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Accelerated Ring-Opening Metathesis Polymerization of a Secondary Amide of 1-Cyclobutene by Hydrogen-Bonding Interaction

Kil Sun Lee and Tae-Lim Choi*

*Department of Chemistry, Seoul National University, 599 Gwanak-ro, Gwanak-gu,
Seoul, Korea, 151-747*

tlc@snu.ac.kr

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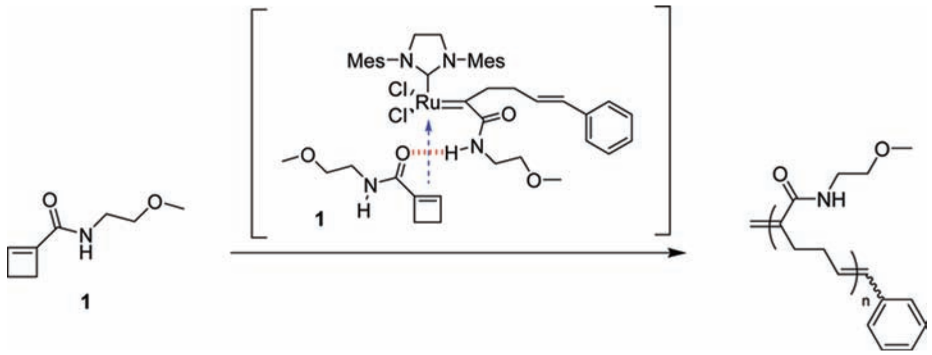
ABSTRACT



A hydrogen-bond-assisted model is proposed for ring-opening metathesis polymerization (ROMP) of a secondary amide of 1-cyclobutene, resulting in the fastest reaction rate in a nonpolar solvent, toluene. This new model was supported by the investigation on how the solvent effect affected the NMR spectra, ROMP kinetic studies, and the copolymerization of monomers 1 and 2.

Ring-opening metathesis polymerization (ROMP) has attracted a great deal of attention because it provides a versatile method for the synthesis of functional polymers[1] such as hydrogels,[2] biologically active polymers,[3] and liquid crystalline polymers.[4] This versatility has been mainly driven by the remarkable development of well-defined transition-metal catalysts on the basis of W, Mo, and Ru complexes,[5] which readily polymerize many strained cycloalkenes such as norbornene derivatives, cyclobutene, cyclooctene, and dicyclopentadiene.[6] In particular, Grubbs catalysts based on Ru complexes are widely used in ROMP because they are tolerant to protic functional groups, oxygen, and moisture.[7] However, the drawback of Grubbs catalysts is that they generally give less stereoregular polymers than the catalysts based on Mo and W complexes.[8]

Among the few studies on the stereoregular polymerization by Grubbs catalysts,[9] recent studies conducted by Sampson and Parker caught our attention. Although many examples of the ROMP of substituted cyclobutenes have been reported, these polymers have low

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10.1021/ol2014363

regio- and stereoselectivity in general.[10,11] On the other hand, Sampson and Parker synthesized regioregular head-to-tail polymers that strictly had an *E*-olefin geometry by using third-generation Grubbs catalyst with secondary amides of 1-cyclobutenes as monomers.[12] Moreover, the ROMP allowed controlled polymerization to give polymers with a low to moderate polydispersity index (PDI) as well. These polymers might find applications both as materials and in chemical biology, where well-defined stereoregular structures would be advantageous. Parker and Sampson demonstrated the origin of the regio- and stereoselectivity of the polymers using computational analysis and schematic models. However, one distinct drawback of the ROMP was that during homopolymerization, 1-cyclobutenecarboxylic acid ester underwent stoichiometric ring-opening metathesis with only one turnover, and they proposed the chelation model of ester oxygen coordinated to the ruthenium center, which resulted in the deactivation of the catalyst and hence hindered further propagation.[13]

Herein, we propose a new model of hydrogen bond-assisted ROMP of the secondary amide of a 1-cyclobutene monomer to explain why the secondary amides of 1-cyclobutenes are the most active monomers among the 1-cyclobutenecarboxylic acid derivatives. To verify this model, a study on the solvent effect is conducted and a copolymerization experiment is performed. To the best of our knowledge, this is the first example of hydrogen bond-assisted ROMP between monomers that results in faster polymerization in a nonpolar solvent.[14,15]

Although highly strained cyclobutene derivatives are good monomers for ROMP, the secondary amides of 1-cyclobutene are not good monomers for ROMP as compared to 3-substituted cyclobutenes and norbornene monomers.[12,13] This is because they contain challenging trisubstituted α,β-unsaturated carbonyl olefins that are not only sterically hindered but also electron deficient. Moreover, the inevitable formation of energetically unstable enoic carbenes as propagating species[16] decreases the ROMP activity even further. Therefore, the secondary amides of 1-cyclobutenes, which are the best monomers for ROMP among the cyclobutene-1-carboxylic acid derivatives, require an elevated temperature to produce regioregular polymers with a degree of polymerization (DP) of 35 or higher.[12] Furthermore, the catalyst fails to homopolymerize the 1-cyclobutenecarboxylic acid esters and the tertiary amides.[13a]

We began our investigation to improve the efficiency of this ROMP by inspecting the monomer structures, and we realized that the presence of a secondary amide might prove important. This led to a proposal that the hydrogen of secondary amides in the enoic carbene intermediate might have hydrogen-bonding interaction with the carbonyl oxygen of an incoming monomer (Figure 1). If this hypothesis was correct, then one could increase the ROMP activity by enhancing the hydrogen bonding interaction, which could be achieved by simply changing the polarity of the solvent. To support this hypothesis, monomers **1** and **2** were synthesized (see the Supporting Information).[13]

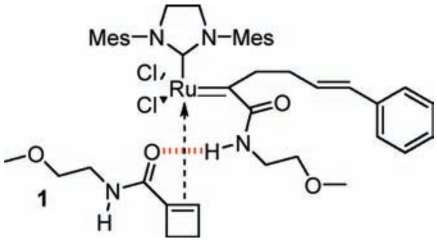

Figure 1. Proposed model for hydrogen-bond-assisted ROMP.[17]

To study the solvent effect on the hydrogen-bonding interaction, dichloromethane (DCM), which was used in the original report, and two other solvents were chosen: tetrahydrafuran (THF) for interrupting the hydrogen bonding and toluene as a nonpolar solvent. First, we characterized **1** in these solvents by ^{1}H NMR so as to shed light on the interaction between **1** and the various solvents (Figure S1, Supporting Information). When the ^{1}H NMR spectra of **1** in non-hydrogen bonding solvents were taken, chemical shifts for the N–H amide peak were observed at 6.06 ppm and 6.02 ppm in DCM-d_2 and toluene-d_8, respectively. On the other hand, the N-H peak shifted downfield to 7.14 ppm when recorded in the hydrogen-bonding solvent, THF-d_8, indicating that THF interacted with **1** by hydrogen bonding and perhaps the ROMP activity might be influenced by the choice of solvents.

In order to obtain more direct evidence to support the proposed model (Figure 1), kinetic studies of ROMP in three different solvents were conducted by monitoring the conversion of **1** in NMR tube reactions. As shown in Figure 2, the initial rate of ROMP in nonpolar toluene was much faster than that in more polar DCM. Moreover,

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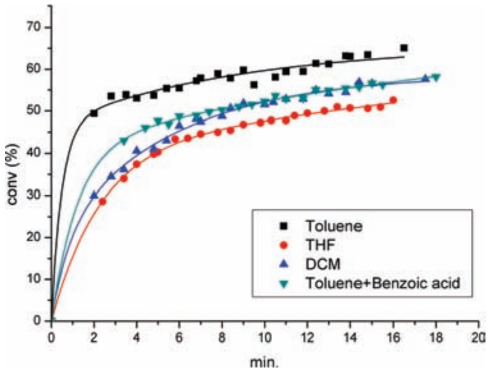


Figure 2. Time−conversion plots for ROMP of **1** in various solvents: [M] = 0.2 M, cat. = **A**, [M]/[C] = 10, 25 °C, benzoic acid = 25 mol %.

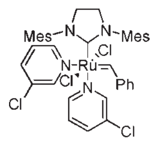
the rate of ROMP was slowest in the hydrogen-bonding solvent, THF, even though it was reported that the propagation rate for typical ROMP was faster in THF than in toluene and DCM.[18] On the other hand, the activity of Grubbs catalysts is known to increase by the addition of catalytic amount of acids.[19] Contrary to these reports, when we added 25 mol % of benzoic acid in toluene, the polymerization rate decreased. The results of theses kinetic studies indicate that the ROMP of **1** was accelerated by the hydrogen-bonding interaction between the propagating carbenes and the monomers, and this effect was the maximum in nonpolar toluene, whereas THF and benzoic acid as the additive slowed down the ROMP because of the competing hydrogen bonding between them and the propagating carbenes.

To further verify the acceleration of the ROMP of **1** in toluene, the reaction time for the ROMP of various $[M]_0/[C]$ values in toluene was compared with that in dichloromethane. According to the previous report, it took 3 h to achieve an 85% conversion for $[M]_0/[C] = 10$ in DCM,[13] but in toluene, the reaction was completed within 1 h (Table 1, entry 1). The reaction in toluene was completed in 5 h for DP of 20 (Table 1, entry 2), whereas it required more than 20 h to achieve 100% conversion when $[M]_0/[C]$ was 18 in DCM.[12] These results clearly indicate that the rate of the ROMP of **1** was enhanced in toluene because of the hydrogen-bonding interaction. To obtain a polymer with a higher molecular weight, the ROMP with a higher DP at an elevated temperature was required. For $[M]_0/[C] = 50$, the polymerization was carried out at 45 °C, but the conversion was incomplete in toluene even after 24 h. Under similar conditions, we achieved a slightly higher conversion rate (86% to 90% conversion, Table 1, entries 3 and 4) by changing the catalyst to the more stable Hoveyda−Grubbs catalyst **B** $[(\mathrm{IMesH_2})\mathrm{RuCl_2}(=\mathrm{CH}\text{-}o\text{-}\mathrm{OiPrC_6H_4})]$. Consequently, the ROMP for $[M]_0/[C] = 100$ at 60 °C in toluene using the Hoveyda−Grubbs catalyst led to a 66% conversion, which was the highest DP reported among the ROMP of this family of monomers. These results again indicate that the ROMP of the secondary amide of 1-cyclobutene was a challenging reaction.

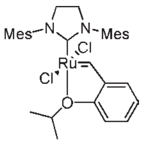
Table 1. Polymerization Results[a]

entry	$[M]_0/[C]$	cat.	temp (°C)	time (h)	M_n[b] (g/mol)	PDI[b]	conv[c] (%)
1	10	**A**	rt	<1	2600	1.10	>99
2	20	**A**	rt	5	2800	1.16	>99
3	50	**A**	45	24	6400	1.13	86
4	50	**B**	45	24	6500	1.17	90
5	100	**B**	60	24	7100	1.21	66

[a] Reaction conditions: [M] = 0.15 M in toluene. [b] Determined by THF-SEC calibrated by PS standards. [c] Conversion calculated by crude ^{1}H NMR.



A



B

Based on the hydrogen bond-assisted ROMP model, we investigated how the solvents influenced not only the initial rates but also the final conversion of the polymerization. Using catalyst **B**, we chose a challenging reaction condition of $[M]_0/[C] = 50$ to directly compare the effect of a solvent on the conversion. The reaction temperature was set to 40 °C owing to the low boiling point of DCM, and in all cases, the conversion did not increase after 24 h. Based on the results presented in Table 2, we can conclude that the highest conversion and molecular weight were obtained for the ROMP in toluene, thus confirming that toluene was the best solvent for the ROMP of the secondary amide of the 1-cyclobutene monomer.

Table 2. Solvent Screening Results[a]

entry	$[M]_0/[C]$	solvent	temp (°C)	M_n[b] (g/mol)	PDI[b]	conv[c] (%)
1	50	THF	40	3400	1.21	47
2	50	DCM	40	3200	1.16	54
3	50	toluene	40	4100	1.22	67

[a] Reaction conditions: [M] = 0.15 M, cat. = **B**, 24 h. [b] Determined by THF-SEC calibrated by PS standards. [c] Conversion calculated by crude ^{1}H NMR.

After improving the conditions for the ROMP of **1**, we focused our attention to the polymerization of **2**, the ester of 1-cyclobutenecarboxylic acid, which was reported to undergo a stoichiometric ring-opening metathesis reaction with only one turnover. It was proposed that the ester enoic ruthenium carbene formed an intramolecular chelate,

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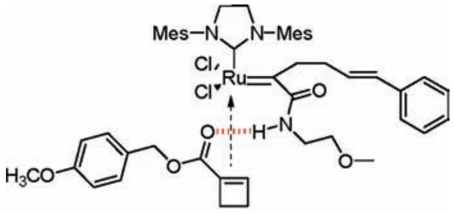
deactivating the catalyst from further ROMP. By using our hydrogen-bond-assisted ROMP model, we predicted that if ester **2** and amide **1** were subjected to copolymerization in toluene, ester monomer **2** would undergo random ROMP with more than one turnover because the hydrogen-bonding between the carbonyl oxygen of ester **2** and the NH of amide **1** would enhance the ROMP activity (Figure 3). On the other hand, if the hydrogen-bond-assisted ROMP was not operative, the copolymer would incorporate only 1 equiv of **2** or the ROMP would be inhibited by the chelation.



2

Figure 3. Model for activity **2** during random copolymerization.

To test this premise, a mixture of 10 equiv of **1** and 20 equiv of **2** was added to catalyst **B** in toluene at 45 °C. After 24 h, complete consumption of **1** and 20% incorporation of **2** was observed by ^{1}H NMR (**a**:**b** = 2.5:1) after purification of the copolymer, implying that on average, the obtained copolymer contained 10 units of **1** and 4 units of **2** (Scheme 1, Table 3, entry 1). When more polar DCM used in the reaction, the obtained copolymer contained 10 units of **1** and 2 units of **2** (Table 3, entry 2). On the other hand, the reaction incoporated only 1 unit of **2** and 10 units of **1** after the ROMP in hydrogen-bonding solvent, THF (Table 3, entry 3). Although the low incorporation of **2** in non-hydrogen-bonding solvents might not appear to be significant, these results further validated the hydrogen-bond-assisted ROMP model, in which the nonactive monomer **2** was incorporated into the copolymer by an amount greater than the stoichiometric amount, whereas only one turnover of **2** occurred as expected in THF.

Scheme 1. Random Ring-Opening Metathesis Polymerization

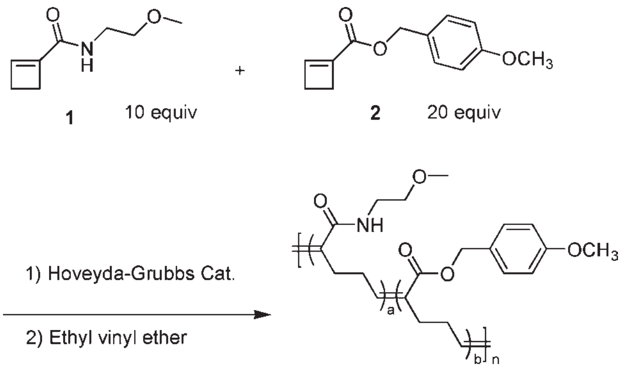


Table 3. Random ROMP Results[a]

entry	solvent	temp (°C)	M_n[b] (g/mol)	PDI[b]	Polymer **a**:**b** ratio[c]
1	toluene	45	3900	1.42	10:4
2	DCM	40	3200	1.60	10:2
3	THF	45	3000	1.61	10:1

[a] Reaction conditions: [M] = 0.2 M, cat. = **B**, 12 h. [b] Determined by chloroform-SEC calibrated by PS standards. [c] Ratio determined by ^{1}H NMR analysis of the copolymers.

In conclusion, we demonstrated the accelerated ROMP of **1** in a nonpolar solvent, toluene. This rate enhancement was explained by the hydrogen-bond-assisted model which was strongly supported by the results of the kinetic studies of the ROMP and the copolymerization experiment. Our findings should expand the scope and utility of the synthesis of regio- and stereoregular polymers.

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Supporting Information Available. Experimental procedures and NMR characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.