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Synthesis and Hydrolysis Behavior of Side-Chain Functionalized Norbornenes

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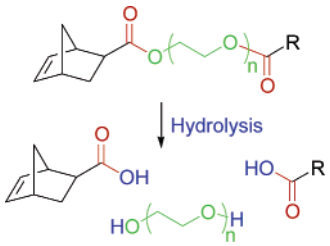

The stabilities of various functionalized norbornenes that are monomers for the ring-opening metathesis polymerization (ROMP) in aqueous solution were evaluated toward hydrolysis under a range of temperatures (37, 60, and 80 °C) and pH values (3−9). All monomers contain hydrolyzable linkages to pendant functional groups, and conclusions were drawn relating to how the chemical diversity of these pendant functional groups, in accordance with the pH and temperature variations, affect hydrolysis of the aforementioned linkages. The hydrolysis was monitored by reverse phase HPLC analysis, and/or NMR spectroscopy. As expected, monomers containing ester linkages were fairly labile at higher pH values, while acetal-based linkers were cleaved at lower pH values. β-Amino ester groups experienced a significant increase in hydrolysis rate, while carboxylic acid-containing monomers did not follow any clear trend. Saccharide-containing monomers exhibited unique behaviors for various pH values and temperature ranges.

Introduction

Norbornene has been used extensively as a monomer for ring-opening metathesis polymerization (ROMP) across a broad spectrum of applications,[1] in fields as diverse as drug delivery[2] and biochemical applications,[3] luminescent materials and devices,[4] liquid crystalline[5] and nonlinear optical materials,[6] and polymer-supported catalysis.[7] ROMP is a highly efficient method of polymerization,

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both in organic and aqueous media, the latter being a convenient route toward a number of biologically relevant materials.[3] For example, poly(norbornene) homo- and copolymers substituted with oligopeptides have been used to study competitive inhibition of fibroblast cell adhesion.[3d] In another example, Kiessling and co-workers have used ROMP for the synthesis of neoglycopolymers to study cellular binding with L-selectin, a surface protein.[3b]

It is well-known that polymer degradation is the major cause for change or loss of materials properties in many poly(norbornene)-based materials.[8] A primary mode of degradation of poly(norbornene)s in biological applications might be the hydrolysis of water-labile moieties within the polymer. In most norbornene monomer designs a linkage between the polymerizable group and the functional moiety is introduced.[9] The choice of linker is crucial since it will influence and partially determine the conditions under which hydrolysis occurs. In the vast majority of cases these linkages are carboxylic esters, with other functionalities such as ethers, pure alkyl chains, amides, etc. being the exception.[1] Esters are known to be sensitive to hydrolysis under both acidic and basic conditions, and depending upon the structure can hydrolyze in minutes (esters that give strong acids and stable anions) or be stable for years (hydrophobic esters of weak acids).[10] Another important functional group in biomaterials containing biological moieties such as saccharides is the acetal. In contrast to esters, acetals can be cleaved rapidly in strongly acidic aqueous media and are stable to basic conditions. Additionally, the structure of a neighboring functional group greatly influences the hydrolysis rate through steric and hydrophobic interactions but also by the stability of the charged intermediates.[11]

A detailed study of the hydrolytic stability of functionally diverse norbornene monomers is of utmost importance to be able to predict and tailor important polymer properties in aqueous solution and to relate polymer performance to function. Despite the extensive use of functionalized poly(norbornene)s in biomaterials, no study has been carried out to gain a deeper understanding of the hydrolysis behavior of these materials. This report provides a study of the hydrolysis behavior of various norbornene-based monomers, with a variety of linker choices and pendant functional groups, each one being subject to a range of pH values and temperatures.

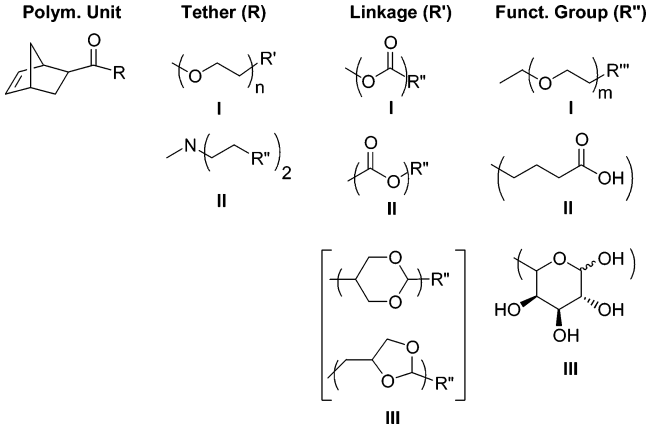

FIGURE 1. Structures corresponding with combinations in Table 1.

TABLE 1. Building Blocks 1 and 2, along with Monomers 3−9, for Which the Hydrolysis Behavior Was Investigated in This Study[a]

	tether (R)			linkage (R′)		functional group (R″)		
compd no.	type	*n*	R′	type	R″	type	*m*	R‴
1	I	3	OH					
2	I	2	Cl					
3	I	3	OCH_3					
4, **5**	I	2	R′	III	R″	I	2	OCH_3
6	I	3	R′	I	R″	I	2	OCH_3
7	I	3	R′	I	R″	II		
8	I	3	R′	I	R″	III		
9	II	1	R′	II	R″	I	3	OCH_3

[a] The compound number on the left corresponds with a specific combination of tethers to norbornene, hydrolyzable linkages, and functional groups, which are depicted in Figure 1.

Design Strategy

To gain a better understanding of the hydrolysis behavior of norbornene monomers in aqueous media, where hydrolysis may have the most significant influence on polymer performance and properties, linkers and functional moieties had to be chosen that were both water soluble and hydrolyzable. All monomers studied herein contain a norbornene as the polymerizable unit. Spacer molecules, such as ethylene glycols and pure alkyl chains, are attached to the norbornene via carboxylic ester linkages. Finally, several functional groups are introduced at the end of the spacer molecules. Figure 1 and Table 1 outline the general monomer design and describe the library of monomers that were studied. Two common functionalities within the linkers were examined: esters and acetals. The terminal functional groups that have been employed in our design include saccharides, acids, esters, and amines. Galactose was chosen as the saccharide functional group because it has been shown by Kiessling and co-workers that 7-oxonorbornene polymers with pendant galactoses are very potent binding agents to cellular recognition sites.[12] The use of these oligo- or polysaccharides to deliver drugs to specific sites at cellular surfaces, or to the cellular interior via endosomal transport is advantageous, provided that the drug can

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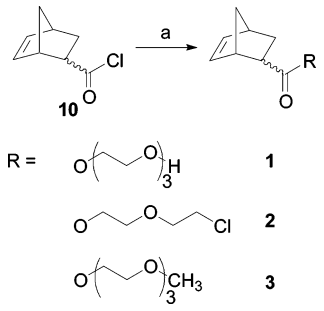
SCHEME 1. Synthesis of Norbornene Spacer Molecules 1, 2, and 3[a]



[a] Reagents: (a) For **1**: triethylene glycol (excess), THF, triethylamine; For **2**: chloroethoxyethanol, triethylamine, THF; For **3**: triethylene glycol monomethyl ether, triethylamine, THF.

be cleaved efficiently from the polymer backbone. Other pendant functional groups employed in this study are carboxylic acids, ethers, and tertiary amines. These side-chain models represent a wide range of functional groups and interactions and will allow for insights into the effect of functional groups on the hydrolysis behavior of functionalized norbornenes.

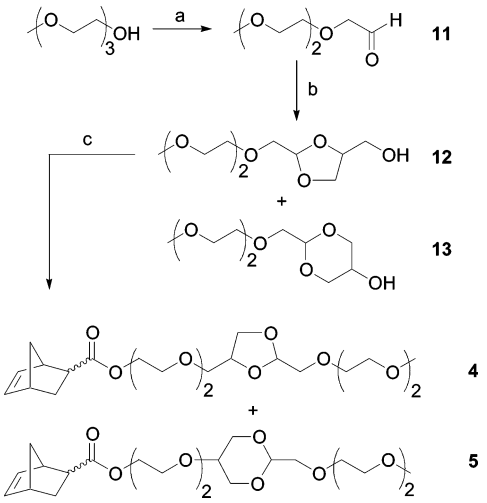
Results and Discussion

A. Synthesis: Norbornene PEG Esters 1−3. Synthesis of norbornene derivatives **1**−**3**, norbornene triethylene glycol ester derivatives, was accomplished by treatment of the norbornene acyl chloride **10**[13] with triethylene glycol, 2-(2-chloroethyoxy)ethanol, and triethylene glycol methyl ether, respectively (Scheme 1), giving yields in excess of 70%. The synthesis of compounds **1**−**3** resulted in mixtures of endo/exo isomers in approximately 4:1 ratios.

PEG-Based Norbornenes Containing Acetals in Their Side-Chains: Monomers 4 and 5. Oxidation of triethylene glycol monomethyl ether under Swern conditions resulted in the formation of aldehyde **11** in 44% yield.[14] Treatment of **11** with glycerol and *p*-toluenesulfonic acid in toluene gave a 1:1 mixture of **12** and **13** in 89% yield. The formation of the five-membered-ring adduct **12** is kinetically favored, while the six-membered-ring adduct **13** is the thermodynamic product. Each of the isomers exists as a diastereomeric pair and four sets of triplets for the acetal proton are evident in the ^{1}H NMR spectrum of the mixture. Purification of the products, either by distillation or column chromatography, did not allow for isolation of the two compounds and in all cases mixtures are obtained. Coupling of **12** and **13** to compound **2** under basic conditions resulted in the formation of acetals **4** and **5** in 64% yield as mixtures of five- and six-membered adducts and endo/exo isomers (Scheme 2).

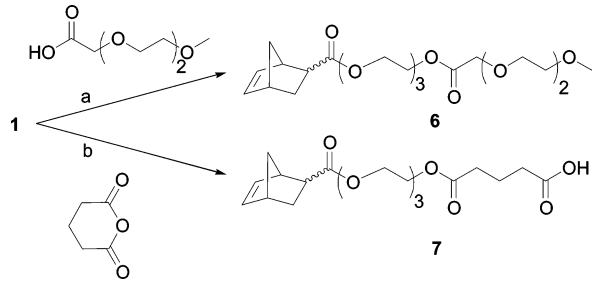
Norbornene Monomers Containing PEG-Ester and Acid-Ester in Their Side-Chains: Monomers 6 and 7. The esterfication of **1** with 2-[2-(2-methoxyethoxy)-ethoxy]acetic acid was carried out at ambient temperatures with DCC/DMAP in CH_2Cl_2 to give the PEG-ester monomer **6** in 52% yield. Compound **7** was synthesized by the reaction of **1** with glutaric anhydride in 82% yield (Scheme 3).

SCHEME 2. Synthesis of PEG-Acetal Monomers 4 and 5[a]



[a] Reagents: (a) oxalyl chloride, DMSO, triethylamine; (b) glycerol, *p*-TsOH, toluene; (c) NaH, **2**, THF.

SCHEME 3. Synthesis of Compounds 6 and 7[a]



[a] Reagents: (a) DCC, DMAP, CH_2Cl_2; (b) pyridine, THF.

Norbornene Linked to Galactose via Triethylene Glycol Ester: Monomer 8. The synthesis of **8** started with the oxidation of 1,2:3,4-di-*O*-isopropylidene galactopyranose, using Jones conditions to give **14** in 81% yield.[15] Coupling of **14** to **1** with use of DCC/DMAP gave the acetal protected saccharide ester **15** in 60% yield. Removal of the acetal protecting groups to give the free tetra-ol **8** (Scheme 4) was achieved by treatment of **15** with 80% TFA (aq). Conversion after 1 h was 100% by NMR analysis but isolation and purification of the product resulted in lower yields (84%).

Synthesis of Monomer 9. Synthesis of **9** required the triethylene glycol monomethyl ether monoacrylate **16**, which was synthesized from the condensation of triethylene glycol monomethyl ether and acryloyl chloride in 84% yield. Addition of 2 equiv of **16** to ethanolamine at room temperature gave the bis-Michael addition product **17** in nearly quantitative yield (97%) after 24 h. Coupling of **17** to **10** in THF with triethylamine at ambient temperature gave product **9** in 64% yield after chromatography (Scheme 5).

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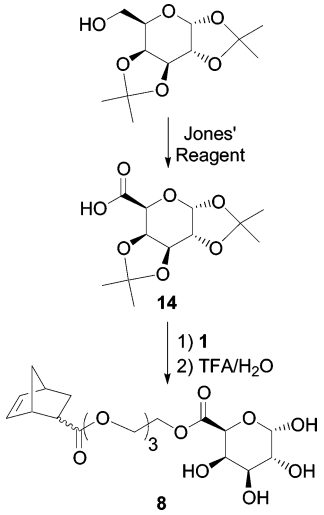
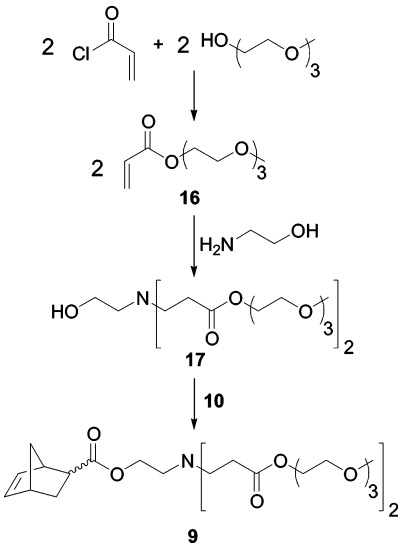
SCHEME 4. Synthesis of Compound 8



SCHEME 5. Synthesis of Compound 9



B. Hydrolysis. To investigate the effect of pH on the hydrolysis of compounds **3**–**9**, measurements were carried out in the range of pH 3.1 to 8.9. A phosphate/citric acid buffer was used for pH 3.1, acetate buffers were employed for pH 4.6 and 5.6, phosphate buffers for pH 6.9 and 7.4, and borate buffer for pH 8.9. All buffers were made to 0.1 M ionic strength, with the exception of pH 7.4, which was an isotonic phosphate buffered saline solution. Solutions of 5 mM analyte were employed to give conditions that would result in pseudo-first-order kinetics. Temperatures of 80, 60, and 37 °C were investigated to study the influence of temperature on the hydrolysis rate. The hydrolysis rates were measured by HPLC analysis, using refractive index and/or UV detection and/or proton NMR.

Hydrolysis of 4 and 5. The hydrolyses of monomers **4** and **5** were achieved under the same conditions as outlined above for **6** (Figures 2–4 and Table 2). However, the formation of aldehyde was not detected, and the expected aldehyde product was not retained under the analysis conditions. Therefore, HPLC analyses were carried out by measuring the consumption of starting material. However, to verify this method and to quantify

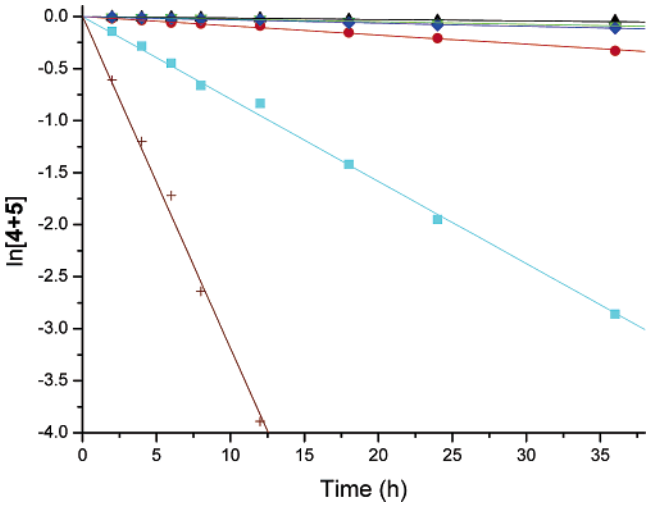


FIGURE 2. Pseudo-first-order hydrolysis kinetics for compounds **4** and **5** at 37 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.6; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

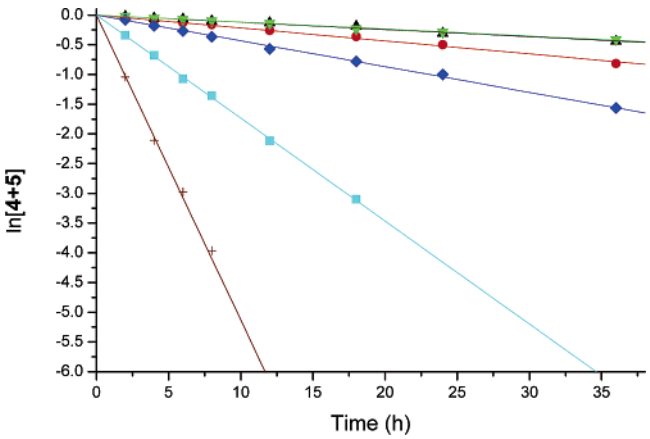


FIGURE 3. Pseudo-first-order hydrolysis kinetics for compounds **4** and **5** at 60 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.6; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

the amount of aldehyde produced in the hydrolysis reactions, a general method of aldehyde derivatization was used: sample aliquots were treated with 2,4-dinitrophenyl hydrazine to form the corresponding DNP hydrazone, and the resulting sample was analyzed by UV detection at 365 nm. At high pH, no detectable aldehyde was produced, suggesting that the ester at the 2-position of the norbornene unit is undergoing hydrolysis. The amount of aldehyde produced at pH 3.1 does not correlate with the extent of hydrolysis measured by the disappearance of starting material, suggesting that an additional decomposition product may be forming upon cleavage of the acetal. Within the range of error, we are not able to elucidate which hydrolysis mechanism is predominating at low temperatures. At 37 °C, no significant hydrolysis was detected from pH 4.6 to 7.4. Hydrolysis occurred at the low and high pH values of 3.1 and 8.9. The calculated half-life at pH 3.1 and 37 °C was 8.8 h, compared to 2.2 h at pH 8.9 and 37 °C.

The acetal moiety is well-known for its rapid hydrolysis at low pH values, as well as its relative stability in alkaline media. This common characteristic of acetals matches well with our hydrolysis data for compounds **4**

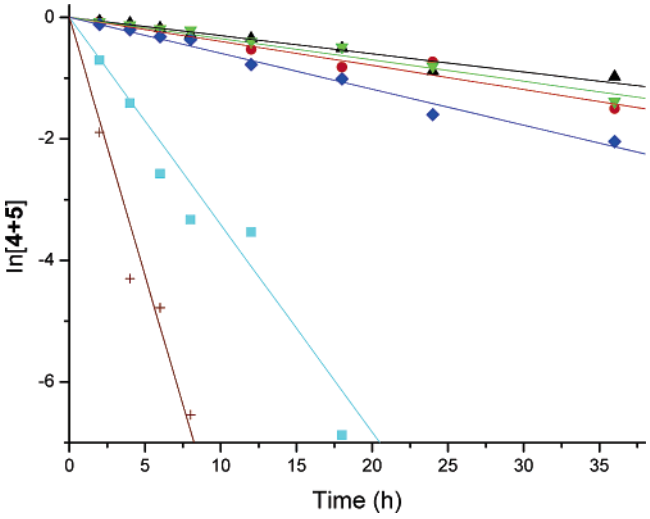


FIGURE 4. Pseudo-first-order hydrolysis kinetics for compounds **4** and **5** at 80 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.6; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

TABLE 2. Hydrolysis Data for a Mixture of Compounds 4 and 5

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
	compounds **4** and **5**, 80 °C		
3.1	0.341	0.988	2.0
4.6	0.040	0.977	17
5.7	0.030	0.975	23
6.9	0.035	0.976	20
7.4	0.059	0.982	12
8.9	0.850	0.943	0.82
	compounds **4** and **5**, 60 °C		
3.1	0.215	0.991	3.2
4.6	0.022	0.995	32
5.7	0.012	0.992	58
6.9	0.012	0.996	58
7.4	0.043	0.996	16
8.9	0.513	0.996	1.4
	compounds **4** and **5**, 37 °C		
3.1	0.079	0.996	8.8
4.6	0.0089	0.994	78
5.7	0.0013	0.942	530
6.9	0.0024	0.996	290
7.4	0.0031	0.988	220
8.9	0.319	0.994	2.2

and **5**, at all temperature ranges (Figures 2−4), where at low pH, rapid acetal hydrolysis is observed. The monomer was substantially more stable in both weakly acidic and neutral aqueous solutions, but showed rapid decomposition at pH 8.9. In terms of the acetal group, this effect cannot be explained. To investigate if the hydrolysis occurs at the ester linkage to the norbornene instead of at the acetal for this set of circumstances, we synthesized monomer **3**, a monomer with a triethylene glycol monomethyl ether directly linked to the norbornene polymerizable unit via an ester. This monomer models the ester linkage of **4** and **5** without any further hydrolyzable moieties. The hydrolysis behavior of this monomer at 60 and 80 °C correlated closely with the unexpected hydrolysis data observed for **4** and **5** at pH values of 8.9, giving a plausible explanation: cleavage of the base-labile norbornene ester bond is occurring at this slightly basic pH value. In **3** the pH value of 8.9 is the only set of conditions where hydrolysis is achieved

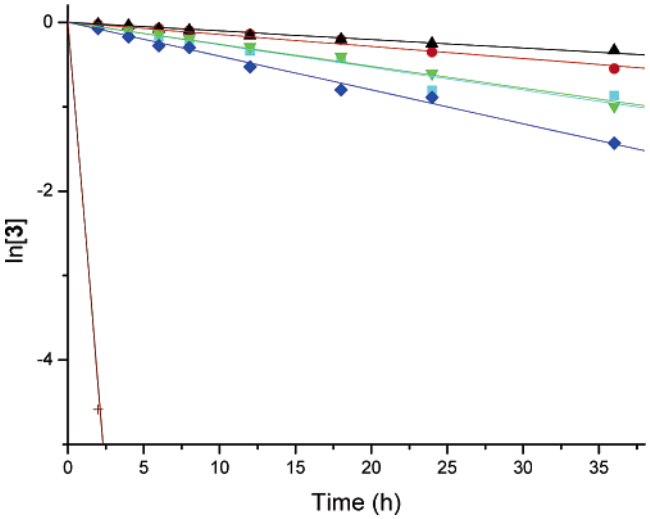


FIGURE 5. Pseudo-first-order hydrolysis kinetics for compound **3** at 80 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

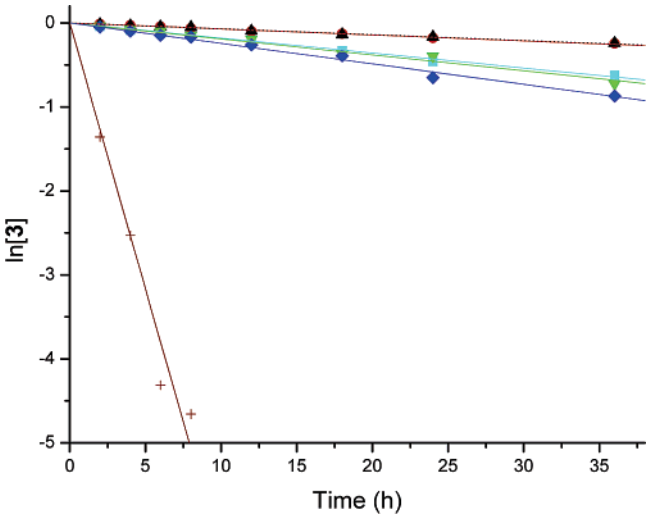


FIGURE 6. Pseudo-first-order hydrolysis kinetics for compound **3** at 60 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

TABLE 3. Hydrolysis Data for Compound 3

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
	compound **3**, 80 °C		
3.1	0.027	0.943	27
4.6	0.014	0.980	50
5.7	0.010	0.976	70
6.9	0.026	0.990	27
7.4	0.040	0.990	17
8.9	2.15	0.996	0.32
	compound **3**, 60 °C		
3.1	0.018	0.994	39
4.6	0.0071	0.992	98
5.7	0.0069	0.992	100
6.9	0.019	0.982	36
7.4	0.024	0.986	29
8.9	0.632	0.946	1.1

fairly rapidly, due to the base sensitivity of the ester (Figures 5 and 6 and Table 3). This suggests that the same hydrolytic cleavage of the ester may be occurring for **4** and **5**. At low pH, cleavage of the acetal is the

TABLE 4. Hydrolysis Data for Compound 6

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
	compound **6**, 80 °C		
4.6	0.044 ± 0.002	0.989	15.8
5.7	0.034 ± 0.001	0.994	20.7
6.9	0.311 ± 0.014	0.994	2.2
7.4	0.443 ± 0.048	0.976	1.6
	compound **6**, 60 °C		
3.1	0.050 ± 0.004	0.940	13.7
4.6	0.032 ± 0.001	0.995	21.9
5.7	0.017 ± 0.001	0.964	41.9
6.9	0.099 ± 0.007	0.950	6.9
7.4	0.121 ± 0.011	0.970	5.7
	compound **6**, 37 °C		
3.1	0.006 ± 0.004		≈100
4.6	0.002 ± 0.001	0.933	450
5.7	0.006 ± 0.003		≈100
6.9	0.017 ± 0.004	0.951	40
7.4	0.042 ± 0.006	0.895	17

dominant decomposition pathway, while at high pH, ester hydrolysis predominates.

Hydrolysis of 6. The dependence of the hydrolysis of **6** on pH and temperature is shown in Figures 7−9 and Table 4. At 80 °C, hydrolysis of **6** at pH 8.9 was rapid, with a 45% to 50% loss in 2 h. Under acidic conditions, the rate of hydrolysis is consistent with the expected trend of the rate being inversely proportional to pH. At near neutral or basic pH values, the rates of hydrolysis are greatly enhanced when compared to data collected at low pH conditions (Figure 7). Complete loss of **6** was seen within 18 h near pH 7 and 80 °C. This does not correlate with the accepted mechanisms of ester hydrolysis under either acidic or basic conditions, which depend on an increase in electrophilicity of the carbonyl by protonation under acidic conditions, or by the relatively high nucleophilic character of hydroxide compared to water, under basic conditions. The rate would be dependent upon the nucleophilic character of water, which should produce exceedingly slow reactions. The accelerated rates near pH 7 suggest that the buffer identity might play a significant role in the hydrolysis mechanism at this pH. The same trends were observed for the hydrolysis at 60 °C (Figure 8) and at 37 °C (Figure 9). The pseudo-first-order half-lives range from 6 to 20 h.

Hydrolysis of 7. By investigating the hydrolysis behavior of compound **7**, we observed virtually no hydrolysis at 37 °C (half-lives of >200 h for all pH values) (Figure 10), first-order kinetics at 60 °C (Figure 11), and finally, great deviations from first-order kinetics at 80 °C (Figure 12), which are not accompanied by a substantial rate increase. It is evident that this behavior does not follow a clear hydrolysis trend.

While we are not able to unequivocally determine the reason for this hydrolysis behavior, several possibilities exist. During this study, we have observed that the ester directly next to the norbornene hydrolyzes significantly slower than other hydrolyzable sites that are further removed from the norbornene (see the study of **3**). This has been evidenced by comparison of the hydrolysis data for monomers **3**−**6**. Hydrolysis data for **3** reflect only hydrolysis at the ester adjacent to the norbornenyl group, since this site is the only water labile site on the molecule. Significant hydrolysis of **3** only occurs at basic pH values. At lower pH values, monomers **4** and **5** exhibited the

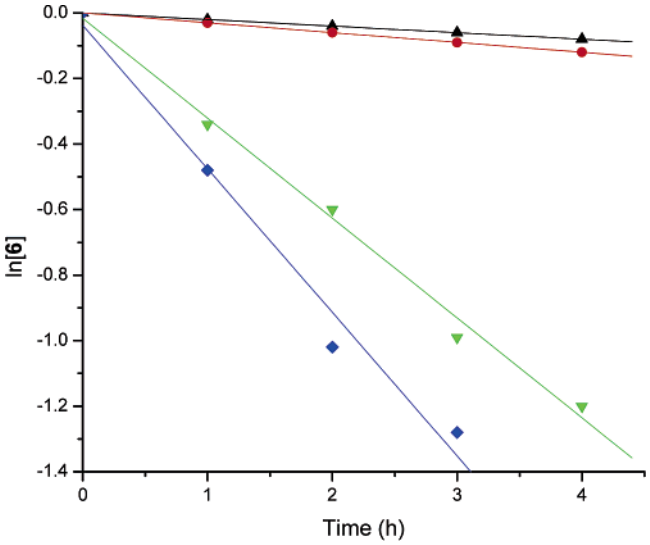


FIGURE 7. Pseudo-first-order hydrolysis kinetics for compound **6** at 80 °C: ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4.

expected acetal cleavage, but as pH increased, trends began to mimic those of **3**, suggesting that the ester was hydrolyzing instead under that set of conditions. For **6**, we observed faster hydrolysis than that of **3** under all conditions, suggesting that the ester farther removed from the norbornenyl group was more labile under the conditions used in the study. However, one of the initial decomposition products observed for **6** showed subsequently further decomposition on a time scale identical with that of **3**, suggesting that this second hydrolysis step matches the behavior of **3**. These results thus confirm the identities of the individual hydrolysis sites, recognizable by their own unique characteristic hydrolysis behaviors. The observed rate decrease for the norbornenyl ester is most likely due to the hydrophobic nature of the norbornene, the steric bulk generated by this bridged aliphatic group, or both. In compound **7**, the ester that is not directly attached to the norbornene is partially in a highly hydrophobic environment, potentially shielding

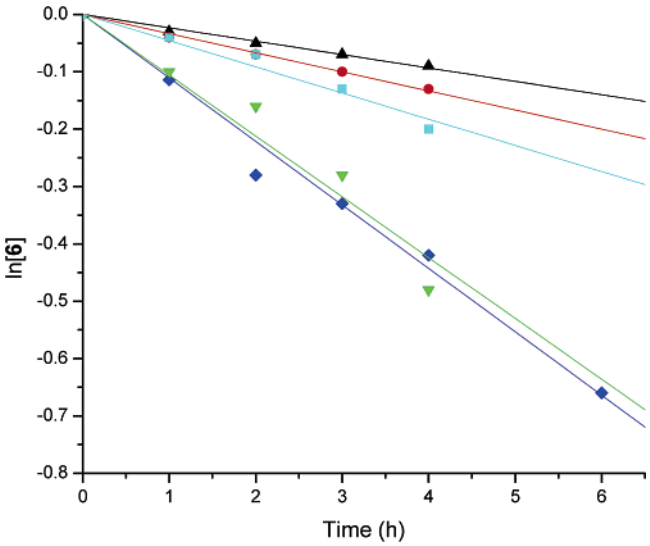


FIGURE 8. Pseudo-first-order hydrolysis kinetics for compound **6** at 60 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4.

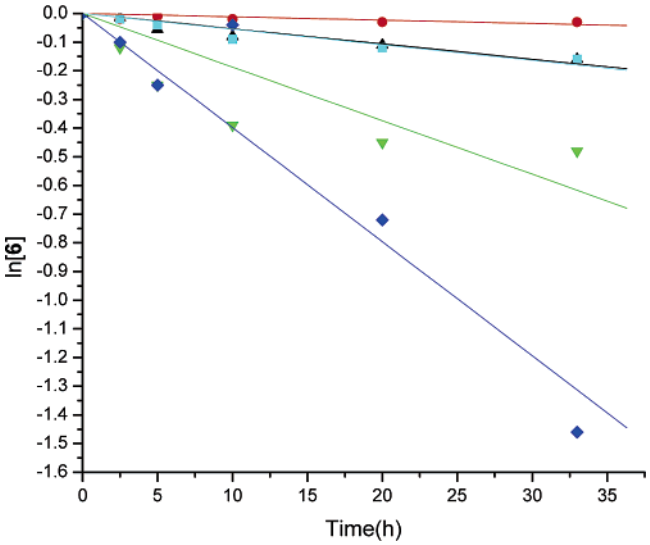


FIGURE 9. Pseudo-first-order hydrolysis kinetics for compound **6** at 37 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4.

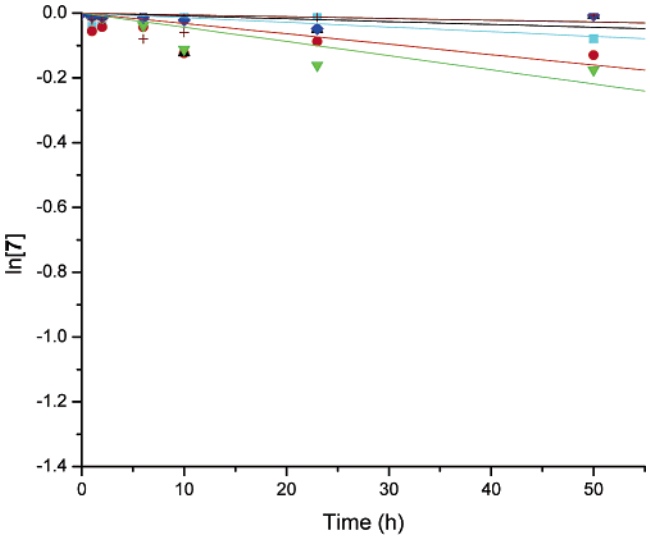


FIGURE 10. Pseudo-first-order hydrolysis kinetics for compound **7** at 37 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

it from easy access by water molecules. It is also a common behavior of molecules bearing a hydrophobic end on one side of the molecule, and an ionic charge on the other, to form aggregates in solution, such is the case with many common surfactants. In aqueous media, the charged end of these molecules appears on the periphery of any aggregates formed, further protecting any hydrophobic esters on the interior from hydrolysis. As the temperature increases, noncovalent forces that aid in the swelling of aggregates or the desolvation of molecules may be overcome, causing the aggregates to collapse. This behavior could potentially lead to a change in mechanism at high temperature.

Hydrolysis of 9. The rate of hydrolysis of **9** at 80 and 60 °C at all pH values was too fast to be measured by the methods employed in this study. It is estimated that in buffered aqueous solution the half-lives of all monomers are on the order of 5 to 10 min at all pH values.

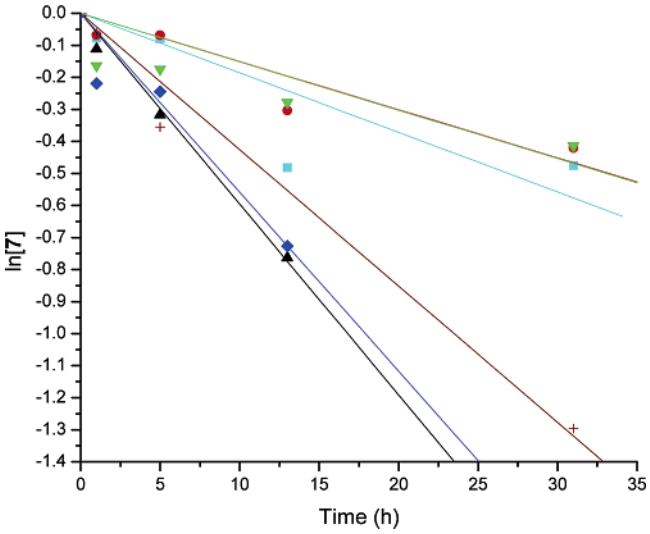


FIGURE 11. Pseudo-first-order hydrolysis kinetics for compound **7** at 60 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

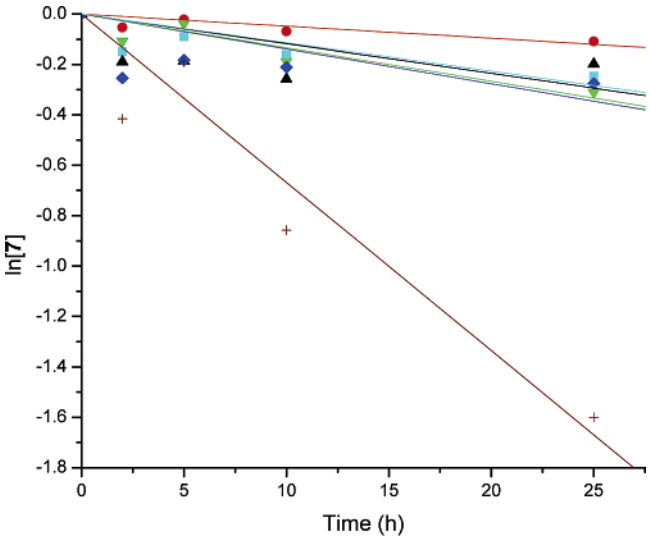


FIGURE 12. Hydrolysis kinetics for compound **7** at 80 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

While the half-lives are noticeably longer (approximately 20 min) at 60 °C, the rate of hydrolysis is still too fast to quantitatively determine rate constants by HPLC analysis. The increased rate of hydrolysis for this compound may be due to several factors. It is hypothesized in the literature that neighboring amine functionalities can act as intramolecular nucleophilic catalysts in ester hydrolysis, thus contributing to higher degradation rates.[16] Langer and Lynn also point out the possibility of a potential retro-Michael addition occurring in molecules synthesized via Michael addition reactions.[17] In their study, they employed a polymer containing esters and tertiary amines along the polymer backbone to study the cytotoxicity of the degradation products of their polymer as a new transfection vector. They found that hydrolysis

(16) Lim, Y.-B.; Kim, C.-H.; Kim, K.; Kim, S. W.; Park, J.-S. *J. Am. Chem. Soc.* **2000**, *122*, 6524.
(17) Lynn, D. M.; Langer, R. *J. Am. Chem. Soc.* **2000**, *122*, 10761.

TABLE 5. Hydrolysis Data for Compound 7

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
	compound **7**, 80 °C		
3.1	0.011 ± 0.003	0.712	61.2
4.6	0.005 ± 0.001	0.794	144
5.7	0.012 ± 0.005	0.227	58.9
6.9	0.013 ± 0.002	0.866	52.0
7.4	0.014 ± 0.005	0.371	50.1
8.9	0.067 ± 0.007	0.929	10.4
	compound **7**, 60 °C		
3.1	0.019 ± 0.004	0.733	32.3
4.6	0.015 ± 0.002	0.904	46.0
5.7	0.060 ± 0.002	0.996	11.6
6.9	0.015 ± 0.003	0.840	45.8
7.4	0.056± 0.007	0.929	12.4
8.9	0.043 ± 0.003	0.987	16.3

TABLE 6. Hydrolysis Data for Compound 9 at 37 °C

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
4.6	0.027 ± 0.001	0.993	26.1
5.7	0.073 ± 0.002	0.995	9.5
6.9	0.095 ± 0.001	0.999	7.3
7.4	0.090 ± 0.002	0.996	7.7
8.9	0.149 ± 0.003	0.997	4.7

occurred faster at pH 7.4 than at 5.1. However, they observed no retro-Michael addition products in their system—only ester hydrolysis products, which suggests that retro-Michael addition is not the primary degradation pathway for **9**. Nucleophilic attack of the amine to the ester carbonyl gives a positively charged quaternary amide, which would be very active toward hydrolysis.

At 37 °C, the rates of hydrolysis are slow enough to observe via HPLC analysis, and are described in Table 6 and Figure 13 below. The rate of hydrolysis increases

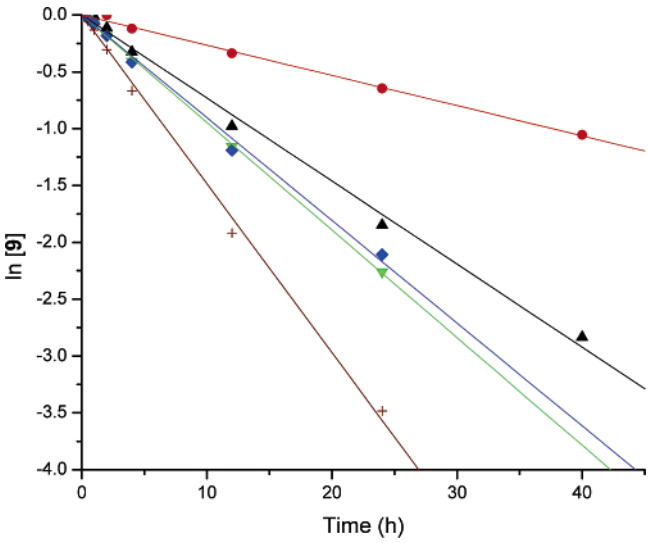


FIGURE 13. Pseudo-first-order hydrolysis kinetics for compound **9** at 37 °C: ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

with pH, and was fastest at pH 8.9, consistent with the findings of Langer and Lynn for their similar system.

Hydrolysis of 8. Compound **8** showed no significant hydrolysis at 37 °C, with the exception of pH 8.9, which appeared to decompose faster than the methods employed in this study are able to measure. At 60 °C, there was

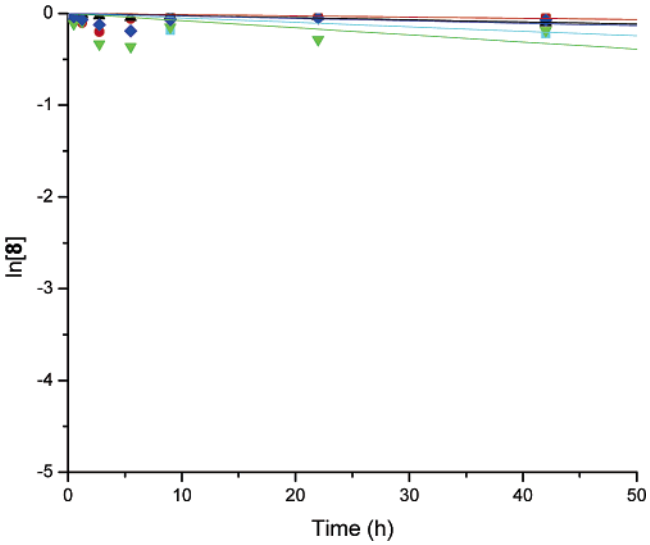


FIGURE 14. Hydrolysis kinetics for compound **8** at 37 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4.

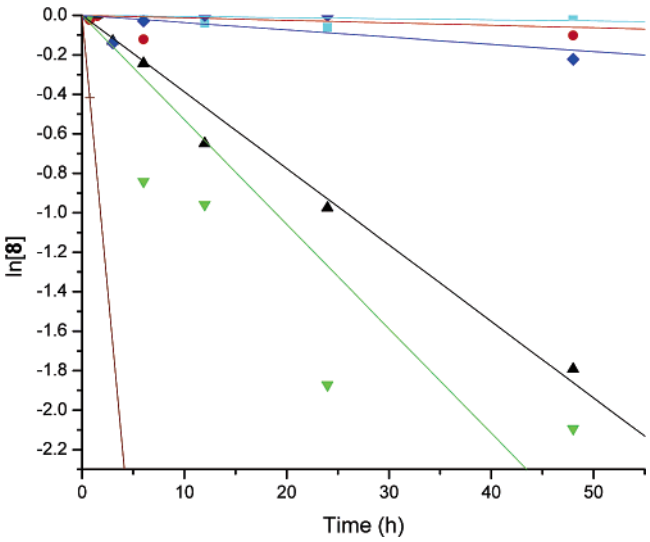


FIGURE 15. Hydrolysis kinetics for compound **8** at 60 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4; +, pH 8.9.

again extremely rapid decomposition at pH 8.9, while pH values of 3.1, 4.6, and 7.4 once again showed no observable hydrolysis. However, pH 5.7 and 6.9 exhibited pseudo-first-order kinetics. At 80 °C, decomposition at pH 8.9 again was too fast to measure, while pH 3.1, 4.6, and 5.7 gave fairly well-behaved pseudo-first-order kinetics, displaying half-lives in the range of 5.1 h for pH 5.7 to 63 h for pH 3.1. As displayed in Figure 16, hydrolysis of pH 6.9 was nonlinear. This result suggests the occurrence of side reactions or interactions of **8** with the buffer. Hydrolysis kinetics measured for pH 7.4 did not follow first order for any temperature range.

Conclusion

In conclusion, we have synthesized a library of chemically diverse norbornene compounds, an important class of monomers for ROMP. Furthermore, we have investigated their decomposition via hydrolysis in aqueous

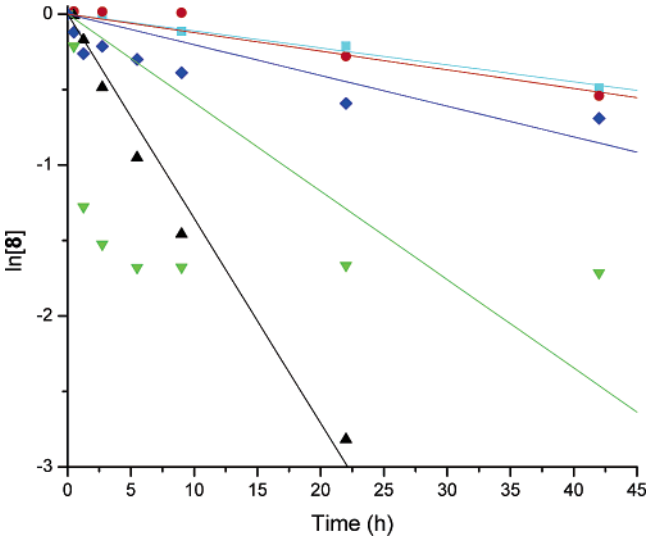


FIGURE 16. Hydrolysis kinetics for compound **8** at 80 °C: ■, pH 3.1; ●, pH 4.6; ▲, pH 5.7; ▼, pH 6.9; ◆, pH 7.4.

TABLE 7. Hydrolysis Data for Compound 8

pH	k (h^{-1})	R^2	$t_{1/2}$ (h)
	compound **8**, 80 °C		
3.1	0.011 ± 0.001	0.947	63
4.6	0.012 ± 0.001	0.961	57.8
5.7	0.136 ± 0.006	0.982	5.1
6.9	0.059 ± 0.021	0.272	11.7
7.4	0.020 ± 0.004	0.822	34.7
	compound **8**, 60 °C		
3.1	0.001 ± 0.001		700
4.6	0.001 ± 0.001		700
5.7	0.034 ± 0.001	0.985	20.4
6.9	0.053 ± 0.008	0.833	13.1
7.4	0.004± 0.001		170
	compound **8**, 37 °C		
3.1	0.005 ± 0.001		140
4.6	0.001 ± 0.002		700
5.7	0.002 ± 0.001		350
6.9	0.008 ± 0.004		90
7.4	0.003 ± 0.002		230

solution under a variety of pH and temperature ranges. The investigated monomers contained either ester and/or acetal linkages, as well as terminal functional groups including esters, acids, ethers, and saccharides. During the hydrolysis studies, the two extremes that we investigated were the amine/ester-based and the saccharide-based monomers. The hydrolysis of tertiary amine/ester-based monomers was very fast with half-lives of below 10 h for all temperatures and pH values investigated. In contrast, the saccharide/ester-based monomer showed the slowest hydrolysis at acidic conditions of any monomer and condition studied.

A variety of important trends were observed during these studies. First, the chemistry of the acetal functional group allows for selective hydrolysis of the side-chain either at the ester linkage of the norbornene at the 2-position (at high pH) or at the acetal group (at low pH). Second, the presence of a β-amino functionality greatly enhances the rate of hydrolysis and also changes the pH dependence of the rate constants. This suggests a change in the mechanism of hydrolysis by the involvement of intramolecular assistance, but the experiments conducted in this study do not conclusively show which mechanisms may be predominating. Third, the presence of a carboxylic acid in the monomer structure results in the unpredictable hydrolysis of the monomer with non-first-order kinetics. Fourth, saccharide-containing monomers hydrolyze rapidly in alkaline media while they are stable under acidic conditions, an important finding for polymers based on similar monomers has been suggested as biomaterial. Furthermore, it is important to note that the hydrolysis behavior of the monomers under some temperature and pH conditions, in particular at neutral pH values, does not follow the expected trends. We rationalize that these cases include either the participation of neighboring groups and/or interactions of the monomers with the buffer. Finally, we observed significant hydrolysis of the ester linkage directly bonded to the norbornene. The use of ester linkages to support side-chains on poly(norbornene)s is also the most commonly employed method for water-soluble polymers. Our results clearly demonstrate that these esters are not stable under a wide variety of temperatures and pH values, suggesting that the stability of side-chain functionalized poly(norbornene)s containing ester linkages is limited and this inherent instability must be considered when designing functionalized poly(norbornene)s.

Experimental Section

Typical Esterfication Method 1: Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid 2-[2-(2-Hydroxyethoxy)ethoxy Ethyl Ester, 1. To a solution of triethylene glycol (3.66 g, 24.4 mmol) and triethylamine (4.90 g, 48.8 mmol) in THF (200 mL) was added compound **10** (3.63 g, 23.2 mmol) dropwise at 0 °C. The mixture was warmed to ambient temperature and stirred for 8 h. The mixture was diluted with diethyl ether and washed with 5% NaOH (aq), 5% HCl (aq), sat. $NaHCO_3$ (aq), and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo to give bicyclo[2.2.1]hepta-5-ene-2-carboxylic acid 2-[2-(2-hydroxvethoxy)ethoxy]ethyl ester as a clear colorless liquid (5.21 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (m, 1H), 6.10 (m, 2 H), 5.90 (m, 1H), 4.14−4.24 (m, 2H), 3.72−3.65 (m, 8H), 3.60 (t, J = 8 Hz, 2H), 3.19 (br, 1H), 3.02 (br, 1H), 2.94 (m, 1H), 2.88 (br, 1 H), 2.22 (m, 1 H), 1.93−1.84 (m, 1H), 1.49−1.23 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 174.6, 137.9, 137.6, 135.6, 132.2, 72.4, 70.4, 70.2, 69.1, 63.2, 63.1, 61.6, 49.5, 46.5, 46.2, 45.6, 43.1, 42.9, 41.5, 30.2, 29.1. IR (neat): 3460 (br, −OH), 3060, 2940, 2870, 1730, 1630 (shoulder), 1450, 1190, 1110, 712 cm^{-1}. MS(EI, 70 keV): m/z 139, 58 (100). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20, H, 8.20. Found: C, 62.28, H, 8.29.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid 2-(2-{2-[2-(2-Methoxyethoxy)ethoxymethyl][1,3]dioxolan-4-ylmethoxy}ethoxy)ethyl Ester and Bicyclo[2.21]hept-5-ene-2-carboxylic Acid 2-(2-{2-[2-(2-Methoxyethoxy)ethoxymethyl][1,3]dioxan-5-yloxy}ethoxy)ethyl Ester, 4 and 5. NaH (58.6 mg, 2.44 mmol) was added to a solution of a mixture of **12** and **13** (0.53 g, 2.22 mmol) in THF (10 mL) under argon. The mixture was stirred for 1 h at room temperature, **2** (0.56 g, 2.33 mmol) was added, and the resulting mixture was refluxed for 24 h. KI (2 crystals) was added and reflux was continued for an additional 24 h. The mixture was then cooled to room temperature, the organic layer diluted with diethyl ether (30 mL) and washed with water (20 mL), and the organic layer concentrated under reduced pressure. The residue was subjected to column chromatography (1:3 ethyl acetate:hexane, silica) to yield a mixture of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2-(2-{2-[2-(2-methoxyethoxy)ethoxymethyl][1,3]dioxolan-4-ylmethoxy}ethoxy)ethyl ester and bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2-(2-{2-[2-(2-methoxyethoxy)ethoxymethyl]-

[1,3]dioxan-5-yloxy}ethoxy)ethyl ester as a clear colorless liquid (0.819 g, 83%). ^{1}H NMR (400 MHz, $CDC1_3$): δ 6.13−6.16 (m, 0.5H, vinyl endo), 6.08−6.10 (m, 0.5H, vinyl exo), 6.04−6.06 (m, 0.5H, vinyl exo), 5.86−5.88 (m, 0.5H, vinyl endo), 5.13−5.17 (m, 0.5H), 5.02−5.05 (m, 0.5H), 4.20−4.35 (m, 1.5H), 3.89−4.13 (m, 4H), 3.74−3.79 (m, 0.5H), 3.49−3.68 (m, 12H), 3.33 (s, 3H), 2.87−3.16 (m, 3H), 2.19−2.23 (m, 0.5H), 1.82−1.89 (m, 1.5H), 1.22−1.47 (m, 3H). ^{13}C NMR (100 MHz, $CDC1_3$): δ 186.9, 186.8, 185.4, 185.3, 149.0, 148.8, 146.5, 143.1, 114.3, 114.0, 113.9, 88.3, 88.0, 87.7, 84.8, 83.0, 82.9, 82.8, 82.1, 81.4, 78.0, 75.2, 74.8, 69.9, 60.5, 57.6, 57.2, 56.6, 54.1, 53.9, 53.4, 52.5, 41.3, 40.1, 35.0. IR (neat): 3060.1, 2944.4, 2872.6, 1734.7, 1623.8, 1455.1, 1334.6, 1112.8, 717.4 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_9$: C, 59.44, H, 8.16. Found: C, 59.43, H, 8.18.

Typical Esterfication Method 2: Bicyclo[2.2.l]hept-5-ene-2-carboxylic Acid 2-[2-(2-{2-[2-(2-Methoxyethoxy)-ethoxy]acetoxy}ethoxy)ethoxy]ethyl Ester, 6. A solution of 2-(2-[2-methoxyethoxy]ethoxy)acetic acid (0.28 g, 1.55 mmol) and **10** (0.42 g, 1.55 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. DMAP (0.19 g, 1.57 mmol) was slowly added and the solution was stirred for 5 min. Then DCC (0.33 g, 1.58 mmol) was added and the solution was allowed to warm to ambient temperature over a period of 12 h, during which a white precipitate was formed that was removed by filtration and washed with additional CH_2Cl_2. The filtrate was washed with aqueous NH_4Cl (sat.), $NaHCO_3$, and water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (1:2 ethyl acetate:hexane, silica) to afford bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]acetoxy}-ethoxy)ethoxy]ethyl ester as a clear colorless liquid (0.346 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06−6.16 (m, 1.5H), 5.89−5.91 (m, 0.5H), 4.10−4.36 (m, 7H), 3.51−3.72 (m, 17H), 3.35 (s, 3H), 3.13 (s, br, 1H), 2.79−3.01 (m, 2H), 2.21−2.50 (m, 1.5H), 1.84−1.91 (m, 1.5H), 1.61−1.76 (m, 0.5H), 1.23−1.50 (m, 3.5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 170.3, 138.0, 137.6, 135.6, 132.2, 77.3, 77.0, 76.7, 71.8, 70.8, 70.5, 70.4, 69.2, 68.9, 68.4, 63.6, 63.1, 58.9, 49.5, 46.6, 46.2, 45.6, 43.1, 42.9, 42.4, 41.5, 36.9, 30.2, 29.1, 27.2. IR (neat): 2949.7, 2872.6, 1754.0, 1734.7, 1455.1, 1199.6, 1117.6, 847.6 cm^{-1}. MS (CI, isobutane): *m/z* 431 (M^+ + H), 365, 293, 205 (100), 165, 133. Anal. Calcd for $C_{21}H_{34}O_9$: C, 58.59, H, 7.96. Found: C, 58.54, H, 7.99.

Pentanedioic Acid Mono(2-{2-[2-(bicyclo[2.2.1]hept-5-ene-2-carbonyloxy)ethoxy]ethoxy}ethyl) Ester, 7. A solution of **1** (1.28 g, 4.75 mmol) and pyridine (3 mL) in THF (20 mL) was added to glutaric anhydride (0.57 g, 4.98 mmol) in THF (10 mL) at ambient temperature and the mixture was stirred for 12 h. The reaction mixture was diluted with diethyl ether and washed with 10% HCl (aq), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (1:1 ethyl acetate:hexane, silica) to give pentanedioic acid mono(2-{2-[2-(bicyclo[2.2.1]hept-5-ene-2-carbonyloxy)ethoxy]ethoxy}ethyl) ester as a clear colorless liquid (1.49 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (m, 1H), 5.91 (m, 1H), 4.23−4.14 (m, 4H), 3.82−3.73 (m, 8H), 3.19 (s, br, 1H), 2.98−2.87 (m, 2H), 2.43−2.36 (m, 4H), 2.02−1.84 (m, 3H), 1.42−1.23 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 174.7, 172.8, 138.0, 137.7, 135.6, 132.3, 72.4, 70.4, 70.3, 69.2, 63.5, 63.2, 61.6, 49.5, 46.6, 46.2, 45.6, 43.1, 43.0, 42.4, 41.5, 33.0, 32.8, 30.3, 29.2, 19.9, 19.7. IR (neat): 3296 (br, −OH), 2963, 2880 (CH stretch), 1760, 1722 (C=O), 1447, 1139, 717 cm^{-1}. MS(El, 70 keV): *m/z* 385 (M + H), 367, 301, 247, 205. 159. 120, 99 (100). 66. 55. HRMS: calcd for $C_{19}H_{28}O_8$ 384.1784, obsd 384.1779. Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36, H, 7.34. Found: C, 59.31, H, 7.45.

Galactopyranose-6-uronic Acid 2-{2-[2-(Bicyclo[2.2.1]-hept-5-ene-2-carbonyloxy)ethoxy]ethoxy}ethyl Ester, 8. Compound **15** (0.29 g, 0.55 mmol) was dissolved in 8 mL of a solution of 80% TFA (aq) and stirred for 3 h at ambient temperatures. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, 1:1 ethanol:ethyl acetate) to give galactopyranose-6-uronic acid 2-{2-[2-(bicyclo[2.2.1]hept-5-ene-2-carbonyloxy)-ethoxy]ethoxy}ethyl ester as a clear colorless viscous liquid. Yield: 0.206 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.12−6.15 (m, 0.5H, vinyl endo), 6.04−6.08 (m, 1H, vinyl exo), 5.86−5.89 (m, 0.5H, vinyl exo), 5.46 (s, br, 1H), 5.30 (s, br, 0.5H), 4.86 (m, 0.5H), 4.70 (m, 1H), 4.33 (m, 3H), 4.04 (m, 2H), 3.95 (m, 1H), 3.61 (m, 9H), 3.16 (s, br, 1H), 2.95 (m, 1H), 2.85 (s, br, 1H), 2.62, (m, 1H), 2.19 (m, 1H), 1.88 (m, 1H), 1.63 (m, 1H), 1.36 (m, 2H), 1.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 138.2, 138.1, 136.2, 132.5, 81.4, 70.6, 70.5, 69.4, 69.3, 65.0, 64.9, 63.6, 49.9, 47.0, 46.0, 44.1, 43.5, 42.6, 40.1, 30.2. IR (KBr): 3379 (br, −OH), 2947, 2877 (CH stretch), 1734 (C=O), 1452, 1340, 1205 (sp^2 C−O), 1105, 1018 (sp^3 C−O), 939, 808 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_{11}$: C, 53.81, H, 6.77. Found: C, 53.74, H, 6.68.

[2-(2-Methoxyethoxy)ethoxy]acetaldehyde, 11. To a solution of oxalyl chloride (3.59 g, 28.2 mmol) in dry CH_2C1_2 (50 mL) at −78 °C under argon was added freshly distilled DMSO (5 mL) slowly. The mixture was stirred for 30 min, and then freshly distilled dry triethylene glycol monomethyl ether (3.86 g, 23.6 mmol) was added via a syringe. The mixture was stirred for an additional 30 min, triethylamine (20 mL) was added over 10 min, and the mixture was stirred for 15 min and then warmed to ambient temperature. Dilution with CH_2Cl_2 (50 mL), washing with water, and distillation of the organic layer under reduced pressure yielded [2-(2-methoxyethoxy)-ethoxy]acetaldehyde as a clear colorless liquid (2.10 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, J = 0.8 Hz, 1H), 4.06 (d, J = 0.8 Hz, 2H), 3.59−3.67 (m, 4H), 3.54−3.57 (m, 2H), 3.43−3.47 (m, 2H), 3.28 (s, 3H). ^{13}C NMR (100 MHz, $CDC1_3$): δ 171.6, 76.7, 71.8, 70.9, 70.7, 59.0, 40.1. IR (neat): 2872, 1727, 1452, 1357, 1086 cm^{-1}. MS(EI, 70 keV): *m/z* 87, 59 (100), 45, 31, 29, 15. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84, H, 8.70. Found: C, 51.76, H, 8.66.

{2-[2-(2-Methoxyethoxy)ethoxymethyl][1,3]dioxolan-4-yl}methanol and 2-[2-(2-Methoxyethoxy)ethoxymethyl]-[1,3]dioxan-5-ol, 12 and 13. A solution of freshly distilled dry glycerol (0.49 g, 5.37 mmol), **11** (0.67 g, 4.13 mmol), and *p*-TsOH (1 crystal) in $PhCH_3$ was heated at reflux under argon for 12 h with a Dean−Stark trap half filled with $CaCl_2$. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (1:3 ethyl acetate:hexane, silica) to give a mixture of {2-[2-(2-methoxy-ethoxy)ethoxymethyl][1,3]dioxolan-4-yl}methanol and 2-[2-(2-methoxyethoxy)ethoxymethyl][1,3]dioxan-5-ol as a clear colorless liquid (0.81 g, 83%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 5.15 (t, J = 4.0 Hz), 5.04 (t, J = 2.7 Hz), 4.73 (t, J = 4.4 Hz), 4.57 (t, J = 4.5 Hz; total 1H), 4.24−4.12 (m, 1H), 4.08−3.49 (m, 14 H), 3.33 (s, 3H), 2.75 (br, 1H). ^{13}C NMR (75 MHz, $CDC1_3$): δ 102.9, 102.8, 100.3, 99.5, 76.7, 76.4, 72.3, 72.1, 71.8, 71.7, 71.4, 71.2, 71.1, 71.1, 71.0, 70.5, 70.4, 66.8, 66.5, 64.1, 64.0, 63.5, 62.4, 61.1, 59.0. IR (neat): 3437 (br), 2883.2, 1108.9, 863.0 cm^{-1}. MS (CI, isobutene): *m/z* 237 (M), 163, 121 (100), 117, 103. Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.84, H, 8.53. Found: C, 50.79, H, 8.52.

2:3,4:5-Diisopropylidine Galactopyranose-6-uronic Acid, 14. A solution of 2:3,4:5-diisopropylidine galactopyranose (2.61 g, 10.0 mmol) in acetone (10 mL) was slowly added to a solution of CrO_3 (1.49 g, 15.0 mmol) in acetone (30 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 5 h. Ethyl acetate was carefully added to the mixture and the reaction was washed with water. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica, 1:1 ethyl acetate: hexanes) to give 2:3,4:5-diisopropylidine galactopyranose-6-uronic acid as a clear, colorless, viscous liquid that crystallized upon standing. Yield: 2.23 g (81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.52 (d, J = 5.02 Hz, 1H), 4.64 (dd, J = 2.43, 7.73, 1H), 4.49 (dd, J = 2.15, 7.73, 1H), 4.39 (dd, J = 2.49, 5.02, 1H), 4.17 (d, J = 2.14, 1H), 1.42 (s, 3H), 1.31 (s, 3H),

1.27 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.9, 108.7, 108.3, 95.8, 71.5, 70.1, 69.6, 67.4, 25.8, 25.7, 24.7, 24.4. IR (KBr): 3491 (br, O−H) 2985, 2937 (sp^3 CH stretch), 1722 (acid C=O), 1456, 1375, 1211, (sp^2 C−O), 1164, 1118, 1070, 1022 (sp^3 C−O), 904, 840, 790, 692, 511 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55, H, 6.62. Found: 52.41, H, 6.63.

***N*-(2-Hydroxyethyl)-4-azaheptanedicarboxylic Acid Di-(2-[2-{2-methoxyethoxy}ethoxy]ethyl ester), 17.** Ethanolamine (0.28 g, 4.6 mmol) was added dropwise to a stirred sample of **16** (2.06 g, 9.45 mmol) at ambient temperature. The flask was capped and the mixture stirred for 24 h. The mixture was subjected to column chromatography (silica, 49:1 CH_2Cl_2:MeOH) to give *N*-(2-hydroxyethyl)-4-azaheptanedicarboxylic acid di(2-[2-{2-methoxyethoxy}ethoxy]ethyl ester) as a clear colorless liquid. Yield: 2.10 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (t, 4H, J = 4.7 Hz), 3.69−3.50 (m, 22 H), 3.35 (s, 6H), 2.98 (br, 1H), 2.77 (t, 4H, J = 6.9 Hz), 2.55 (t, 2H, J = 4.9 Hz), 2.46 (t, 4H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 71.9, 70.6, 70.5, 70.5, 69.0, 63.7, 59.1, 59.1, 56.0, 49.1, 32.6. IR (neat): 3408.1 (br), 2878.4, 1735.2, 1456.1, 1253.6, 1181.2, 1108.9, 853.4. MS (CI, isobutene): *m/z* 498.4 (M + 1, 100) 466, 334, 292, 103. HRMS: calcd for $C_{22}H_{43}NO_{11}$ 497.2836, obsd 497.28353. Anal. Calcd for $C_{22}H_{43}NO_{11}$: C, 53.10, H, 8.71, N, 2.81. Found: C, 53.18, H, 8.65, N, 2.79.

General Procedure for Hydrolysis. The hydrolysis of all monomers was carried out with 5 mM solutions of analyte in buffers of pH 3.1 (phosphate/citric acid), 4.6 (acetate), 5.7 (acetate), 6.9 (phosphate), 7.4 (phosphate-buffered saline), and 8.9 (borate). The samples were heated to 37, 60, and 80 °C (±0.1 °C) in a thermostatic oil bath and samples (50 μL) were withdrawn and diluted to 1.00 mL in the appropriate mobile phase prior to HPLC analysis. Samples were stored at −15 °C when not immediately analyzed.

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Supporting Information Available: General experimental details, additional experimental procedures and characterization, and instrumental setup for the HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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