Controlled Synthesis of Reactive Polymeric Architectures Using 5-Norbornene-2-carboxylic Acid Pentafluorophenyl Ester

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Summary: Exo-5-norbornene-2-carboxylic acid pentafluorophenyl ester was synthesized from 5-norbornene-2-carboxylic acid and polymerized by ring-opening metathesis polymerization. The obtained polymers were soluble polymeric active esters that could be used for the preparation of multifunctional polymers. The molecular weight of the polymers was controlled by variation of the monomer to initiator ratio. The precursor polymers reacted quantitatively with primary and secondary amines. Time resolved FT-IR studies at different temperatures of the polymer analogous reactions were performed and rate constants were determined.

Keywords: active ester monomers; functionalization of polymers; living polymerization; ring-opening metathesis polymerization (ROMP)

Introduction

Due to their applications in growing research fields such as nanotechnology, biotechnology or organic electronics, highly functionalized polymers continue to be in the focus of interest. A way of designing tailor-made macromolecules is the polymerization of functionalized monomers. This approach, however, has some major drawbacks. First of all, the so-obtained polymer is fixed in its characteristics and can be used only in its specific application. On the other hand, some functional monomers are known to cause difficulties in polymerization reactions involving transition metal catalysts for their ability to coordinate to the catalyst and thus, turning it inactive towards the polymerization reaction.

A more versatile approach of synthesising macromolecules containing a high number of functional groups is the use of reactive precursor polymers.[1,2] Starting from a monomer containing a reactive side group, polymer architectures can be synthesized in a straightforward way. From this reactive precursor, a wide variety of desired functionalities can be introduced via polymer analogous reactions, thus, turning the reactive polymer scaffold into a versatile synthetic tool for the construction of tailor-made polymers with high density of functionalities.

Formally famous as reactive agents in peptide synthesis,[3] esters of pentafluorophenol have become useful as reactive precursor polymers[4,5] for their good performance in polymer analogous substitution reactions with primary and secondary amines and their excellent solubility in common organic solvents as well as the convenient monitoring of polymer analogous substitution reactions by ^{19}F-NMR spectroscopy.

In the search for high performance polymer architectures, bicyclo[2.2.1]hept-2-ene, better known by its trivial name norbornene and its derivatives have recently been in the centre of interest due to their interesting characteristics of the accessible polymers.[6]

The monomer can be polymerized via ring opening metathesis polymerization

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(ROMP)[7–11] and vinyl-type polymerization[6] leading to macromolecules with completely different characteristics. A third way of polymerizing norbornene is a cationic process leading to 2.7-connected oligomers.[12]

Materials generated by ROMP feature a double bond in the backbone. They have been extensively used as bioactive scaffolds for the investigation of a diverse range of biological systems.[13,14] In particular, ROMP has been used to synthesize potent inhibitors of cell binding interactions,[15,16] novel antibiotics[17] and mechanistic probes of multivalent interactions.[17,18]

However, a major drawback to this point is the difficulty in attaching functional groups to the norbornene polymers because polymerization of functional monomers are likely to fail because of the coordinating abilities of polar groups to the catalyst as mentioned before.

In this paper, we focus on the synthesis of 5-norbornene-2-carboxylic acid pentafluorophenylester, its ring-opening metathesis polymerization to form a reactive polynorbornene precursor polymer and polymer analogous reactions that demonstrate the versatility of this approach towards highly functionalized polymers. To our best knowledge, no literature exists to this point describing the synthesis of the above mentioned polymer.

Experimental Part

Materials

All chemicals were commercially available and used without further purification unless otherwise stated. Anhydrous toluene and THF were distilled over sodium and benzophenone, dichloromethane was dried using CaH_2.

Instrumentation

NMR spectra were measured using a Bruker AMX 300 in $CDCl_3$ if not stated otherwise. FT-IR measurements were performed using a Bruker Vector 22. GPC measurements were performed using tetrahydrofuran (THF) as eluent (flow rate = 1 ml/min) at 25 °C. Molecular weights and molecular weight distribution were measured by light scattering and RI detector. Polystyrene standards were used for calibration.

Norbornene-5-exo-carboxylic Acid (2)

The procedure of Pontrello et al.[19] was followed. Briefly, commercially available racemic Norbornene-5-exo-carboxylic acid **(1)** was dissolved in 0.75M aqueous $NaHCO_3$ and treated with iodine and KI to convert the *endo* acid into an iodolactone. After separation of the organic phase containing the iodolactone, NaS_2O_3 was added to the water phase and pH = 2 was adjusted using 1M sulphuric acid. Extraction with diethylether yielded 21% of pure exo-compound.

^{1}H-NMR ($CDCl_3$, 300MHz): σ (ppm) = 6.14 (ddd, 2H, J = 7.8, 5.7, 2.7 Hz), 3.11 (s, 1H), 2.94 (s, 1H), 2.27 (ddd, 1H, J = 8.60, 4.40, 1.95 Hz), 1.95 (td, 1H, J = 12.08, 4.09, 4.09 Hz), 1.59 (d, 1H, J = 8.43Hz), 1.44-1.37 (m, 2H).

Exo-norbornene-5-pentafluorophenylester (3)

One equivalent of norbornene-5-exo-carboxylic acid (**2**) was dissolved in dry toluene under a nitrogen atmosphere. 1.1 equivalents of oxalylchloride were added dropwise at room temperature. After complete addition, the reaction mixture was stirred for one hour at 80 °C. After removal of the solvent dry dichloromethane was added under nitrogen atmosphere. Then, a mixture of 2,6-lutidine and pentafluorophenol in anhydrous dichloromethane was added by syringe at 0 °C. The mixture was stirred at room temperature for 24 hours and the product was purified by column chromatography using petrol ether as eluent with 80% yield.

^{1}H NMR ($CDCl_3$, 300MHz): σ (ppm) = 6.20 (ddd, 2H, J = 14.69, 5.58, 2.99 Hz), 3.27 (s, 1H), 3.03 (s, 1H), 2.587, (dd, 1H, J_1 = 8.83, 4.42 Hz), 2.07 (td, 1H, J = 12.08, 3.95, 3.95 Hz), 1.64-1.40 (m, 3H).

General Procedure for ROMP

The polymerizations were performed as described in the literature with minor modifications.[20] Under nitrogen atmosphere, first generation Grubbs catalyst and monomer were weighted into separated flasks and dissolved in 1 ml dichloromethane (catalyst) and approximately 0.5 ml dichloromethane for every 100 mg of monomer. The solutions were degassed three times. The reaction was initiated by adding the catalyst to the vigorously stirred monomer solution. The reaction mixture was allowed to stir for 5 h. To cleave the catalyst, a small amount of ethyl vinyl ether was added. The polymer was precipitated into methanol. For further purification, the polymer was dissolved in THF and reprecipitated from methanol several times.

1H-NMR ($CDCl_3$, 300 MHz): σ (ppm) = 5.57–5.28 (m, br, 2H), 3.29–2.89 (m, br, 2H), 2.75 (s, br, 1H), 2.27 (s, br, 1H), 2.06 (s, br, 1H), 1.87 (s, br, 1H), 1.40–1.21 (m, br, 1H).

Polymer Analogous Reactions

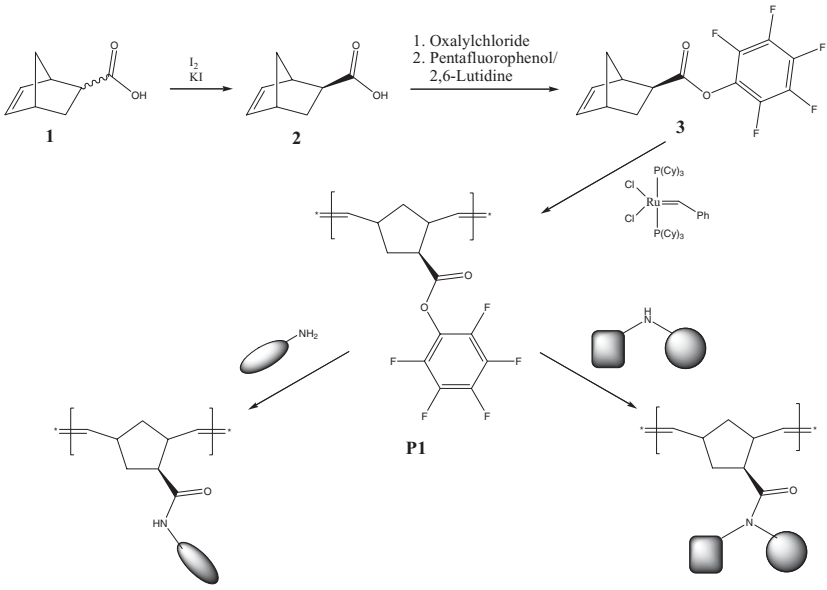
A general procedure as described in the literature[4] was followed with minor modifications: 0.1 mg of **P1** was dissolved in 3 ml dry chloroform. 2 equivalents (primary amines) or 1.1 equivalents (secondary amines) in 1 ml dry chloroform were added using syringes. The mixture was stirred at 50 °C under nitrogen atmosphere. After evaporation of the solvent in vacuum, the polymers were redissolved in THF and precipitated in n-hexane. The isolated product was dried in vacuum at 50 °C.

Kinetic FT-IR Measurements

A general method to follow the polymer analogous reactions by FT-IR was performed as follows: the polymers were dissolved in anhydrous chloroform at a concentration of 0.02 mol/l. Then, the amine was added in two equivalents and the solution was placed in a FT-IR transmission liquid cell. Measurements were performed at different temperatures. Time resolved conversion was calculated by the decrease of the area of the carbonyl peak assigned to the active ester.

Results and Discussion

This work focuses on the synthesis of 5-norbornene-2-carboxylic acid pentafluorophenyl ester **3** as a new reactive monomer



Scheme 1.
Synthesis of ROMP-poly(norbornene pentafluorophenyl ester).

and its polymerization via ring opening metathesis to form reactive polymer precursors. Scheme 1 outlines the described synthetic strategy. Polymer analogous reactions with primary and secondary amines were investigated to demonstrate the versatility of the approach to prepare highly functionalized polymers.

Monomer Synthesis

Starting from commercially available *racemic* norbornene-5-carboxylic acid, the active ester monomer was synthesized as shown in Scheme 1. The first step, isolation of the *exo*-carboxylic acid is necessary because *endo*-derivatives of norbornene are known to be less reactive towards ring opening metathesis as well as vinyl-type polymerizations.[21,22]

The norbornene-exo-5-carboxylic acid was transformed to its acid chloride using oxalylchloride in slight excess. Reaction of the acid chloride with pentafluorophenol in presence of the auxiliary base 2,6-lutidine resulted in the active ester monomer **3** as a colorless liquid in high yields. Figure 1a shows the ^{1}H-NMR spectrum of monomer **3**. The FT-IR spectrum showed a dominant peak at 1778 cm^{-1} that can be assigned to the carbonyl bond of the active ester.

Due to the presence of fluorine atoms, an easy method to control purity and formation of the reactive ester monomer is ^{19}F-NMR spectroscopy. The ^{19}F-NMR spectrum of **3** shows the expected signals of the five fluorine atoms attached to the aromatic ring at −153.51 ppm, −158.75 ppm and −162.90 ppm that can be assigned to the fluorine atoms in *ortho, para* and *meta* position, respectively, with a peak integration ratio of 2:1:2. Pentafluorophenol itself shows signals at −163.9 ppm, −164.2 ppm and −168.7 ppm that are not present in the spectrum of 3, thus confirming the purity of the monomer.

The substance was soluble in common organic solvents such as aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, ethers and alcohols. Furthermore, the active ester was stable, not air sensitive

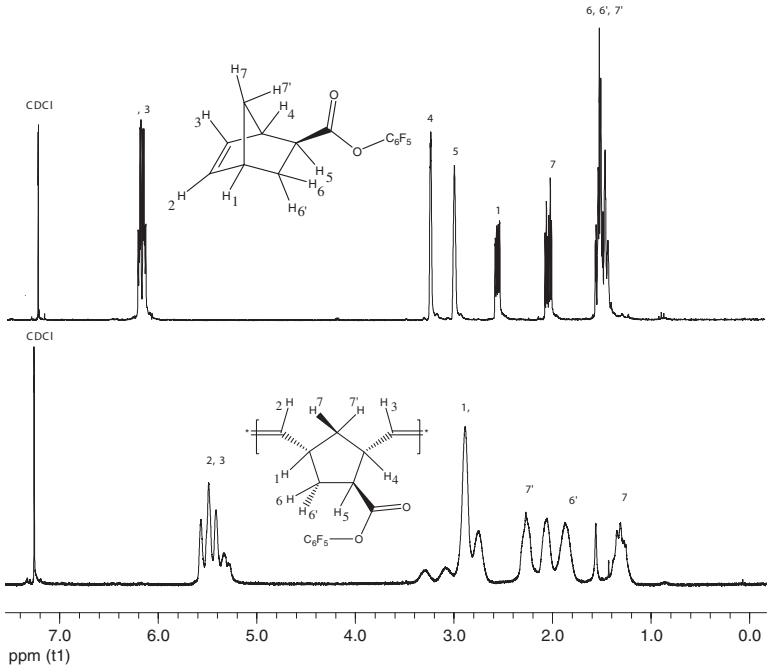


Figure 1.
a) ^{1}H-NMR-spectra of norbornenepentafluorophenyl ester monomer **3** and b) the corresponding polymer **P1**.

Table 1.
Polymerization results.

[M]/[I]	Mn (GPC)	Mw (GPC)	PDI
50	22,610	29,510	1,305
75	30,390	43,640	1,436
100	37,110	58,570	1,578
125	45,790	64,810	1,416
150	62,480	90,320	1,446
200	75,390	101,610	1,407

and robust against hydrolysis in air. Even after storage in the freezer for several weeks, no signs of decomposition could be detected.

Polymerizations

Ring-opening metathesis polymerizations were performed using first generation Grubbs catalyst in dichloromethane. After polymerization, the polymers were isolated by precipitation in methanol. Several re-precipitation steps from THF into methanol resulted in pure polymers in good yields. They were characterized using ^{1}H- and ^{19}F-NMR as well as FT-IR spectroscopy. The ^{1}H-NMR spectrum of **P1** is shown in Figure 1b. The broad peaks could be assigned to the polymeric protons while no signs of sharp monomer peaks could be detected, thus stating the purity of the polymer. The ^{19}F-NMR spectrum of **P1** shows three broad peaks at −153.46 ppm, −158.52 ppm and −162.84 ppm were detected. No monomeric peaks were present in the spectrum. The same dominant peak at 1777 cm^{-1}, assigned to the carbonyl bond of the monomer, could be observed in the FT-IR spectrum of **P1** as shown in Figure 4a.

All polymers were soluble in many organic solvents such as chlorinated hydrocarbons, aromatic hydrocarbons, diethylether and THF, acetone, DMF and DMSO, but insoluble in n-hexane, methanol and water.

For a polymerization to be considered living the monomer must be polymerized to completion in the absence of any chain transfer or chain termination reactions and subsequent addition of monomer should lead to further polymerization of the chain ends.

To examine the living nature of the these polymerizations, the monomer to initiator ratio R = [M]/[I] was varied from 50 to 200. Results are given in Table 1. As illustrated in Figure 2, a linear correlation between the molecular weight and the [M]/[I] ratio was observed, thus, approving the living nature of the polymerization.

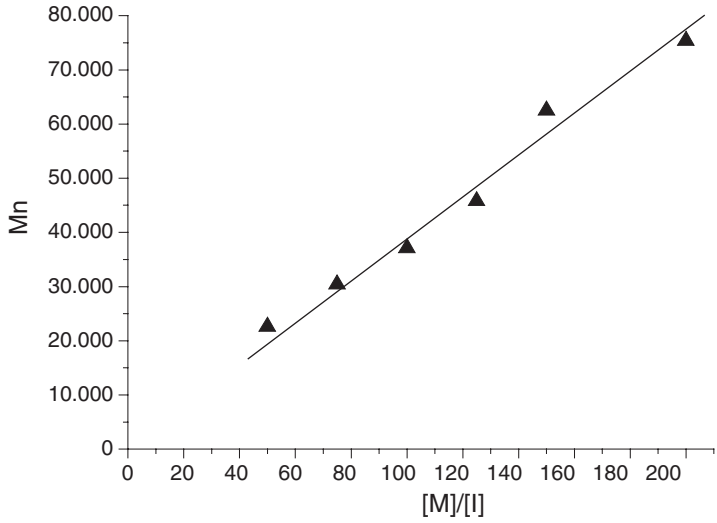


Figure 2.
Dependence of M_n on the [M]/[I] ratio.

To gain control over the functional group density, experiments to copolymerize the active ester monomer with normal norbornene were conducted by polymerization of a 1:1 mixture of active ester **3** and norbornene resulting in statistical copolymers with 3:1 excess of active ester groups as determined by integration of the ^{1}H NMR spectra. The active ester monomer seems to be more reactive in ROMP polymerizations. However, the NMR signals clearly show the incorporation of norbornene units in the polymer, see Figure 3.

Therefore, a controlled decrease of functionalities along the polymer chain can be achieved. This can be useful especially for the attachment of bulky substituents in polymer analogous reactions.

Polymer Analogous Reactions

Esters of pentafluorophenol are known to react quantitatively with primary and secondary amines.[4] This turns them into attractive precursor materials especially for biological applications as amino acids or peptides can be attached to the polymer conveniently. With this approach, difficult work-up and purification is not necessary as the functionalized polymers can easily be precipitated. Furthermore, the excellent solubility of the precursor polymers in common solvents makes them superior in comparison to other active precursor systems such as N-hydroxy-succinimide-functionalized systems.[4]

In order to examine the performance of the novel polymeric precursor, polymer analogous reactions with *n*-hexylamine and *n*-hexylmethylamine as model compounds for primary and secondary amines were conducted. To monitor the conversion, FT-IR measurements proved to be both simple and powerful as the peaks assigned to the carbonyl bond of the pentafluorophenyl ester and the amide bond are easy to distinguish.

To prove the quantitative conversion with both primary and secondary amines, the polymers were allowed to react for 24 hours at 50 °C in chloroform. Figure 4a shows the FT-IR spectra of **P1** and poly-norbornene-5-n-hexylamide **P2** as well as poly-norbornene-N,N-hexyl-methylamide **P3**. In the spectra of both **P2** and **P3**, the peak assigned to the carbonyl bond of the ester at 1777 cm^{-1} disappeared while a new peak at 1657 cm^{-1} (**P2**) or 1636 cm^{-1} (**P3**) belonging to the amide bond was detected. A quantitative reaction of the active ester with primary as well as secondary amines took place within 24 hours.

Further, to determine the reactivity towards amines, kinetic measurements were performed using FT-IR spectroscopy to monitor the progress of the reaction. The polymers were dissolved in chloroform, two equivalents of amine were added and the mixture was placed in a tempered FT-IR liquid cell. Measurements were recorded at 5, 25 and 45 °C for the reaction with the

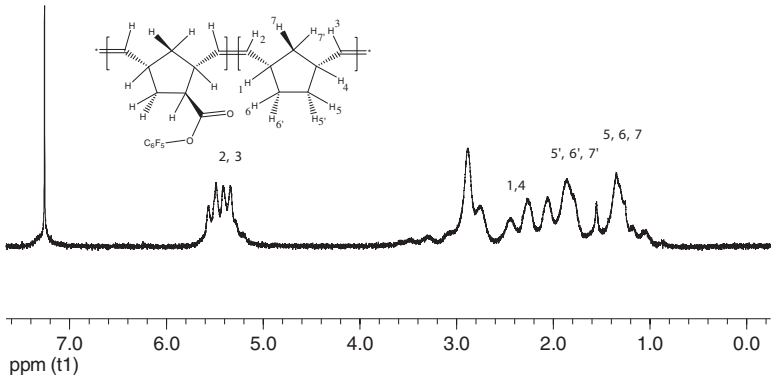


Figure 3.
^{1}H-NMR spectrum of poly-(norbornene-pentafluorophenyl ester-co-norbornene).

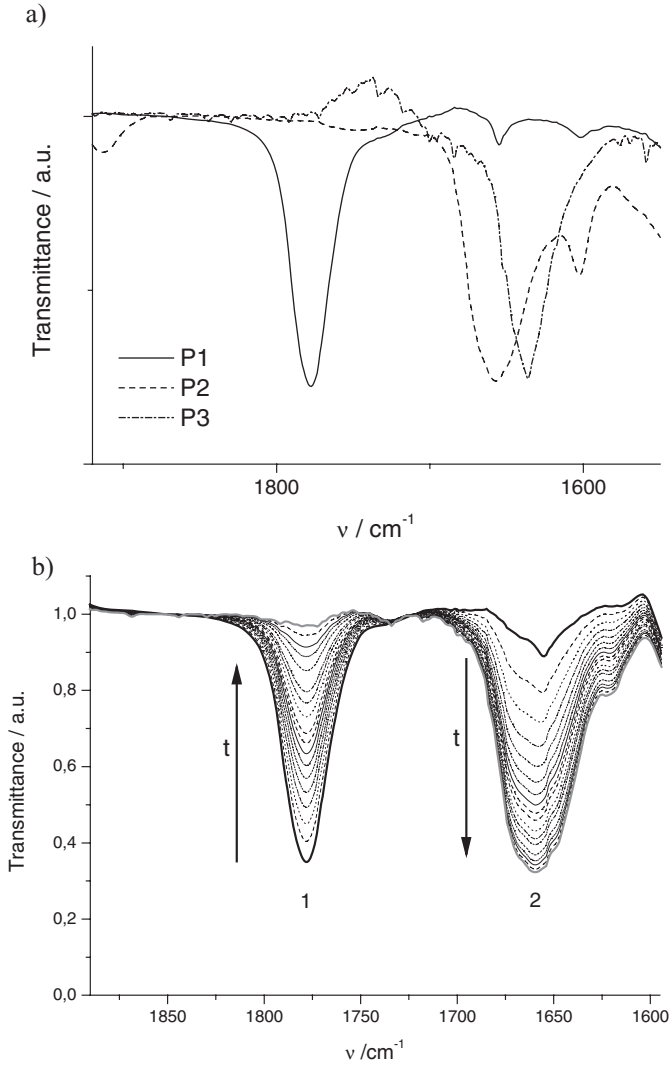


Figure 4.
a) FT-IR spectra of poly-norbornene-pentafluorophenyl ester **P1**, poly-norbornene-n-hexylamide **P2** and poly-norbornene-n-hexylmethylamide **P3**. b) Time resolved FT-IR measurements of the reaction of **P1** with n-hexylamine between 2 and 120 minutes.

primary amine and at 45 °C for the reaction with the secondary amine.

During the reaction, pentafluorophenol is released from the polymer. Due to its high acidity, it forms a salt with the basic amines and thus turns them into unreactive species towards nucleophilic substitution. Hence, two equivalents of amines were used.

As an example, Figure 4b shows the development of the reaction of **P1** with *n*-hexylamine at 45 °C in the time range from 2 to 120 minutes. Clearly, it shows the decrease of the activated carbonyl peak (1) at 1777cm^{-1} with ongoing reaction time while a new peak assigned to the newly formed amide bond (2) at 1657 cm^{-1} is emerging during the reaction.

Quantitative calculation of the conversion was determined by the decrease of the area of the activated carbonyl peak between 1850 and 1730 cm^{-1}. Figure 5 shows the time dependent behaviour of

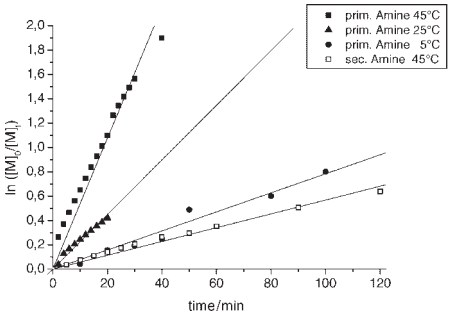


Figure 5.
Determination of the rate constants for the reaction with n-hexylamine at 5, 25 and 45 °C and the reaction with n-hexylmethylamine at 45 °C.

the polymer analogous conversion reactions with the primary- and secondary amine respectively as calculated.

Out of the kinetic FT-IR experiments, the rate constants of the reactions at different temperatures were calculated. In Figure 8, the plots of $\ln([M]_0/[M]_t)$ versus time t, with $[M]_0$ being the integral value of the activated carbonyl peak at $t = 0$ s and $[M]_t$ being the integral value of the activated carbonyl peak at time t, are shown. A linear correlation between $\ln([M]_0/[M]_t)$ and time was observed for the starting phase of all investigated conversions, stating that all conducted polymer analogous reactions follow a first order kinetic. The slope of the linear regression directly gives the rate constant k of the polymer analogous reaction that can be converted into the half-life time $\tau_{1/2}$, the time at which the concentration of the reactant is half of the initial concentration. For first order kinetics, it is given by $\tau_{1/2} = (\ln 2)/k$. Calculated results for the values of k and $\tau_{1/2}$ are listed in Table 2.

Table 2.
Kinetic data of polymer analogous reactions.

Reactant	T/°C	k/s^{-1}	$\tau_{1/2}$/min
n-hexylamine	5	1.06×10^{-4}	109
n-hexylamine	25	3.74×10^{-4}	31
n-hexylamine	45	8.97×10^{-4}	13
n-hexylmethylamine	45	9.47×10^{-5}	122

Conclusions

We could demonstrate the successful synthesis and polymerization of the new active ester monomer *exo*-norbornene-5-pentafluorophenyl ester **3** using ring-opening metathesis polymerization into the corresponding reactive precursor polymer **P1**. The obtained polymers were soluble in common organic solvents. The living character of the polymerization allowed easy control of the molecular weight of the polymeric materials. Polymer analogous reactions with *n*-hexylamine and *n*-hexylmethylamine as model compounds for primary and secondary amines were investigated. It was shown that quantitative conversion with both primary and secondary amine was achieved within 24 hours at 50 °C reaction temperature. A detailed study of the reactivity was performed using time-resolved FT-IR measurements, revealing that all investigated polymer-analogous reactions followed first order kinetics. Form the kinetic measurements, the rate constants k and half-life time $\tau_{1/2}$ were calculated. The good solubility and quantitative reaction with primary and secondary amines give easy access to highly functionalized polynorbornenes.

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