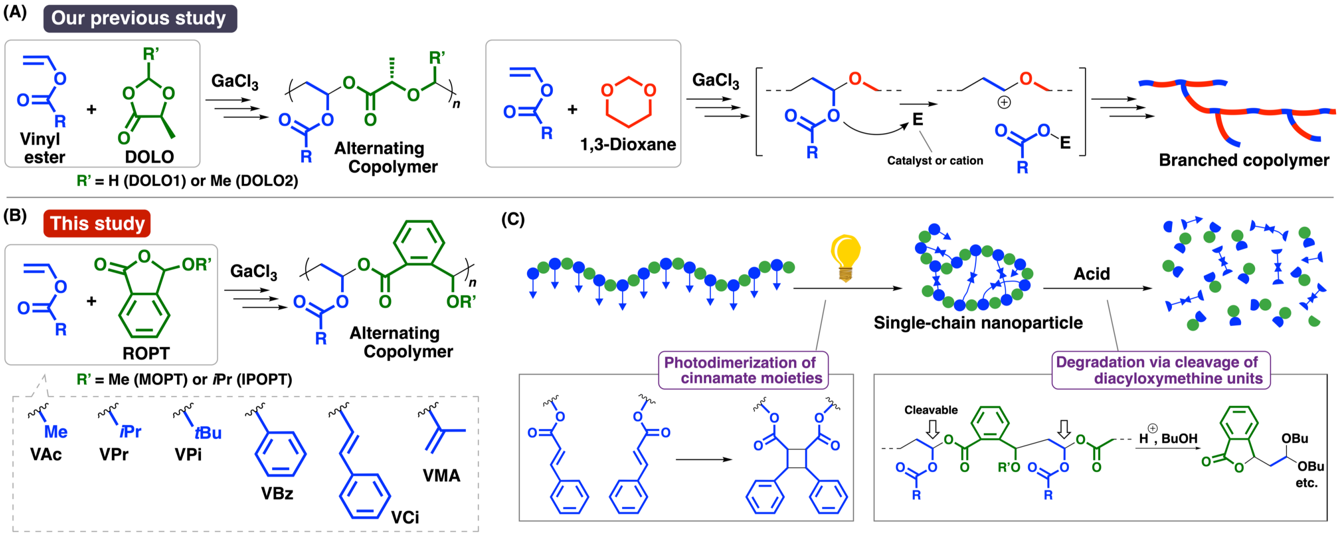
A potential application of copolymers with multiple functions is the synthesis of single-chain nanoparticles (SCNPs).[7–15] SCNPs are synthesized from a single polymer chain by intramolecular crosslinking reactions via covalent or non-covalent bonding. Various methods for SCNP synthesis have been devised due to promising possibilities of SCNPs for applications in many fields, such as catalysis, biomedicine, and nanomaterials. In most cases, however, SCNPs were synthesized from copolymers derived from monomers with the same polymerizable groups, such as methacrylic, styrenic, and acrylamide moieties. Unlike such copolymers with uniform main-chain structures, copolymers with crossover reaction-derived functional moieties in the main chains, which are derived from copolymerizations of monomers with different skeletons, are promising as substrates for synthesis of characteristic SCNPs.

Vinyl esters, such as vinyl acetate (VAc), are representative non-conjugated monomers that undergo radical polymerization. Unlike a common recognition that radical polymerization is an exclusive way for polymer generation from vinyl esters, researchers have focused on the possibility of vinyl esters as cationically polymerizable monomers.[16] This is because the oxygen atom adjacent to the vinyl group of vinyl esters potentially exerts an electron donating-resonance effect in a manner similar to that in vinyl ethers. However, cationic homopolymerization of vinyl esters did not proceed even when various acidic catalysts were used under various conditions.

Recently, we devised a strategy to produce polymers from vinyl esters by cationic copolymerization instead of unsuccessful homopolymerization. Specifically, we focused on monomers incapable of homopolymerization as comonomers for vinyl esters.[17] 1,3-Dioxolan-4-ones (DOLOs) and 1,3-dioxane do not give homopolymers by cationic polymerization. When these monomers were used as comonomers for vinyl esters, cationic copolymerization successfully proceeded using $GaCl_3$ as a Lewis acid catalyst (Scheme 1A). Alternating copolymers were obtained from vinyl esters and DOLOs, while branched copolymers were generated from vinyl esters and 1,3-dioxane via branching reactions that occurred at the structures derived from the crossover reactions from vinyl ester to 1,3-dioxane. In addition, the obtained copolymers were degraded under acidic conditions due to the cleavage of the structures derived from the crossover reactions. However, these cationic polymerizations hold unsatisfying aspects such as long reaction time and moderate molecular weight (MW).

To both demonstrate a potential of vinyl ester-derived alternating copolymers and overcome the drawbacks, in this study, we aimed to develop cationic copolymerizations of functional group-containing vinyl esters and a different monomer from DOLOs and 1,3-dioxane (Scheme 1B). 3-Alkoxyphthalides (ROPTs) were selected as comonomers. ROPTs have a cyclic hemiacetal ester structure and do not exhibit homopolymerizability, which is similar to DOLOs. In our previous study, oxiranes were demonstrated to undergo cationic copolymerizations with ROPTs.[18] In particular, ROPTs exhibited superior copolymerizability to DOLOs in terms of polymer MWs and the frequency of crossover reactions. By examining various reaction conditions in the present study, alternating copolymerizations of vinyl esters and ROPTs were found to proceed effectively to yield main-chain degradable copolymers with high MWs. Moreover, reactive group-containing vinyl esters such as vinyl cinnamate and vinyl methacrylate also underwent copolymerizations with ROPTs, resulting in alternating copolymers with reactive side chains. We examined SCNP synthesis for the purpose of demonstrating a possible application of the degradable copolymers containing reactive side groups. Acid-degradable SCNPs were successfully obtained by the intramolecular crosslinking reactions of these copolymers via the photoinduced dimerization of cinnamoyl groups or the radical reaction of the methacryloyl groups.

Scheme 1. Summary of (A) Our Previous Study and (B), (C) This Study



We explored appropriate conditions for copolymerizations of VAc and ROPTs. GaCl$_3$ was used as a Lewis acid catalyst at the polymerization temperature of –40 ºC, which are conditions based on our previous study on cationic copolymerizations of vinyl esters and DOLOs.[17] When equal amounts of VAc and 3-methoxyphthalide (MOPT) (0.80 M) were used, the copolymerization proceeded and the conversion reached 34–35% in 3 h, resulting in a copolymer with an M_n of 4.8 × 10^3 (entry 1 in Table 1). The copolymerization at higher concentrations of VAc (1.6 or 3.2 M) resulted in polymers with M_n values of 8.6 × 10^3 or 11 × 10^3 (entries 2 and 3; Figure 1A). Moreover, copolymers with higher MWs were obtained when 3-isopropoxyphthalide (IPOPT) was used as a comonomer instead of MOPT. Copolymers obtained at the VAc concentrations of 1.6 or 3.2 M had M_n values of over 20 × 10^3 (entries 4 and 5; Figure 1B). ROPTs were superior to DOLOs (DOLO1 and DOLO2 in Scheme 1A) as comonomers for cationic copolymerization with VAc in terms of copolymerization rates and polymer MWs, judging from the polymerization results under similar conditions (entries 3, 5, 14, and 15).[17]

Copolymerizations were conducted at different temperatures or with other Lewis acids; however, the above conditions were the most suitable for copolymerization. Polymerization did not proceed at –78 ºC (entry 6 in Table 1), while only oligomers were obtained at 0 ºC (entry 7). The results likely indicate that the activity of GaCl$_3$ was not exerted sufficiently at –78 ºC and side reactions, which have not been revealed, were not suppressed at 0 ºC. Other Lewis acids such as TiCl$_4$, In(OTf)$_3$, BF$_3$OEt$_2$, EtAlCl$_2$, and B(C$_6$F$_5$)$_3$ were not effective for copolymerization (entries 9–13). Copolymerization proceeded with SnCl$_4$ as a catalyst (entry 8), although the activity was inferior to GaCl$_3$. The reason why GaCl$_3$ is effective for the copolymerization is unclear presently. In addition, both VAc and IPOPT did not undergo cationic homopolymerization under the conditions suitable for the copolymerization (Table S1).[17,18]

^{1}H NMR analysis of the copolymerization products suggested that alternating copolymers were obtained from VAc and ROPTs. In the spectrum of the product by the copolymerization of VAc and IPOPT (Figure 1C), the peak assigned to the methine group resulting from the crossover reaction from IPOPT to VAc was detected at 5.5–6.0 ppm (peak *e*). The peak of the methine group derived from the crossover reaction from VAc to IPOPT (peak *b*) likely overlapped with the aromatic peaks (peak *d*). Other peaks were consistently assigned to the methylene and methyl groups of VAc units (peaks *a* and *c*) and the isopropyl group of IPOPT units (peaks *f* and *g*). Importantly, the integral ratios of these peaks agreed with the values expected for alternating sequences consisting of VAc and IPOPT. ^{13}C and 2D (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC) NMR analyses also exhibited peaks and peak correlations that were consistent with alternating sequences (Figure S1–S8).

Table 1. Cationic Copolymerization of VAc and ROPTs [a]

entry	vinyl ester	conc (M)	cyclic monomer	Lewis acid	temp (°C)	time (h)	conv (%) vinyl	conv (%) ROPT	$M_n \times 10^{-3}$ [b]	M_w/M_n [b]
1	VAc	0.80	MOPT	$GaCl_3$	–40	3	35	34	4.8	1.88
2		1.6	MOPT	$GaCl_3$	–40	3	36	70	8.6	2.02
3		3.2	MOPT	$GaCl_3$	–40	2.5	20	77	11	1.96
4		1.6	IPOPT	$GaCl_3$	–40	46	30	56	22	2.17
5		3.2	IPOPT	$GaCl_3$	–40	50	18	69	21	2.15
6		1.6	MOPT	$GaCl_3$	–78	49	trace	trace	–	–
7		1.6	MOPT	$GaCl_3$	0	24	26	34	0.6	1.54
8		1.6	MOPT	$SnCl_4$	–40	42	27	54	3.7	1.98
9		1.6	IPOPT	$TiCl_4$	–40	140	trace	trace	–	–
10		1.6	IPOPT	$In(OTf)_3$	–40	142	trace	trace	–	–
11		1.6	IPOPT	BF_3OEt_2	–40	140	trace	trace	–	–
12		1.6	IPOPT	$EtAlCl_2$	–40	213	trace	trace	–	–
13		1.6	IPOPT	$B(C_6F_5)_3$	–40	213	trace	trace	–	–
14[c]		3.2	DOLO1	$GaCl_3$	–40	816	9	32	3.4	2.20
15[c]		3.2	DOLO2	$GaCl_3$	–40	216	25	92	6.4	3.00
16	VPr	1.6	IPOPT	$GaCl_3$	–40	73	46	90	18	1.79
17	VPi	1.6	IPOPT	$GaCl_3$	–40	95	43	76	15	1.93
18	VBz	1.6	IPOPT	$GaCl_3$	–40	95	41	80	24	3.26
19	VCi	1.6	IPOPT	$GaCl_3$	–40	55	40	80	17	2.67
20	VMA	1.6	IPOPT	$GaCl_3$	–40	77	47	88	16	2.69

[a] $[ROPT]_0$ = 0.80 M, [Lewis acid]$_0$ = 40 mM, in dichloromethane/hexane (6/4 v/v [entries 3 and 5] or 7/3 v/v [except for entries 3 and 5]; the hexane is derived from the stock solution of $GaCl_3$ in hexane). ^{1}H NMR analysis indicated that the products have alternating sequences. [b] By GPC using polystyrene standards. [c] From reference 17.

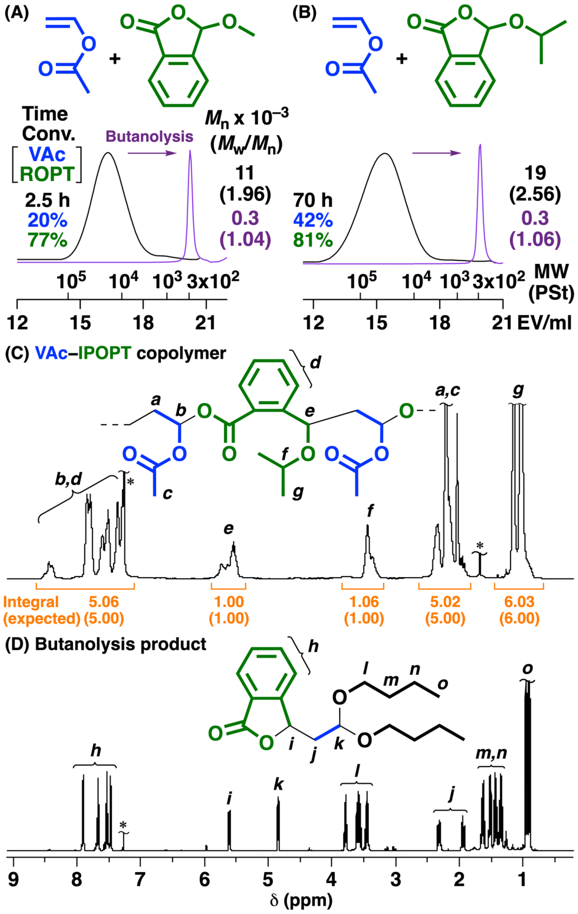


Figure 1. MWD curves of (A) VAc–MOPT copolymer (entry 3 in Table 1), (B) VAc–IPOPT copolymer (obtained under the same conditions as those for entry 4 in Table 1) (black), and their butanolysis products (purple). ^{1}H NMR spectra (in $CDCl_3$ at 30 ºC; * $CHCl_3$ or water) of (C) the VAc–IPOPT copolymer and (D) its butanolysis product. Butanolysis conditions: polymer = 0.5 wt%, $[HCl]_0$ = 0.50 M, $[BuOH]_0$ = 2.5 M, in dichloromethane at room temperature for 72 h. Values in orange parentheses are expected values for alternating copolymers.

A plausible copolymerization mechanism is shown in Scheme 2A. The VAc-derived carbocation reacts with the carbonyl group of an ROPT. The generated ROPT-derived oxonium ion undergoes ring-opening reaction to become a carbocation. This carbocation (oxocarbenium ion) is stabilized by the electron-donation effects of the adjacent alkoxy and aryl groups. The subsequent reaction of the ROPT-derived carbocation with VAc selectively occurs because ROPTs do not exhibit homopolymerizability.[18] VAc also does not exhibit cationic homopolymerizability; hence, alternating copolymers are produced through continuous crossover reactions. The initiation reaction probably occurs via the reaction of $GaCl_3$ with the carbonyl group of an ROPT and/or the reaction of a proton, which is derived from adventitious water[19] and $GaCl_3$, with ROPT or VAc. To reveal the initiation, termination, and chain transfer mechanisms, we tried to characterize chain end structures by NMR and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) analyses (Figure S9); however, the chain end structures are unclear presently. In addition, a cyclic dimer byproduct consisting of VAc and ROPT was detected by analysis of the copolymerization products before purification by reprecipitation (Figure S10), while other byproducts were absent. We hypothesized that the cationic copolymerization of VAc and ROPTs is potentially controlled by using suitable cationogens.[20–28] However, the copolymerization results with alkyl halides or reversible addition-fragmentation chain transfer

(RAFT) agents were not remarkable in terms of MW control and the chain end fidelity (see Figures S11–S13 for the detail). We are currently investigating various conditions to achieve controlled copolymerization.

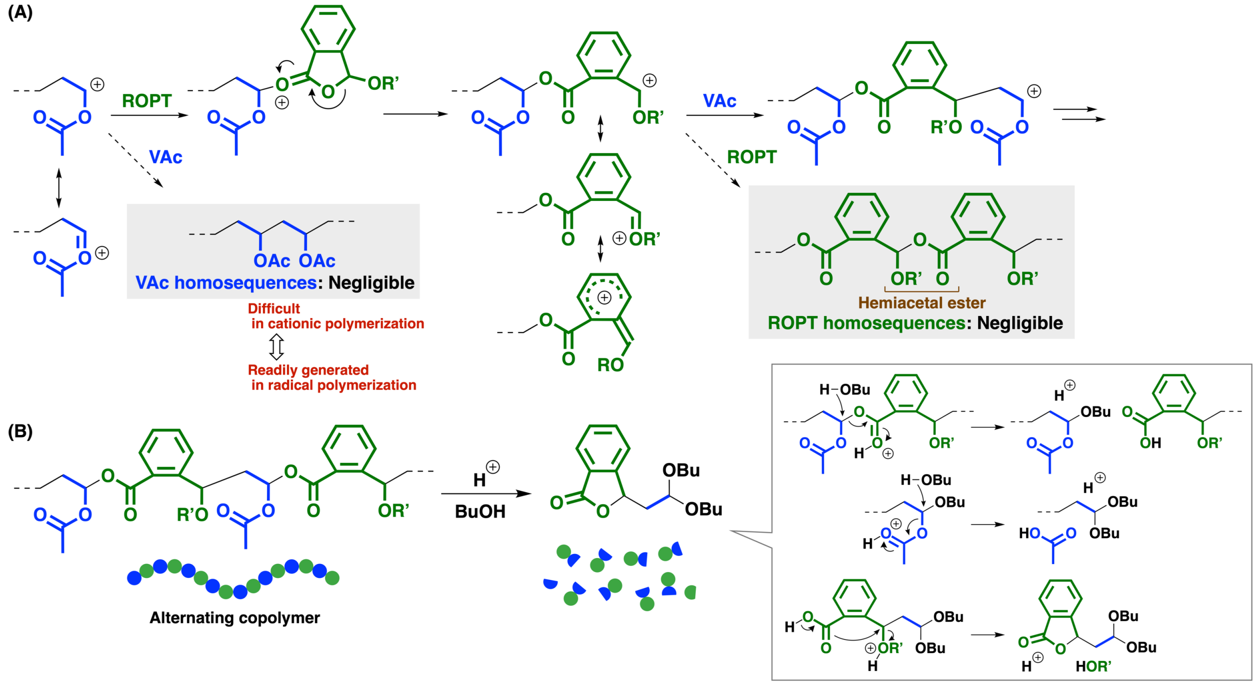
The alternating copolymers could be degraded under acidic conditions via the cleavage of the diacyloxymethine moieties derived from the crossover reactions from VAc to ROPT. The copolymers with M_n values of over 10^4 (black curves in Figure 1A and 1B) were subjected to acid treatments in the presence of butanol, which resulted in low-MW products with very narrow molecular weight distributions (MWDs) (purple curves in Figure 1A and 1B). ^{1}H NMR analysis indicated that a phthalide compound with a dibutoxy acetal moiety was selectively obtained (Figure 1D). Other degradation products including acetic acid and ROPT unit-derived alcohol were removed during the workup process. A plausible mechanism consists of the cleavage of the diacyloxymethine moiety via acid-catalyzed reaction with butanol and the ring-closing reaction[29,30] accompanied by the elimination of the ROPT-derived alkoxy group (Scheme 2B). The selective generation of the phthalide compound by acid butanolysis is additional proof of the alternating sequences in the copolymer chains.

Other vinyl esters than VAc, such as vinyl propionate (VPr), vinyl pivalate (VPi), and vinyl benzoate (VBz), were also successfully copolymerized with ROPTs, resulting in alternating copolymers with high MWs (entries 16–18 in Table 1; Figure S14). Moreover, an advantage of not radical but cationic copolymerization was exerted when monomers bearing radically-reactive side chains were used. Vinyl cinnamate (VCi) (entry 19) and vinyl methacrylate (VMA) (entry 20) underwent cationic alternating copolymerizations with IPOPT, while keeping the cinnamoyl and methacryloyl groups, respectively, intact in the side groups. Past examples of polymerization of cinnamoyl group-containing monomers include the cationic polymerization of cinnamoyl group-containing styrene derivatives or VEs and the anionic ROP of glycidyl cinnamate.[31–33]

The alternating copolymers obtained from various vinyl esters were subjected to degradation by acid butanolysis. The VPr–IPOPT copolymer was smoothly degraded by HCl under the same conditions as those for the degradation of the VAc counterpart (Figures S15A and S16A). In contrast, the other copolymers were not completely degraded under those conditions (Figures S15B–E). High hydrophobicity of the copolymers due to the large side groups may be responsible for the inefficient degradation. Not HCl but trifluoromethanesulfonic acid (TfOH) was found to be effective for degradation of the VPi-, VBz-, VCi-, and VMA-derived copolymers (Figures S15F–J) although the degradation products differed depending on reaction conditions (see the SI for the detail; Figure S16).

Cinnamate-containing polymers are promising substrates for SCNP synthesis[7–15] via photo-induced dimerization reactions of cinnamate moieties. Indeed, cinnamate-containing polymers were used for SCNP synthesis in a few past studies.[34–36] However, in those studies, cinnamate moieties were introduced into side chains of polymethacrylates via postpolymerization modification, such as the reaction of cinnamoyl chloride with poly(2-hydroxyethyl methacrylate), because of radical and anionic (co)polymerizability of cinnamates. In addition, main chain degradability was not attained because polymethacrylates were used as backbones. Compared to the past examples, the strategy devised in the present study is advantageous because of both the absence of postpolymerization modification due to inertness of cinnamate moieties in cationic copolymerization and the acid degradability of alternating copolymers consisting of vinyl esters and ROPTs.

Scheme 2. (A) Cationic Copolymerization Mechanism (Counteranions Are Omitted). (B) Plausible Mechanism of Polymer Degradation via Acid Alcoholysis



The alternating copolymer of VCi and IPOPT was subjected to photochemical reaction using 2,7-dimethoxythioxanthone as a catalyst[37] under dilute conditions (polymer = 0.5 wt%) in toluene[38] for intramolecular crosslinking reaction (Scheme 1C). After the reaction solution was irradiated with a white LED for 24 h, a soluble product was obtained. ^{1}H NMR analysis of the product indicated that the peaks of the cinnamoyl groups, which were observed in the original copolymer (peak *g* in Figure 2B), were absent, while the peaks assignable to the structure resulting from dimerization of the cinnamoyl groups were detected at 3–4 ppm (peaks *j* and *k* in Figure 2C). Moreover, in gel permeation chromatography (GPC) analysis, an MWD curve of the product appeared in the larger elution volume region (red in Figure 2A) than that of the original copolymer (black in Figure 2A), which indicates that the size of a polymer chain became small after photochemical reaction. Notably, the absolute M_n values determined by GPC equipped with a light-scattering detector were comparable before (35×10^3) and after (33×10^3) photochemical reaction. These results indicate that a SCNP was successfully obtained through the intramolecular crosslinking reaction of the VCi–IPOPT copolymer.

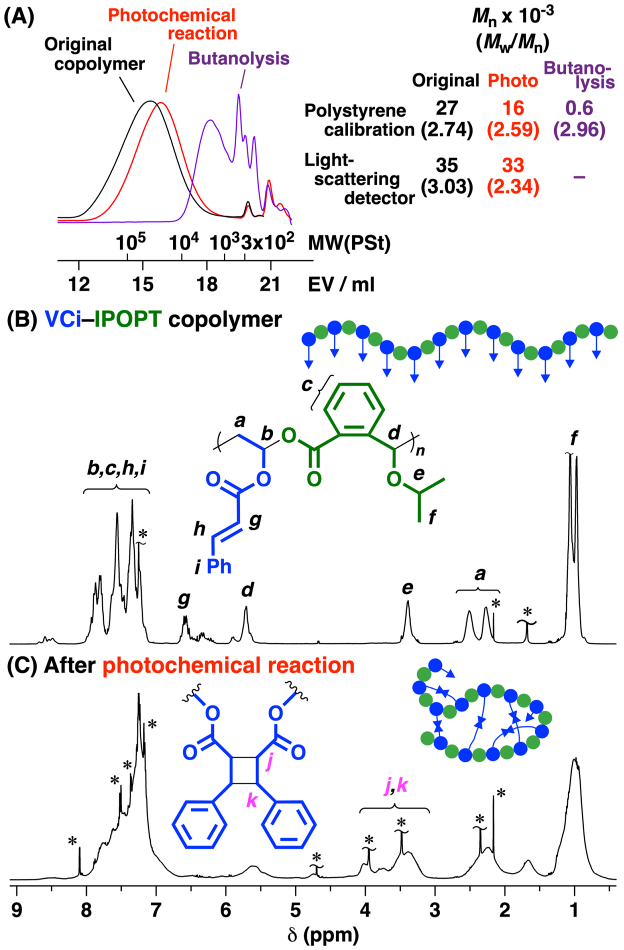


Figure 2. (A) MWD curves of the VCi–IPOPT copolymer (black; obtained under the same conditions as those for entry 19 in Table 1), the product obtained by the intramolecular crosslinking reaction of the copolymer by photochemical reaction (red), and the product obtained by butanolysis of the photochemical reaction product (purple). ^{1}H NMR spectra (in $CDCl_3$ at 30 °C; * $CHCl_3$, water, or 2,7-dimethoxythioxanthone) of (B) the VCi–IPOPT copolymer and (C) the photochemical reaction product (photochemical reaction conditions: polymer = 0.5 wt%, $[\text{2,7-dimethoxythioxanthone}]_0$ = 0.58 mM, in toluene at room temperature, irradiated with a white LED for 24 h; butanolysis conditions: polymer = 0.5 wt%, $[\text{TfOH}]_0$ = 0.20 M, $[\text{BuOH}]_0$ = 0.50 M, in dichloromethane at room temperature for 7 days).

An advantage of using the alternating copolymer consisting of VCi and IPOPT for SCNP synthesis was demonstrated by acid degradability of the main chain (Scheme 1C). Acidically-degradable diacyloxymethine moieties remained intact in the main chain even after SCNP formation. Therefore, acid butanolysis of the SCNP proceeded with TfOH, resulting in low-MW products (purple in Figure 2A). Unlike degradation of a pre-crosslinked copolymer (Figure S15), however, polymer chains were not completely degraded as confirmed by remaining oligomeric portions. Partly dense structures resulting from dimerization of cinnamate moieties are probably responsible for incomplete degradation.

Not SCNP synthesis but side chain-modification was also possible by the photo-induced dimerization between the cinnamate moieties introduced into the alternating copolymers and low-MW cinnamate compounds. When the VCi–IPOPT alternating polymer was reacted with an excess amount of ethyl cinnamate, which was used as a model compound, dimerization reactions smoothly proceeded, resulting in a polymer having ethyl cinnamate-derived side chains as confirmed by ^{1}H NMR analysis (Figure S17). The result suggests possible application of the degradable alternating copolymer as a scaffold for fabrication of functional group-containing polymers through photodimerization with cinnamate compounds.

The alternating copolymer consisting of VMA and IPOPT was also successfully employed for SCNP synthesis. The reaction of the copolymer with an 2,2'-azobis(isobutyronitrile) (AIBN) as a radical generator smoothly occurred in a dilute solution to yield a soluble product (see the SI for the detail; Figure S18).

The VAc–MOPT and VAc–IPOPT copolymers exhibited glass transition temperatures (T_gs) of 80 and 84 ºC (Table 2), respectively, which were much higher than the T_g of the DOLO counterpart (5 ºC; the VAc–DOLO1 copolymer[17]). The ROPT-derived aryl groups in the main chains are responsible for the high T_g values. In addition, the alternating copolymers of VCi and ROPTs had higher T_gs than the VAc counterparts (Table 2). The SCNP obtained by the photochemical reaction of the VCi-IPOPT also exhibited a high T_g probably due to the intramolecularly crosslinked structure. Thermogravimetric analysis (TGA) of the VAc–ROPT copolymers was also conducted. The alternating copolymers were degraded at approximately 250 ºC (Figure S20).

Table 2. T_g Values of Alternating Copolymers [a]

polymer	$M_n \times 10^{-3\,b}$	M_w/M_n [b]	T_g (ºC)
poly(VAc-*alt*-MOPT)	13	1.78	80
poly(VAc-*alt*-IPOPT)	32	1.79	84
poly(VCi-*alt*-MOPT)	10	1.80	100
poly(VCi-*alt*-IPOPT)	24	2.18	108
poly(VCi-*alt*-IPOPT), after crosslinking	22[c]	2.60 [c]	143

[a] Determined by differential scanning calorimetry (DSC). The heating and cooling rates were 10 ºC min^{-1}. The T_g values were determined by the second heating scan. See Figure S19 for the DSC curves. [b] Determined by GPC (polystyrene calibration). [c] Values before crosslinking.

In conclusion, cationic copolymerization of vinyl esters and ROPTs, which are monomers that do not undergo cationic homopolymerization, successfully proceeded via the crossover reactions, resulting in alternating copolymers with M_n values of over 10^4. The alternating copolymers could be degraded under acidic conditions due to the scission of the diacyloxymethine structures derived from the crossover reactions from vinyl ester to ROPT. Vinyl esters with various side groups were also nicely copolymerized with ROPTs to yield alternating copolymers. In particular, VCi and VMA, which have radically-reactive side groups, could be copolymerized without using protecting groups due to the inertness of cinnamoyl and methacryloyl groups in cationic polymerization. An alternating copolymer bearing cinnamoyl groups was subjected to intramolecular crosslinking reactions via photodimerization, resulting in a degradable SCNP. The results obtained in this study will contribute to the development of both the cationic copolymerizations of nonhomopolymerizable monomers and the promising usage of alternating copolymers derived from different kinds of monomers.

ASSOCIATED CONTENT

Supporting Information

Experimental section; polymerization data; NMR, MALDI-TOF-MS, and ESI-MS spectra of products. The Supporting Information is available free of charge on the ACS Publications website.

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NOTES

The authors declare no competing financial interest.

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REFERENCES

1. Zhu, N.; Hu, X.; Fang, Z.; Guo, K. Chemoselective Polymerizations. *Prog. Polym. Sci.* **2021**, *117*, 101397.
2. Deacy, A. G.; Gregory, G. L.; Sulley, G. S.; Chen, T. T. D.; Williams, C. K. Sequence Control from Mixtures: Switchable Polymerization Catalysis and Future Materials Applications. *J. Am. Chem. Soc.* **2021**, *143*, 10021–10040.
3. Chen, G.; Xia, L.; Wang, F.; Zhang, Z.; You, Y.-Z. Recent Progress in the Construction of Polymers with Advanced Chain Structures via Hybrid, Switchable, and Cascade Chain-Growth Polymerization. *Polym. Chem.* **2021**, *12*, 3740–3752.
4. Dirauf, M.; Mulijajew, I.; Weber, C.; Schubert, U. S. Recent Advances in Degradable Synthetic Polymers for Biomedical Applications–Beyond Polyesters. *Prog. Polym. Sci.* **2022**, *129*, 101547.
5. Wang, X.; Huo, Z.; Xie, X.; Shanaiah, N.; Tong, R. Recent Advances in Sequence-Controlled Ring-Opening Copolymerizations of Monomer Mixtures. *Chem. Asian J.* **2023**, e202201147.
6. Kanazawa, A.; Aoshima, S. Concurrent Cationic Vinyl-Addition and Ring-Opening Copolymerization of Vinyl Ethers and Oxiranes. *Polym. J.* **2016**, *48*, 679–687.
7. Altintas, O.; Barner-Kowollik, C. Single Chain Folding of Synthetic Polymers by Covalent and Non-Covalent Interactions: Current Status and Future Perspectives. *Macromol. Rapid Commun.* **2012**, *33*, 958–971.
8. Altintas, O.; Barner-Kowollik, C. Single-Chain Folding of Synthetic Polymers: A Critical Update. *Macromol. Rapid Commun.* **2016**, *37*, 29–46.
9. Terashima, T. Functional Spaces in Star and Single-Chain Polymers via Living Radical Polymerization. *Polym. J.* **2014**, *46*, 664–673.
10. Hanlon, A. M.; Lyon, C. K.; Berda, E. B. What Is Next in Single-Chain Nanoparticles? *Macromolecules* **2016**, *49*, 2–14.
11. Chen, R.; Berda, E. B. 100th Anniversary of Macromolecular Science Viewpoint: Reexamining Single-Chain Nanoparticles. *Macromolecules* **2020**, *9*, 1836–1843.
12. Alqarni, M. A. M.; Waldron, C.; Yilmaz, G.; Becer, C. R. Synthetic Routes to Single Chain Polymer Nanoparticles (SCNPs): Current Status and Perspectives. *Macromol. Rapid Commun.* **2021**, *42*, 2100035.
13. Mundsinger, K.; Izuagbe, A.; Tuten, B. T.; Roesky, P. W.; Barner-Kowollik, C. Single Chain Nanoparticles in Catalysis. *Angew. Chem. Int. Ed.* **2024**, *63*, e202311734.
14. Hamelmann, N. M.; Paulusse, J. M. J. Single-Chain Polymer Nanoparticles in Biomedical Applications. *J. Control. Release* **2023**, *356*, 26–42.
15. Kröger, A. P. P.; Paulusse, J. M. J. Single-Chain Polymer Nanoparticles in Controlled Drug Delivery and Targeted Imaging. *J. Control. Release* **2018**, *286*, 326–347.
16. Higashimura, T.; Okamura, S. The Behavior of Vinyl Acetate and Acrylic Acid Derivatives in Cationic Polymerization. *Kobunshi Kagaku* **1960**, *17*, 635–640.
17. Azuma, J.; Kanazawa, A.; Aoshima, S. Cationic Polymerizability of Vinyl Acetate: Alternating Copolymerization with 1,3-Dioxolan-4-ones and Branched Copolymer Formation with Cyclic Acetals. *Macromolecules* **2022**, *55*, 6110–6119.
18. Takahashi, Y.; Kanazawa, A.; Aoshima, S. 3-Alkoxyphthalides as Nonhomopolymerizable, Highly Reactive Comonomers for ABC Pseudo-Periodic Terpolymers and Degradable Polymers via Cationic Co- and Terpolymerizations with Oxiranes and/or Vinyl Ethers. *Macromolecules* **2023**, *56*, 4198–4207.
19. It is difficult to completely remove adventitious water from reaction solutions even when solvents are purified by solvent purification columns, monomers are dried by an azeotropic method, and glass apparatus is dried with a heat gun.
20. Sawamoto, M. Modern Cationic Vinyl Polymerization. *Prog. Polym. Sci.* **1991**, *16*, 111–172.
21. Kennedy, J. P.; Iván, B. *Designed Polymers by Carbocationic Macromolecular Engineering: Theory and Practice*; Hanser: New York, 1992.
22. Matyjaszewski, K.; Sawamoto, M. In *Cationic Polymerizations*; Matyjaszewski, K., Ed.; Marcel Dekker: New York, 1996; Chapter 4.
23. Kennedy, J. P. Living Cationic Polymerization of Olefins. How Did the Discovery Come About? *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2285–2293.
24. Puskas, J. E.; Kaszas, G. Living Carbocationic Polymerization of Resonance-Stabilized Monomers. *Prog. Polym. Sci.* **2000**, *25*, 403–452.
25. De, P.; Faust, R. In *Macromolecular Engineering. Precise Synthesis, Materials Properties, Applications*; Matyjaszewski, K., Gnanou, Y., Leibler, L., Eds.; Wiley-VCH GmbH & Co. KGaA: Weinheim, 2007; Chapter 3.
26. Goethals, E. J.; Du Prez, F. Carbocationic Polymerizations. *Prog. Polym. Sci.* **2007**, *32*, 220–246.
27. Aoshima, S.; Kanaoka, S. A Renaissance in Living Cationic Polymerization. *Chem. Rev.* **2009**, *109*, 5245–5287.
28. Uchiyama, M.; Satoh, K.; Kamigaito, M. Cationic RAFT Polymerization Using ppm Concentrations of Organic Acid. *Angew. Chem. Int. Ed.* **2015**, *54*, 1924–1928.
29. Curtin, D. Y.; Fletcher, M. J. The Metalation of Dibenzhydril Ether and Carbonation with Allylic Rearrangement. *J. Org. Chem.* **1954**, *19*, 352–356.
30. Tamura, Y.; Sasho, M.; Akai, S.; Kishimoto, H.; Sekihachi, J.; Kita, Y. An Efficient, Regiospecific Synthesis of 4-

Demethoxydaunomycinone, and Daunomycinone. *Chem. Pharm. Bull.* **1987**, *35*, 1405–1412.

31. Kato, M.; Ichijo, T.; Ishii, K.; Hasegawa, M. Novel Synthesis of Photocrosslinkable Polymers. *J. Polym. Sci. Part A-1* **1971**, *9*, 2109–2128.
32. Aoshima, S.; Hasegawa, O.; Higashimura, T. Living Cationic Polymerization of Vinyl Ethers with a Functional Group. 2. Polymerization of Vinyl Ethers with an Unsaturated Ester Pendant. *Polym. Bull.* **1985**, *13*, 229–235.
33. Maciol, K.; Shuttner, S.; Blankenburg, J.; Johann, T.; Frey, H. Glycidyl Cinnamate: Copolymerization with Glycidyl Ethers, In-Situ NMR Kinetics, and Photocrosslinking. *Macromol. Chem. Phys.* **2022**, *224*, 2200366.
34. Tao, J.; Liu, G. Polystyrene-*block*-poly(2-cinnamoylethyl methacrylate) Tadpole Molecules. *Macromolecules* **1997**, *30*, 2408–2411.
35. Xie, M. X.; Jiang, L.; Xu, Z. P.; Chen, D. Y. Monofunctional Polymer Nanoparticles Prepared through Intramolecularly Cross-Linking the Polymer Chains Sparsely Grafted on the Surface of Sacrificial Silica Spheres. *Chem. Commun.* **2015**, *51*, 1842–1845.
36. Thanneeru, S.; Li, W.; He, J. Controllable Self-Assembly of Amphiphilic Tadpole-Shaped Polymer Single-Chain Nanoparticles Prepared through Intrachain Photocrosslinking. *Langmuir* **2019**, *35*, 2619–2629.
37. Jiang, Y.; Zhu, H.; Chen, J.; Liao, S. Organocatalytic [2 + 2] Photopolymerization under Visible Light: Accessing Sustainable Polymers from Cinnamic Acids. *Macromol. Rapid Commun.* **2022**, *44*, 2200702.
38. Solvents in which a polymer chain has a contracted conformation are suitable for SCNP synthesis. There may be more suitable solvents than toluene.

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Cationic Alternating Copolymerization of Vinyl Esters and 3-Alkoxyphthalides: Side Chain-Crosslinkable Polymers for Acid-Degradable Single-Chain Nanoparticles

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