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AAB-Sequence Living Radical Chain Copolymerization of Naturally Occurring Limonene with Maleimide: An End-to-End Sequence-Regulated Copolymer

Kotaro Satoh, Masaru Matsuda, Kanji Nagai, and Masami Kamigaito*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan

Received May 17, 2010; E-mail: kamigait@apchem.nagoya-u.ac.jp

Abstract: Sequence control in chain-growth polymerization is still one of the most challenging topics in synthetic polymer chemistry in contrast to natural macromolecules with completely sequence-regulated structures like proteins and DNA. Here, we report the quantitative and highly selective 1:2 sequence-regulated radical copolymerization of naturally occurring (+)-*d*-limonene (L) and a maleimide (M) in fluoroalcohol giving chiral copolymers with high glass transition temperatures (220−250 °C) originating from the specific rigid cyclic structures of the monomers. Furthermore, the combination with a reversible addition−fragmentation chain transfer (RAFT) agent (C−S) via the controlled/living radical polymerization resulted in end-to-end sequence-regulated copolymers [C-(M-M-L)$_n$-M-S] with both highly sequenced chain ends and main-chain repeating units as well as controlled molecular weights.

Nature produces completely defined macromolecules via biosynthetic procedures, such as proteins and DNA, which feature special functions with specific and often complicated structures. In synthetic polymer chemistry, the precise control of polymer structures and architectures, which may rival those of natural polymers, has still been one of the unattained and most active research areas. Among the various controlling factors in synthetic polymers, the control over sequences in a polymer main chain has been the most challenging via chain-growth polymerization, whereas natural polymeric products are configured in well-ordered sequences of nucleotides or peptides via the step-growth biosynthesis for their individual traits and behaviors.[1,2] In the field of polymer synthesis, controlled/living radical polymerization has marked a new era over the past decade, which produces precisely defined polymers from a wide range of industrially important vinyl monomers in terms of their controlled molecular weights and end-functionality.[3−6] These polymerizations are based on a methodology of controlling the propagation by chemical equilibrium at the growing polymer terminus between the active radical species and stable covalent dormant bonds although it cannot control the sequence of multiple monomer units in copolymerization. Apart from the molecular weight control in the living polymerizations, radical copolymerization sometimes produces 1:1 alternating copolymers under certain conditions by combining electrophilic and electron-donating monomers. These include the copolymerizations of a pair of nonhomopolymerizable monomers, such as maleic anhydride and α-olefin, and a combination of an electron-donating monomer and a homopolymerizable acrylate, acrylonitrile, or maleimide especially in the presence of strong Lewis acids.[7] Recently, we also found that fluorinated alcohols as solvents enhance the copolymerizability between polar acrylic monomers and nonpolar hydrocarbon olefins to produce copolymers with predominant 1:1 alternating sequences as Lewis acids do.[8] These alternating copolymerizations have also been combined with the controlled/living polymerization to afford novel functional copolymers.[9]

Meanwhile, another basis for the recent increasing demand for novel polymeric materials is for the development of renewable resources especially those obtained from plants in place of petroleum-derived materials from the viewpoint of sustainability. Although this viewpoint is still controversial in some aspects, the suitable and judicious application of specific or complicated structures originating from natural products is definitely beneficial for developing high performance or functional polymeric materials.[10] Some terpenes occurring in the natural products of plants are nonpolar and mono- or bicyclic olefins with their characteristic structures sometimes containing chirality. Among them, (+)-*d*-limonene (Lim) is representatively popular and abundant, of which the annual production could be estimated to be hundreds of thousands of tons per year, and is mainly used in the flavor and fragrance industry.[11] However, Lim is also known to rarely undergo radical homopolymerization although their cationic polymerizations or oligomerizations had been intensively investigated since the 1950s.[12] A few examples were reported only for its radical copolymerizations with polar monomers, such as maleic anhydride and acrylates, which resulted in cyclocopolymerization or quite low consumption of Lim along with its low incorporation into the copolymers.[13]

Here, we report that a fluoroalcohol mediates the quantitative radical copolymerization of naturally occurring Lim with a maleimide, one of the petroleum-derived monomers with rigid structures. Interestingly, the copolymerization not only proceeded very well, but also spontaneously afforded an almost complete 1:2 sequence-regulated copolymer. In addition, the combination with the controlled/living radical polymerization using a reversible-addition fragmentation transfer (RAFT)[3,6] agent resulted in an end-to-end regulation in sequence as found in the naturally produced copolymers.

The copolymerizations of Lim with maleimide derivatives, such as *N*-phenylmaleimide (PhMI) and *N*-cyclohexylmaleimide (CyMI), were examined in DMF, cumyl alcohol [$PhC(CH_3)_2OH$], and fluorinated cumyl alcohol [$PhC(CF_3)_2OH$]. The copolymerizations were performed using 2,2′-azobisisobutyronitrile (AIBN) as a radical initiator at 60 °C. Irrespective of the monomer feed ratios (1:1, 1:2, or 1:3), Lim and maleimide were smoothly consumed in the fluorinated alcohol [$PhC(CF_3)_2OH$] at an almost 1:2 ratio to produce copolymers with moderate molecular weights (Figure S1 in the Supporting Information). In contrast, in DMF or the nonfluorinated alcohol [$PhC(CH_3)_2OH$], the copolymerizations did not reach quantitative conversions along with the lower incorporation of Lim into the products (Figure S2 and Table S1). In $PhC(CF_3)_2OH$, especially when the initial charge ratio of $[Lim]_0/[PhMI]_0$ was 1:2, both monomers were simultaneously and quantitatively consumed at almost the same rate (Figure 1A), again indicating the highly predominant consumption of the two monomers at the 1:2 ratio. Table 1 summarizes the copolymerizations in $PhC(CF_3)_2OH$, in which the monomer compositions in the copolymers (Figure S3) agreed well with the values calculated from the initial charge ratio and

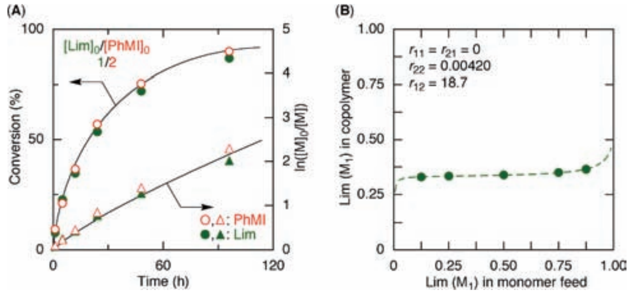


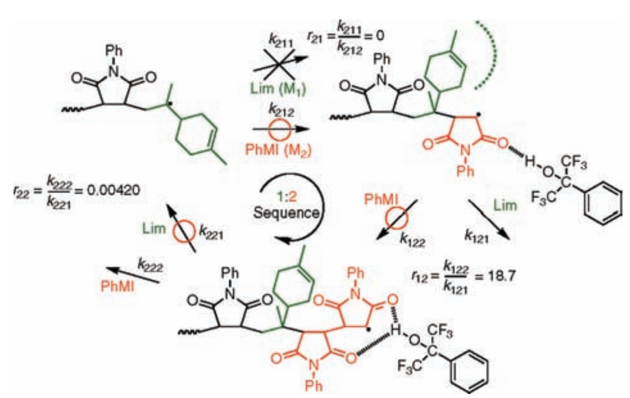
Figure 1. (A) Time−conversion and first-order kinetic plots ($[Lim]_0/[PhMI]_0$ = 400/800 mM, $[AIBN]_0$ = 8.0 mM) and (B) copolymer composition curves ($[Lim]_0+[PhMI]_0$ = 1200 mM, $[Lim]_0/[PhMI]_0$ = 1/7, 1/3, 1/1, 3/1, 7/1, $[AIBN]_0$ = 8.0 mM) for the Lim/PhMI copolymerization with AIBN in $PhC(CF_3)_2OH$ at 60 °C. The dotted lines in plot B were fitted by the Kelen−Tüdõs method, where $r_{11} = r_{21} = 0$, $r_{22} = 0.00420$, and $r_{12} = 18.7$.

Table 1. Radical Copolymerization of Olefin (M_1) and Maleimides (M_2) in $PhC(CF_3)_2OH$[a]

M_1	M_2	Conv, (%)[b] M_1/M_2	M_n[c]	M_w/M_n[c]	Incorp, (%)[d] M_1/M_2	T_g (°C)[e]	$[\alpha]_D$[f]
Lim	PhMI	88/85	9200	1.98	34/66	243	1.5
Lim	CyMI	85/88	9100	1.92	33/67	226	7.7
1-Hexene	PhMI	77/94	22 000	1.64	43/57	145	–
2-Methyl-1-pentene	PhMI	71/94	72 500	2.59	46/54	189	–

[a] Polymerization condition: $PhC(CF_3)_2OH$, 60 °C, $[M_1]_0 + [M_2]_0$ = 1200 mM, $[M_1]_0/[M_2]_0$ = 0.5 (for Limonene), or 1.0 (for 1-hexene and 2-methyl-1-penetene), $([M_1]_0 + [M_2]_0)/[AIBN]_0$ = 150. [b] Determined by ^1H NMR analysis of residual monomers in the reaction mixture. [c] The weight-average molecular weight (M_w) and distribution (M_w/M_n) were determined by size-exclusion chromatography. [d] Determined by ^1H NMR analysis of the isolated copolymers. [e] Evaluated by a differential scanning calorimetry. [f] Measured in THF.

Scheme 1. Schematics of AAB-Sequence Radical Copolymerization of *d*-Limonene (M_1) and Phenylmaleimide (M_2)



conversions of the two monomers. The copolymers obtained from limonene and maleimides exhibited relatively high glass transition temperatures (T_g = 220−250 °C) than those obtained from the usual α-olefins, such as 1-hexene, due to the higher incorporation of maleimides as well as the rigid alicyclic structure of the terpenes (Figure S4).[14] In addition, the copolymers obtained from the chiral Lim showed optical activities and circular dichroisms because the chiral center of the monomer units retained its configuration during the polymerization (Figure S5).

The copolymerization of Lim (M_1 or L) and PhMI (M_2 or M) in $PhC(CF_3)_2OH$ was further discussed in terms of the monomer reactivity ratio, which can be estimated by varying the comonomer feed compositions (Table S2). The copolymer composition curve showed a distinctive plateau region, in which the content of the terpene (M_1) in the copolymers is approximately one-third (0.33) irrespective of the feed ratio (Figure 1B). This is in sharp contrast to conventional 1:1 alternating copolymerizations, which showed a similar plateau region but at the comonomer content of 0.50. The monomer reactivity ratio was best fitted by a penultimate model as shown in Figure 1B.[7] In this model, there are four parameters for the monomer reactivity ratios, r_{11}, r_{12}, r_{21}, and r_{22}. The curve fitting suggests that r_{11} and r_{21} can be assumed to be zero, which is reasonable because the consecutive addition of unconjugated hydrocarbon olefin monomer units (M_1; Lim) hardly occurs in the radical polymerizations. The validity of this assumption will be further certified by the absence of the successive terpene units in the matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (see below). On this assumption ($r_{11} = r_{21} = 0$), the r_{12} and r_{22} were thus calculated to be 18.7 and 4.20×10^{-3} by the Kelen−Tüdõs method for the penultimate model (Figure S6), respectively, which indicated that the $\sim\sim M_1M_2\bullet$ radical favors M_2 while $\sim\sim M_2M_2\bullet$ exclusively reacts with M_1 (Scheme 1). Based on such consecutive reactions with a high selectivity, the 1:2 radical copolymerization would exclusively proceed.

The selective propagation is most probably due to the interaction of the fluorinated alcohol with the carbonyl groups in the maleimide unit and the bulkiness of the alicyclic structure in Lim. The interaction of the fluorinated alcohol was investigated by ^1H NMR with cyclohexyl maleimide or its dimer, which can be regarded as one of the simplest models of the growing terminus $\sim M\bullet$ or $\sim MM\bullet$ (Figure S7). For both of the cases, the stoichiometry evaluated by Job's method suggested a 1:1 interaction between the alcohol and imide compounds, which indicates a bidendate or bridging interaction of the alcohol with two carbonyl groups of the dimer as well as at the growing terminal. Furthermore, the ^1H NMR titration exhibited that the association constant (K) with the dimer (11.2 M^{-1}) was higher than that with the monomer (2.46 M^{-1}). Thus, the stronger coordination of the fluoroalcohol at the $\sim MM\bullet$ chain end enhances the addition of electron-rich L monomer, while the addition of L hardly occurs to the $\sim LM\bullet$ chain end due to the bulkier penultimate L unit. These schematic views are supported by the facts that less bulky olefins, 1-hexene and 2-methyl-1-pentene, were incorporated into the copolymers at higher molar ratios (~0.45) in $PhC(CF_3)_2OH$ (see Table 1) and that longer M sequences were observed in the copolymerization in CH_2Cl_2, as indicated by the MALDI-TOF-MS analysis (see below).

We then examined the controlled/living radical copolymerization of Lim and PhMI using RAFT agents in $PhC(CF_3)_2OH$. The copolymerization was conducted at the 1:2 ratio of $[Lim]_0/[PhMI]_0$ in the presence of *n*-butyl cumyl trithiocarbonate (CBTC) or *n*-butyl 2-cyano-2-propyl trithiocarbonate (CPBTC) as a RAFT agent with AIBN as the radical reservoir at 60 °C. In both cases, the copolymerizations smoothly occurred and the two monomers were consumed at the same rate (Figure S8). The size-exclusion chromatograms (SEC) of the copolymers showed unimodal curves, and the number-average molecular weights (M_n) increased with the conversions (Figure 2). Although the M_n deviated from the calculated value probably due to the difference in the hydrodynamic volume with a polystyrene standard, the absolute M_n values determined by a multiangle laser light-scattering (MALLS) detector [M_n(MALLS) = 8400 (48% conversion with CBTC) and 7600 (44% conversion with CPBTC)] were close to those calculated by the monomer-RAFT feed ratio and the monomer conversion [M_n(calcd) = 9300 for CBTC and 8500 for CPBTC, respectively]. The slightly broader molecular weight distributions (MWDs) suggest a slow addition−fragmentation process in the copolymerization at such a low monomer concentration. Thus, control-

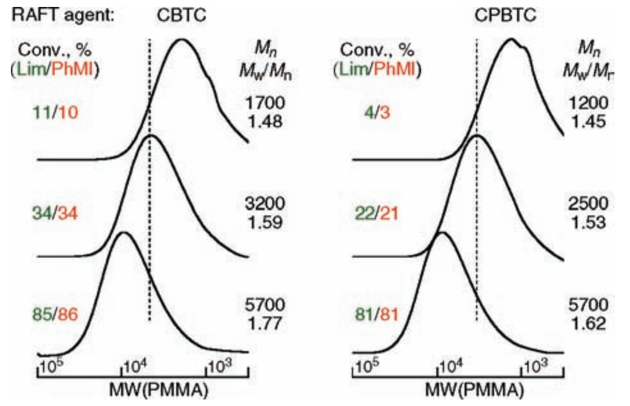


Figure 2. Size-exclusion chromatograms of the copolymers obtained in RAFT copolymerization of limonene and phenylmaleimide with AIBN in the presence of CBTC or CPBTC as a RAFT agent in $PhC(CF_3)_2OH$ at 60 °C ($[Lim]_0/[PhMI]_0 = 400/800$ mM, $[AIBN]_0 = 5.0$ mM, $[CBTC]_0$ or $[CPBTC]_0 = 10$ mM.).

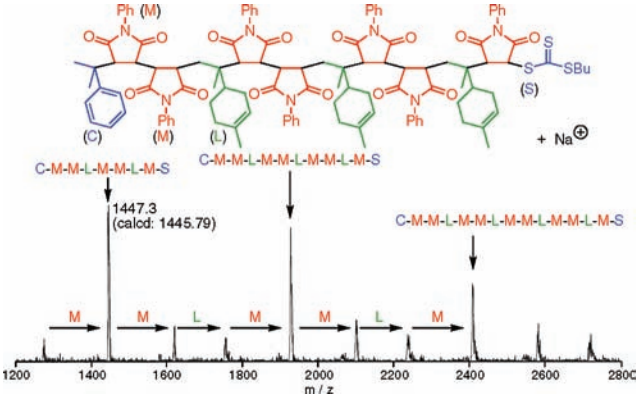


Figure 3. MALDI-TOF-MS spectrum of the copolymer of *d*-limonene and phenylmaleimide obtained with AIBN in the presence of CBTC as a RAFT agent in $PhC(CF_3)_2OH$ at 60 °C ($M_n = 1700$, $M_w/M_n = 1.48$, $[Lim]_0/[PhMI]_0 = 400/800$ mM, $[AIBN]_0 = 5.0$ mM, $[CBTC]_0 = 10$ mM, total conversion =10%).

ling the molecular weights in the radical copolymerization of Lim and PhMI was attained by these RAFT agents.

The MALDI-TOF-MS analysis of the copolymers showed that the copolymers consist of not only the selective -M-M-L- [M: PhMI (M_2); L: Lim (M_1)] sequence but also the well-defined initiating and capping sequence. Figure 3 shows the typical MALDI-TOF spectrum of such highly end-to-end sequenced copolymers obtained from CBTC as the RAFT agent. The highest series of peaks are separated by the total molecular weights (482.6) with one L- unit and two M- units and can be assigned to a series of end-to-end sequenced copolymers [C-(M-M-L)$_n$-M-S] (C: cumyl group; S: trithiocarbonyl group) with a C-M-M-L- unit at the initiating terminal and an -M-M-L-M-S unit at the capping terminal along with the -M-M-L- main-chain repeating sequence. Besides the highest series, there are two minor series of peaks possessing an additional -M- or -M-L- unit, which are mostly attributed to a capping error with other sequenced units, such as the -(M-M-L)$_n$-M-M-S or -(M-M-L)$_{n+1}$-S terminal. These results indicate that the copolymers obtained with CBTC possessed a highly controlled chain-end sequence as well as the nearly perfect main chain sequence. However, the copolymers obtained with another RAFT agent, CPBTC, were contaminated with an additional error at the initiating chain end with a CP-M-L-(M-M-L)$_n$- sequence (CP: cyanopropyl) in addition to the main series of the CP-(M-M-L)$_n$- sequence (Figure S9). Furthermore, the RAFT copolymerization with CBTC in CH_2Cl_2 led to the loss of the -(M-M-L)$_n$- sequence and higher numbers of successive M sequences (Figure S10). The high regulation at the initiating chain end by CBTC is most probably due to the electron-donating and bulky cumyl group, which behaves in a way similar to the growing Lim radical. The predominant -M-L-M-S capping sequence can be ascribed to the electron-deficient and sterically constrained -L-M• radical, which undergoes a relatively facile capping with the electron-rich and less bulky trithiocarbonate group.

In conclusion, the controlled/living radical copolymerizations of plant-derived (+)-*d*-limonene and maleimides in fluoroalcohol produced not only the chiral and high T_g copolymers with their quantitative conversions but also the unprecedented 1:2 sequence-regulated copolymers from the initiating to the growing end. We believe that this unique radical copolymerization would lead to a new approach for sequence regulation in chain-growth polymerization and that such highly sequence-regulated copolymers obtained from natural resources will be promising to mimic natural polymers, forming highly ordered molecular structures and expressing biofunctions.

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Supporting Information Available: Experimental details and polymerization results. This material is available free of charge via the Internet at http://pubs.acs.org.

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