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Ring Opening Metathesis Polymerization of Bicyclic α,β-Unsaturated Anhydrides for Ready-to-be-grafted Polymers Having Tailored pH-Responsive Degradability

*Heejin Kim, Sungwhan Kim, Sunyoung Kang, Youngjun Song, Suyong Shin, Seonju Lee, Minji Kang, So Hee Nam, and Yan Lee**

Abstract: Polymers having α,β-unsaturated anhydrides as repeating units were synthesized via ring opening metathesis polymerization (ROMP). The anhydride moieties were ready-to-be-grafted with amines to form acid-labile *cis*-α,β-unsaturated acid amide linkages. The pH-responsive reversible de-grafting can be controlled by changing the intramolecular accessibility between acid and amide groups. The alendronate-grafted ROMP polymers showed distinct pH-dependent cytotoxicity according to the anhydride structures.

Selective and controllable degradation of pH-responsive polymers in various drug delivery systems is required for the specific release of cargo drugs in the gastrointestinal tract, on skin, in cancerous or inflammatory tissues, or in intracellular organelles, which exhibit distinct pH environments.[1] Many pH-responsive degradable bonds, including imine, hydrazone, acetal, orthoester are introduced to polymers to obtain required pH-responsiveness.[2] In some reports, pH-responsive degradability of acetal or imine bonds could be intentionally tailored by changing the adjacent chemical structures.[3] However, cargo conjugation to polymers often requires complex reactions, including protection and deprotection, due to vulnerability of degradable bonds in the conjugation conditions.[4] In addition, it is preferable to avoid the conjugation in aqueous conditions for minimizing hydrolysis of the bonds.[5]

β-carboxylic acid amide having a *cis*-α,β-double bond has a unique pH-responsive degradability. Unlike other amide bonds that can only be hydrolyzed at extreme pH conditions, β-carboxylic acid amide having a *cis*-α,β-double bond, *i.e.,* maleic acid amide derivative, can be hydrolyzed at mild acidic conditions around pH 3-7. Furthermore, because the intramolecular attack of β-carboxylic acid to amide carbonyl group is the main factor for prompting the amide hydrolysis at mild acidic conditions, the degradation kinetics and responding pH condition can be tuned by controlling substituents on the *cis*-α,β-double bond.[6] Additionally, maleic acid amide derivatives can be easily synthesized via a one-step reaction between corresponding anhydrides and amines even in aqueous conditions. Due to such characteristics, maleic acid amide derivatives have been used as one of the key functionalities in smart biomaterials responding to mild pH change.[7]

Despite their attractive characteristics, the strategy for the introduction of maleic acid amide derivative functionalities into polymers is quite limited. In all previous reports, maleic acid amide derivatives and their corresponding anhydrides have been introduced to pre-formed polymeric backbones.[8] There are few reports on polymerization of monomers containing maleic acid amide/anhydride moieties, probably due to reactivity of the double bond or the anhydride of possible monomers in conditions of traditional radical, cationic, anionic, or other step-growth polymerization.[9]

We intended to polymerize monomers possessing maleic acid anhydride-mimic moieties having both *cis*-double bond and anhydride groups (**Figure 1**). As a polymerization method which is free from reactivity issues that are mentioned above, we selected ring-opening metathesis polymerization (ROMP) using Grubbs' catalysts. The catalyst can polymerize electron-rich olefin monomers but limitedly react with electron-deficient α,β-olefins or anhydrides.[10] Moreover, the possible ROMP monomers having the structure of maleic acid anhydride derivative can be readily synthesized via the Diels-Alder reaction.[11] The expected polymers may possess the amine-reactive anhydrides in every repeating unit and be well 'ready-to-be-grafted' with amine-possessing molecules in high density. The densely grafted polymers may release the grafted molecules in pH-dependent manners. Of course, we can tune the pH-responsive release kinetics of the grafted molecules by controlling the angle between *cis*-substituents.[6] After confirmation of our main concept for the synthesis of the ready-to-be-grafted ROMP polymers having tailored pH-responsive degradability, we checked the potential of the polymers for pH-responsive delivery of a model drug, alendronate, *in vitro*.

Common ROMP monomers are mostly based on the structures of four- or five-membered ring and norbornene-like bicycles having considerable strain enthalpy.[12] In order to produce a maleic anhydride-like moiety having a α,β-*cis*-double bond after the ring opening metathesis, there is a need to

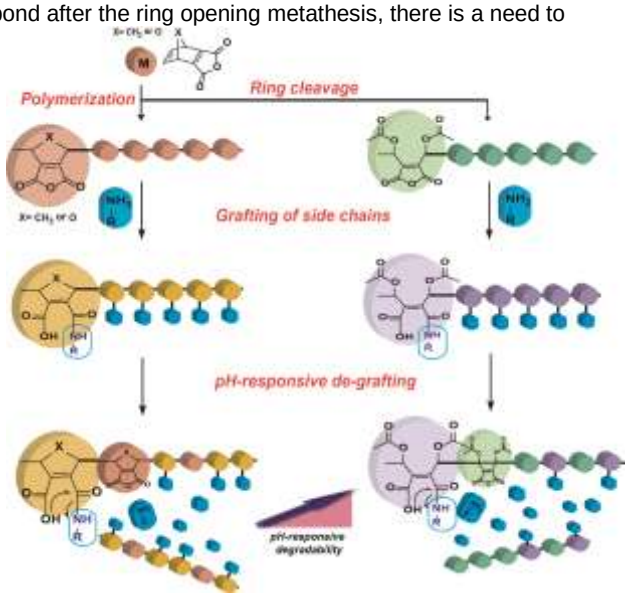

Figure 1. Schematic diagram of synthesis, grafting, and pH-responsive release of ROMP polymers having α,β-unsaturated anhydrides.

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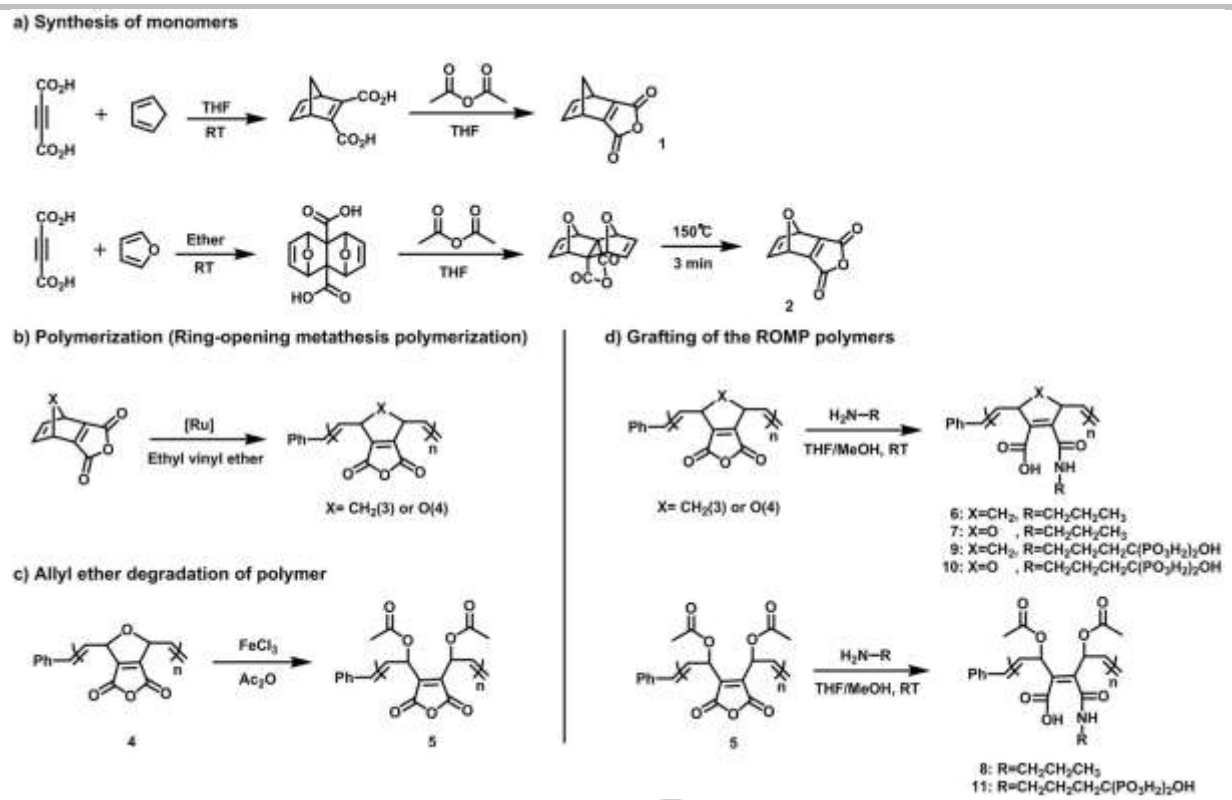

Figure 2. Polymerization and grafting schemes of monomers having α,β-unsaturated anhydrides with different ring structures.

prepare a cyclic monomer possessing two double bonds. One of them is for the metathesis polymerization, while the other is for the α,β-*cis*-double bond. We selected a norbordiene-based structure having a 2,3-dicarboxylic acid anhydride (monomer **1**) because it can be readily synthesized from corresponding cyclodiene and alkyne diacid by Diels-Alder reaction (**Figure 2a**). After the ring opening of **1**, a polymer having cyclopentene 1,2-dicarboxylic anhydride moieties (**3**) can be produced (**Figure 2b**). The polymer **3** can react with amines to produce the grafted polymer **6**, which may release the grafted amines at acidic pH due to the β-carboxylic acid amide moieties (**Figure 1**).

The pH-dependent degradability of maleic acid amide derivatives is highly dependent on the substituents on the α,β-*cis* double bond, which determine the accessibility between the acid and amide groups in the intramolecular cyclization reaction. It was reported that cyclopentene 1,2-acid amide was not readily degraded at mild acidic conditions.[6] On the other hand, a ring-free maleic acid amide showed fast degradation at mild acidic conditions, because the vicinal dialkyl groups can accelerate the cyclization reaction between the acid and amide (Thorpe-Ingold effect) without limitation of freedom in the cyclopentene ring structure.[13] If five-membered ring-free polymers can be obtained by the ring cleavage, the resulted acid amide would be much more labile at mildly acidic pH conditions.

Starting from furan instead of cyclopentadiene, the same Diels-Alder reaction procedure can produce monomer **2** with an oxonorbordiene structure (**Figure 2a**). The dihydrofuran ring in the resulting ROMP polymer **4** could be cleaved by a Lewis acid, such as ferric chloride, because the cyclic ether is a *de facto* allyl ether (**Figure 2c**).[14] The ring-cleaved polymer **5** has a repeating unit similar to dialkyl maleic anhydride. We expected that the amine-grafted polymer **8** can release the side chain at milder pH conditions compared with polymer **6** and **7** that have restricted five-membered ring structures.

The detailed synthetic procedure is described in Supporting Information. Although the corresponding bicyclic mono-ene compound is frequently used in ROMP,[15] the diene compound (**1**) is rarely tried as a ROMP monomer as far as we know.

Table 1. Molecular weight distributions of the ROMP polymers having α,β-unsaturated anhydrides

	Target		Synthesized			
	M_n	DP_n	M_n (NMR / GPC)[a]	M_w (GPC)[a]	PD	DP_n[b]
3	2.43×10^3	15	2.59×10^3 / 2.44×10^3	3.27×10^3	1.34	16
	4.05×10^3	25	3.89×10^3 / 3.71×10^3	5.16×10^3	1.39	24
	8.10×10^3	50	6.81×10^3 / 6.55×10^3	8.32×10^3	1.27	42
4	2.46×10^3	15	2.62×10^3 / 2.54×10^3	3.45×10^3	1.36	16
	4.10×10^3	25	4.27×10^3 / 4.23×10^3	5.80×10^3	1.37	26
	8.20×10^3	50	7.88×10^3 / 7.78×10^3	9.49×10^3	1.22	48
5		15	4.05×10^3 / 2.63×10^3	3.58×10^3	1.36	16
		25	6.64×10^3 / 4.35×10^3	5.92×10^3	1.36	26
		50	1.22×10^4 / 7.91×10^3	9.73×10^3	1.23	48

[a] In GPC, the M_n and M_w (g/mol) were calculated using polystyrene standards.

[b] The *DP* was calculated from NMR data. *DP*s of **3**, **4** and **5** were calculated from the terminal phenyl peak with the -CH_2- peak (**3**) or the –CH- peak (**4**, **5**) of the five-membered ring or olefin.

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Monomer **1** was polymerized with the second-generation Grubbs' catalyst at monomer/initiator ratios ([M]/[I]) of 15, 25 and 50 (**Figure 2b**). The nuclear magnetic resonance (NMR) spectra of polymer **3** are shown in **Figure S6** and **S7**. For the peak characterization, we also synthesized the ring-opened one-mer by treatment of excess catalyst (**Figure S1**). On the basis of the NMR spectra of the one-mer (**12**) (**Figure S2**), we confirmed that polymer **3** was successfully synthesized. The degrees of polymerization (*DP*s) of two shorter polymers (*DP* = 16 and 24) were similar to the targeted values, but that of the long polymer (*DP* = 42) was slightly lower than the targeted value (**Table 1**). Relatively poor solubility of the polymer **3** in the reaction solvent might be one reason causing the low *DP*. The *E*/*Z* ratio of polymer **3** was around 0.5, which is similar to those of ROMP polymers from mono-ene monomers.[16] The Ru-based metathesis catalysts generally showed such *Z*-selectivity in a wide variety of cross-metathesis reactions,[17] although the mechanism has not been fully understood. Gel permeation chromatography (GPC) analysis showed unimodal molecular weight distributions of polymer **3** samples (**Figure S8**). The polydispersity (*PD*) values of the polymer samples with *DP*s of 16, 24, and 42 were 1.34, 1.39 and 1.27, respectively.

For the synthesis of the oxonorbordiene monomer (**2**), furan was reacted with acetylene dicarboxylic acid (**Figure 2a**). After the Diels-Alder reaction followed by flash vacuum pyrolysis,[18] monomer **2** was produced (**Figure S9**). The NMR spectra of polymer **4** (**Figure S10** and **S11**) and the corresponding one-mer (**13**) (**Figure S3**) were compared to support the successful polymerization. GPC analysis showed unimodal molecular weight distribution of polymer **4** (**Figure S12** and **Table 1**).

We intended to cleave the cyclic ether bond in the polymer **4** for delicate control of pH-responsiveness. We treated the one-mer (**13**) with $FeCl_3$ in acetic anhydride as one of the mildest reagents for the cleavage (**Figure S1**).[14] As shown in **Figure S4**, the ether bond of **13** was successfully cleaved to produce **14**, a ring-cleaved product having two acetyl esters. Polymer **4** was then exposed to the same reagent (**Figure 2c**). 65% of the allyl ether bonds were cleaved after 3-h reaction at room temperature. No more cleavage was observed even after further incubation (**Figure S13** and **S14**). The GPC result supported that the ROMP polymeric backbone was not degraded in the condition of the allyl ether cleavage (**Figure S15** and **Table 1**).

Polymer **3**, **4**, and **5** contain α,β-unsaturated anhydride moieties that are able to react with primary or secondary amine molecules in basic conditions. Each polymer was stirred at room temperature in the presence of *n*-propylamine to produce the grafted polymer (**Figure 2d**). The formation of β-carboxylic acid amide could be confirmed by the ^{1}H-NMR spectra of **6**, **7**, and **8** which show characteristic amide and acid peaks at 8.6 and 9.8 ppm, respectively (**Figure S16).** 79% (**6**), 78% (**7**) and 88% (**8**) of anhydride moieties were reacted to form the acid amide linkages by only simple mixing in basic conditions. The polymeric backbone was maintained during the grafting reaction, as shown in the GPC chromatograms (**Figure S17**).

The pH-responsive degradation of the β-carboxylic acid amide linkages were quantified using fluorescamine.[19] The release kinetics of *n*-propylamine from polymer **6**, **7**, and **8** at different pH conditions are shown in **Figure 3**. All three polymers showed negligible degradation at pH 7.4, indicating the stability of the acid amide linkages. On the other hand, incubation at pH 3.0 clearly accelerated the amide hydrolysis in all polymers. At pH 3.0, polymer **6** and **7** showed 60% degradation after 8 h, whereas polymer **8** reached the point of 60% degradation within 4 h. The differences were more dramatic at pH 5.5 and pH 6.5.

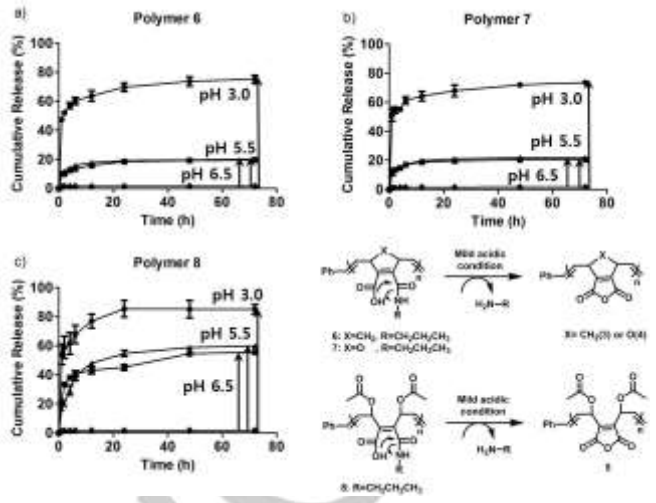


Figure 3. Degradation kinetics of the acid amide side chain in the *n*-propylamine-grafted ROMP polymers at pH 3.0 (●), 5.5 (▲), 6.5 (■) and 7.4 (♦). *DP*s of polymer **6**, **7**, and **8** were 42, 48, and 48, respectively. Error bar means the standard deviation (n=3).

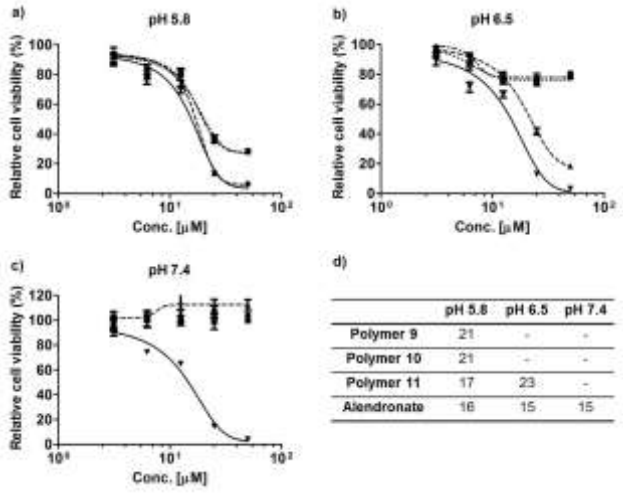
Both polymer **6** and **7** degraded only slowly and hardly reached the point of 10-20% degradation even after 72 h at the mildly acidic conditions. Polymer **8,** however, degraded much faster to show approximately 40% within 8 h. The degradation rates of polymers were not so much changed in the pH range of 5.5-6.5.

As we predicted previously, the five-membered ring cleavage can clearly facilitate the degradation of *cis*-α,β-unsaturated acid amide linkages between the grafted side chain and the backbone of the ROMP polymer. The bond angles in C=C-C(ONH) and (HOO)C-C=C were estimated to be around 132-134° and 131-134° for the five-membered ring monomeric unit in polymer **6** and **7**, which were 119° and 123° for the ring-cleaved monomeric unit in polymer **8** by density functional theory (DFT) calculation (**Figure S22**). The significant decrease of both angles between the amide and the carboxylic acid may cause the elevation of effective concentrations of two reactive groups for the intramolecular cyclization for the pH-responsive degradation of the acid amide linkage. The intramolecular cyclization-based degradation of the acid amid linkage was further confirmed by the regenerated structure of polymer **3**, **4**, and **5** after the release of *n*-propylamine from polymer **6**, **7**, and **8** (**Figure S23**). The cyclization-induced degradation in each monomeric unit was probably one reason for the result that the degradation kinetics was not so much dependent upon *DP*s of the polymers, as shown in **Figure S20**.

In order to show the possible applicability of the ready-to-be-grafted ROMP polymers, we checked cytotoxicity of alendronate released from the polymers in pH-dependent manners. Alendronate is a bisphosphonate possessing a primary amine (**Figure 2d**). It is well-known for the inhibitory effect on osteoclasts, but also exerts toxic effects on cancer cells.[20] Because both osteoporotic and cancerous tissues are characterized as acidic environments, we thought that pH-responsive release of alendronate in the target tissues might be beneficial to reduce possible side effects of alendronate in other tissues (*e.g.* abdominal pain, arthralgia, and osteonecrosis of the jaw).[21] Following the same procedure for the *n*-propylamine grafting, simple mixing of alendronate and ROMP polymers (**6**, **7**, and **8**) in basic conditions produced the alendronate-grafted polymers (**9**, **10**, and **11**). The grafting degrees of alendronate were calculated as 81% (**9**), 83% (**10**) and 83% (**11**),

respectively (**Figure S18**). The polymeric backbone was also maintained during the alendronate grafting as shown in the GPC chromatograms (**Figure S19 and Table S1**).

The pH-dependent cytotoxicity of the alendronate-grafted polymers was compared on *MDA-MB-231* cells (human breast cancer cells). After incubation for 24 h, free alendronate exhibits similar half maximal inhibitory concentration (IC_{50}) values around 15 μM irrespective of pH conditions. However, the cytotoxicity of the alendronate-grafted polymers was highly dependent upon the incubation conditions. At pH 7.4, all three polymers exhibited negligible toxicity up to 50 μM on the cancer cells (**Figure 4c**). However, at pH 6.5, polymer **11** showed only 40% viability at 25 μM, whereas polymer **9** and **10** still showed almost no toxicity in the experimental concentration range (**Figure 4b**). On the other hand, at pH 5.8, all three polymers showed evident toxicity. Among them, polymer **11** showed the highest toxicity similar to free alendronate (**Figure 4a**). The comparison of IC_{50} values clearly showed the induction of toxicity at acidic pH on the cells treated with the alendronate-grafted polymers (**Figure 4d**). Polymer **11** has faster degradability at mildly acidic pH conditions than polymer **9** and **10** (**Figure S21**), while non-grafted polymer **3**, **4**, and **5** showed no toxicity on the cells in the concentration range of the treatment (**Figure S24**). In addition, polymer **11** gave the toxic effect on the cells rather slowly than free alendronate at pH 5.8 (**Figure S25**). Therefore, we inferred that the cytotoxicity of the alendronate-grafted polymers was originated from alendronate released from the polymers in pH-dependent manners. Although further investigation should be required for practical biomedical applications, it was clearly shown that pH-responsive release and efficacy of amine-containing drugs can be delicately controlled by the structure of the *cis*-α,β-unsaturated acid amides in the ROMP polymers.



	pH 5.8	pH 6.5	pH 7.4
Polymer 9	21	-	-
Polymer 10	21	-	-
Polymer 11	17	23	-
Alendronate	16	15	15

Figure 4. Relative viability of *MDA-MB-231* cells treated by the alendronate-grafted ROMP polymers (polymer **9**; ● (dot and dashed), polymer **10**; ■ (short dashed), polymer **11**; ▲ (long dashed)) and free alendronate (▼; line) at pH 5.8 (a), 6.5 (b) and 7.4 (c). Error bar means the standard deviation (*n*=5). (d) IC_{50} values [μM] of the alendronate-grafted ROMP polymers and free alendronate on *MDA-MB-231* cells at each pH condition. The polymer concentration indicated corresponding alendronate grafted on the polymer. *DP*s of polymer **9**, **10**, and **11** were 42, 48, and 48, respectively.

In summary, ROMP polymers having α,β-unsaturated anhydrides were prepared for both efficient grafting and pH-responsive release of side chain molecules. The *cis*-α,β-unsaturated anhydride moieties were ready-to-be-grafted with amine-containing molecules to form acid-labile β-carboxylic acid amide linkages in high density. The ring structure in the ROMP polymer can be cleaved for modulation of pH-responsive degradation of the linkages. The grafted ROMP polymers with different accessibility between acid and amide groups showed distinct kinetics of pH-responsive degradation, especially in mildly acidic conditions at pH 5-6. The ROMP polymers having α,β-unsaturated anhydrides can provide a useful platform for smart materials in the biomedical field where tunable pH-responsiveness is needed in biologically tolerable conditions.

Acknowledgements

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Keywords: ROMP • pH-degradability• bicyclic α,β-unsaturated anhydride • *cis*-α,β-unsaturated acid amide • reversible grafting and release

[1] a) A. E. Felber, M.-H. Dufresne, J.-C. Leroux, *Adv. Drug Deliv. Rev.* **2012**, *64*, 979-992; b) W. Gao, J. M. Chan, O. C. Farokhzad, *Mol. Pharm.* **2010**, *7*, 1913-1920.

[2] a) Y. C. Tao, S. W. Liu, Y. Zhang, Z. G. Chi, J. R. Xu, *Polym. Chem.* **2018**, *9*, 878-884; b) W. N. Wu, H. Wu, Y. Wang, X. J. Mao, B. Z. Liu, X. L. Zhao, Z. Q. Xu, Y. C. Fan, Z. H. Xu, *RSC Adv.* **2018**, *8*, 5640-5646; c) H. L. Cao, C. Chen, D. B. Xie, X. Chen, P. Wang, Y. B. Wang, H. J. Song, W. X. Wang, *Polym. Chem.* **2018**, *9*, 169-177; d) L. Y. Li, Y. Xu, I. Milligan, L. Y. Fu, E. A. Franckowiak, W. J. Du, *Angew. Chem. Int. Edit.* **2013**, *52*, 13699-13702.

[3] a) Y. C. Tao, S. W. Liu, Y. Zhang, Z. G. Chi, J. R. Xu, *Polym. Chem-Uk* **2018**, *9*, 878-884; b) J. Mao, Y. Li, T. Wu, C. H. Yuan, B. R. Zeng, Y. T. Xu, L. Z. Dai, *ACS Appl. Mater. Inter.* **2016**, *8*, 17109-17117; c) H. L. Cao, C. Chen, D. B. Xie, X. Chen, P. Wang, Y. B. Wang, H. J. Song, W. X. Wang, *Polym. Chem-Uk* **2018**, *9*, 169-177; d) S. J. Sonawane, R. S. Kalhapure, T. Govender, *Eur. J. Pharm. Sci.* **2017**, *99*, 45-65.

[4] D. Polyak, A. Eldar-Boock, H. Baabur-Cohen, R. Satchi-Fainaro, *Polym. Adv. Technol.* **2013**, *24*, 777-790.

[5] J. J. Liu, Y. Zhang, J. L. Yan, M. D. Lang, *J. Mater. Chem.* **2011**, *21*, 6677-6682.

[6] a) A. J. Kirby, P. W. Lancaster, *J. Chem. Soc. Perk. T. 2* **1972**, 1206-1214; b) M. F. Aldersley, A. J. Kirby, P. W. Lancaster, R. S. Mcdonald, C. R. Smith, *J. Chem. Soc. Perk. T. 2* **1974**, 1487-1495; c) A. J. Kirby, R. S. Mcdonald, C. R. Smith, *J. Chem. Soc. Perk. T. 2* **1974**, 1495-1504

[7] a) H. J. Kim, A. Kim, K. Miyata, K. Kataoka, *Adv. Drug Deliver. Rev.* **2016**, *104*, 61-77; b) T. Suma, J. W. Cui, M. Mullner, Y. Ju, J. L. Guo, M. Hu, F. Caruso, *ACS Macro. Lett.* **2015**, *4*, 160-164; c) V. Aina, C. Magistris, G. Cerrato, G. Martra, G. Viscardi, G. Lusvardi, G. Malavasi, L. Menabue, *Langmuir* **2014**, *30*, 4703-4715; d) T. Loth, R. Hennig, C. Kascholke, R. Hotzel, M. C. Hacker, *React. Funct. Polym.* **2013**, *73*, 1480-1492; e) S. M. Henry, M. E. H. El-Sayed, C. M. Pirie, A. S. Hoffman, P. S. Stayton, *Biomacromolecules* **2006**, *7*, 2407-2414; f) R. Tahvilian, B. Tajani, K. Sadrjavadi, A. Fattahi, *Int. J. Biol. Macromol.* **2016**, *92*, 795-802

[8] a) D. B. Rozema, D. L. Lewis, D. H. Wakefield, S. C. Wong, J. J. Klein, P. L. Roesch, S. L. Bertin, T. W. Reppen, Q. Chu, A. V. Blokhin, J. E. Hagstrom, J. A. Wolff, *Proc. Natl. Acad. Sci. USA*

10.1002/anie.201806763

2007, *104*, 12982-12987; b) O. Coulembier, P. Degee, J. L. Hedrick, P. Dubois, *Prog. Polym. Sci.* **2006**, *31*, 723-747; c) M. J. Han, K. B. Choi, K. H. Kim, B. S. Hahn, W. Y. Lee, *Makromol. Chem., Macromol. Symp. Ser.* **1990**, *33*, 301-309.
[9] N. Bicak, B. Karagoz, U. Tunca, *J. Polym. Sci. Pol. Chem.* **2003**, *41*, 2549-2555
[10] S. Kanaoka, R. H. Grubbs, *Macromolecules* **1995**, *28*, 4707-4713; J. Louie, R. H. Grubbs, *Organometallics* **2002**, *21*, 2153-2164.
[11] Y. W. Goh, S. M. Danczak, T. K. Lim, J. M. White, *J. Org. Chem.* **2007**, *72*, 2929-2935.
[12] a) C. W. Bielawski, R. H. Grubbs, *Angew. Chem. Int. Edit.* **2000**, *39*, 2903-2906; b) A. Hejl, O. A. Scherman, R. H. Grubbs, *Macromolecules* **2005**, *38*, 7214-7218.
[13] M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735-1766.
[14] a) B. Ganem, V. R. Small, *J. Org. Chem.* **1974**, *39*, 3728-3730; b) J. I. Padron, J. T. Vazquez, *Tetrahedron: Asymmetry* **1995**, *6*, 857-858.
[15] a) C. M. Dettmer, M. K. Gray, J. M. Torkelson, S. T. Nguyen, *Macromolecules* **2004**, *37*, 5504-5512; b) W. J. Feast, V. C. Gibson, A. F. Johnson, E. Khosravi, M. A. Mohsin, *Polymer* **1994**, *35*, 3542-3548; c) D. A. Haigh, A. M. Kenwright, E. Khosravi, *Macromolecules* **2005**, *38*, 7571-7579.
[16] B. K. Keitz, A. Fedorov, R. H. Grubbs, *J. Am. Chem. Soc.* **2012**, *134*, 2040-2043.
[17] P. K. Dornan, Z. K. Wickens, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2015**, *54*, 7134-7138.
[18] D. Margetic, R. N. Warrener, G. X. Sun, D. N. Butlert, *Tetrahedron* **2007**, *63*, 4338-4346.
[19] a) J. V. Castell, M. Cervera, R. Marco, *Anal. Biochem.* **1979**, *99*, 379-391; b) S. De Bernardo, M. Weigele, V. Toome, K. Manhart, W. Leimgruber, P. Bohlen, S. Stein, S. Udenfriend, *Arch. Biochem. Biophys.* **1974**, *163*, 390-399.
[20] a) J. E. Fisher, M. J. Rogers, J. M. Halasy, S. P. Luckman, D. E. Hughes, P. J. Masarachia, G. Wesolowski, R. G. G. Russell, G. A. Rodan, A. A. Reszka, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 133-138; b) R. J. Milner, J. Farese, C. J. Henry, K. Selling, T. M. Fan, L. P. de Lorimier, *J. Vet. Intern. Med.* **2004**, *18*, 597-604.
[21] K. A. Kennel, M. T. Drake, *Mayo. Clin. Proc.* **2009**, *84*, 632-638.

10.1002/anie.201806763

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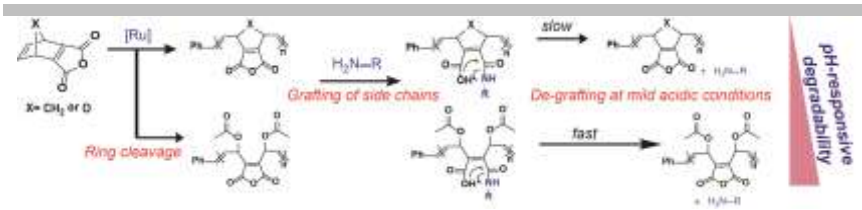

We have synthesized ROMP polymers having α,β-unsaturated anhydrides for high-density grafting and pH-responsive release of amine side chains via acid-labile β-carboxylic acid amide linkages. The pH-responsive degradability of the linkages can be tuned by the modulation of the ring structure for the de-grafting of the side chains in suitable pH conditions.

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Ring Opening Metathesis Polymerization of Bicyclic α,β-Unsaturated Anhydrides for Ready-to-be-grafted Polymers Having Tailored pH-Responsive Degradability