Chiral Polyolefins Bearing Amino Acids

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Introduction. Biopolymers containing amino acid-based moieties are of interest due to their inherent biological compatibility and degradability, making them ideal candidates for a variety of biomaterial applications. Further, amino acid-based chiral polymers can have induced crystallinity with the ability to form higher ordered structures that exhibit enhanced solubility characteristics.[1] These properties result in polymers that are ideal candidates for drug delivery systems, biomimetic systems, biodegradable macromolecules, biomaterials, and as chiral purification media.[1]

Recently, Endo and co-workers have reported the synthesis of several branched and linear polymer systems containing amino acid moieties.[2−4] Several of these polymers indeed form higher ordered structures as proven by circular dichroism.[5] Maynard and Grubbs have produced polymers containing amino acid moieties via the ring-opening metathesis polymerization (ROMP) of oligopeptide-substituted norbornenes and have copolymerized these monomers with penta(ethylene oxide) substituted norbonenes to form water-soluble polymers.[6,7] In addition, Brzezinska et al. have synthesized telechelic polymers as macroinitiators for the addition of polypeptides, yielding triblock copolymers.[8]

We have initiated a study using acyclic diene metathesis (ADMET) to prepare chiral polyolefins bearing amino acid groups. ADMET reactions are straightforward step polymerizations that can lead to precise structure control.[9,10] Given the metathesis catalysts available today, in particular, the second generation Grubbs ruthenium catalyst[11] (**1**) (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride), almost any functional group can be inserted into a polymer, and the protected AA group is just another example. The amino acid (AA) group can be positioned at exact locations either within the polymer backbone or pendant to it, leading to semicrystalline, chiral polymers having considerable tensile strength at moderate molecular weights. It is worth noting that these functionalized polyolefins only require molecular weights between 10 000 and 20 000 g/mol to exhibit useful physical and mechanical properties, a molecular weight range similar to common polycondensation polymers such as nylon and polyester. Our approach to polymer synthesis with amino acid entities involves constructing either linear amino alcohol or branched amino acid diene monomers, followed by their ADMET polymerization (Figure 1). The polymers possessing AA units in the backbone will likely be biodegradable,[3] while the polymers with the AA units pendant to the main chain will be hydrolytically stable. Consequently, two completely different types of materials can be created with this chemistry. Altering the “regularity” of placement also is easy to do, either via diene monomer design or via simple copolymerization. As a result, creating an exact molar concentration of AA groups within the material is easy to accomplish. Finally, the synthesis of polyolefins bearing peptide sequences is within easy reach, where polyolefin surfaces could be designed to achieve specific properties. This communication reports our first work in this area.

Results and Discussion. Linear amino alcohol-containing diene monomers **2** and **3**, each of which has two methylene spacers between the terminal olefins and the amino acid amide and ester carbonyl groups, were subjected to ADMET conditions (Figure 1). Both of these polycondensations were performed using a 100:1 monomer-to-catalyst ratio; the evolution of ethylene ceased after a short period of time leading to oligomers. The resulting oligomers **10** and **11** have $\overline{M}_n$'s of 900 and 930 g/mol, respectively, by GPC, i.e., $\overline{DP} = 3$. The ^{1}H NMR spectra of **10** and **11** showed terminal olefin end groups at 5.5−5.7 and 6.1−6.3 ppm with very little internal olefin formation at 5.7−5.9 ppm. In this case, a dynamic intramolecular complexation of the ruthenium catalyst slows the polycondensation kinetics considerably, a phenomenon which has precedent for both ADMET and ring-closing metathesis (RCM) chemistry.[12] This complexation can be obviated to some extent with the addition of a Lewis acid such as titanium isopropoxide. For example, the addition of 0.3−3 equiv of Ti(O*i*Pr)$_4$ has been shown to preferentially complex with carbonyl groups, permitting successful RCM reactions to be observed.[12]

During our experiments, it became evident that addition of 2.5 mol % Ti(O*i*Pr)$_4$ produced a product containing significantly more internal olefins by ^{1}H NMR end group analysis than without Ti(O*i*Pr)$_4$. However, a new multiplet signal at 2.8−3.2 ppm was observed, indicating a side reaction occurred. Further, GPC analysis showed no increase of molecular weight than when no Ti(O*i*Pr)$_4$ was added under identical conditions. After further examination of the ^{1}H NMR spectrum, it was evident that these observations were due to olefin isomerization. We believe that the reaction temperature used permits Ti(O*i*Pr)$_4$ to isomerize the olefins.

Intramolecular complexation can be avoided to some extent simply by extending the methylene run length in the monomer from two methylene units to three, as is the case for monomer **4** (Figure 1). This monomer has an L-leucinol moiety with three methylene units between the carbonyl and the olefin sites, and it successfully polymerized to generate polymer **12**, $\overline{M}_n$ of 4700 g/mol, as determined by GPC (Table 1). It appears that even with three methylene spacers between the olefin and carbonyl groups, complexation with the catalyst to form a seven-membered ring may still occur. Therefore, monomers **5** and **6** with eight methylene spacers between the olefins and the amino acid functionality were synthesized containing an L-valinol and an L-leucinol moiety, respectively (Figure 1). These monomers easily polymerized with a 250:1 monomer:catalyst ratio, producing polymers **13** and **14** with GPC $\overline{M}_n$'s of 27 000 and 33 000 g/mol, respectively.

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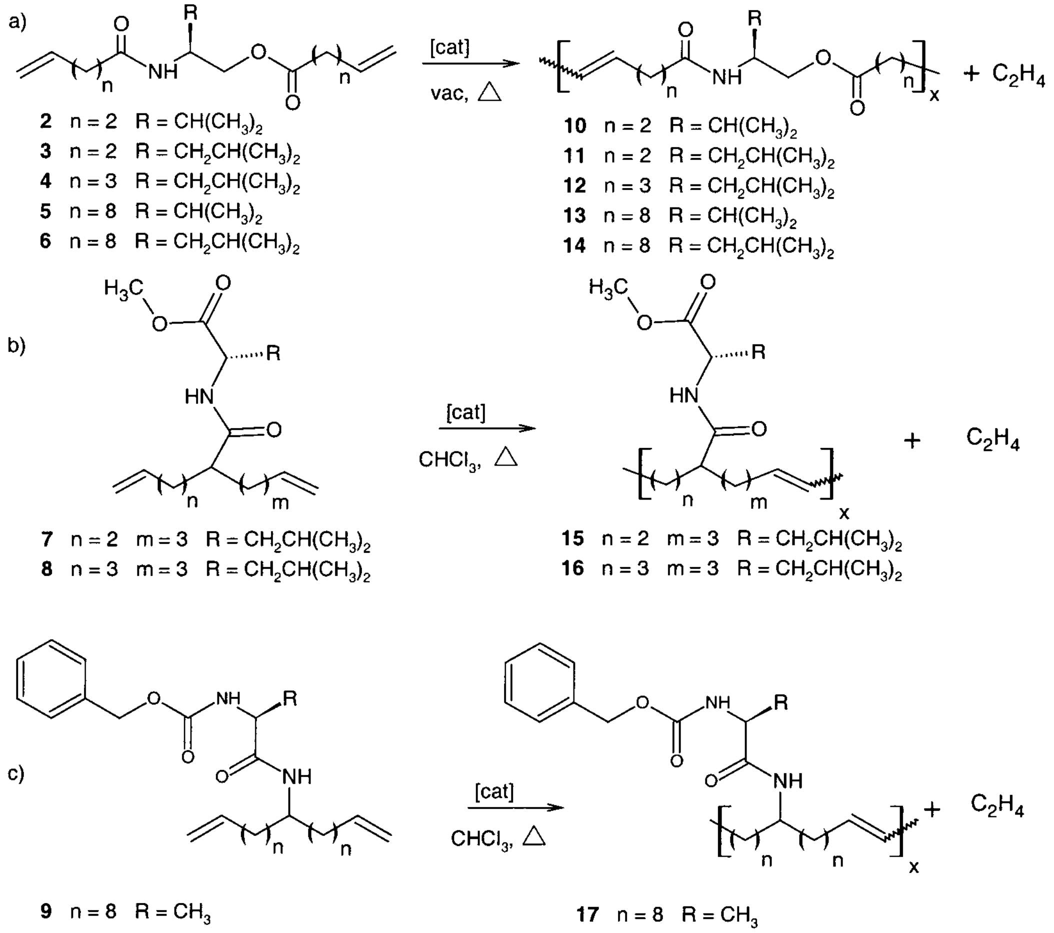

Figure 1. General reaction for the synthesis of linear amino alcohol polymers (a), ester-terminated amino acid branched polymers (b), and an amide-terminated amino acid branched polymer (c).

Table 1. Selected Characterization Data for Polymers 12–17

monomer	polymer	$[\alpha]_m$ (deg)	$[\alpha]_p$ (deg)	$\bar{M}_n$[a] (g/mol)	PDI[b]	T_m[c] (°C)	T_m[d] (°C)
4	**12**	−32	−32	4 700	1.73	*e*	*e*
5	**13**	−34	−20	27 000	1.77	29	38
6	**14**			33 000	1.64	*e*	39
7	**15**	−13	−64	31 000	2.02	114	114
8	**16**	−13	−7	26 000	2.10	135	135
9	**17**			21 000	1.70	*e*	46

[a] $\bar{M}_n$ values were calculated by GPC vs polystyrene standards. Specific rotations were measured in CH_2Cl_2 at 25 °C, where $[\alpha]_m$ is the specific rotation of the monomer and $[\alpha]_p$ is the specific rotation of the polymer. [b] The polydispersity was determined by GPC analysis. [c] Determined by DSC. T_m reported is due to melt crystallization. [d] Determined by DSC. T_m reported is due to solution crystallization. [e] No T_m was detected.

Monomer **7** was synthesized containing an L-leucine methyl ester branch in order to investigate the effect of positioning the amino acid moiety as a pendant group in the polymer. Since the monomer is a solid, polymerization was done in solution under an Ar atmosphere; the catalyst was added to **7** (100:1 monomer:catalyst **1** ratio), followed by the addition of $CHCl_3$ (0.5 mL). An Ar purge removed the ethylene produced during polymerization. Refluxing the solution for 5 days followed by solvent evaporation produced polymer **15**. This polymer was redissolved in $CHCl_3$ and refluxed with a tris(hydroxymethyl)phosphine solution (1 M in 2-propanol, 20:1 equiv of tris(hydroxymethyl)phosphine:catalyst) to remove the catalyst residue. The polymer was then solution cast onto a Teflon plate, yielding a strong, semicrystalline polymer film. Polymer **15** has a $\bar{M}_n$ = 31 500 g/mol by GPC, and thermal analysis confirmed that it is a semicrystalline material with a T_m = 114 °C. Further, optical activity studies in CH_2Cl_2 showed that the polymer exhibited a 5-fold increase in optical activity over its monomer, which suggests that a secondary structure may be formed by polymer **15** in solution.

A possible explanation for this enhancement in optical activity of polymer with respect to monomer is the fact that monomer **7** is asymmetric in methylene spacer units. This structural arrangement most likely leads to a difference in reactivity of the terminal olefin groups toward ADMET chemistry, since as noted above, an olefin spaced two methylene units away from the AA group reacts more slowly than does an olefin spaced three or more methylene units from the AA group. This difference in reactivity could result in a "preordering" of the backbone before complete polycondensation is observed, and this additional degree of order might lead to the generation of secondary structure within the macromolecule in solution. All of the other polymers produced to date are symmetrical in methylene units, and none of these polymers exhibited any enhanced optical activity.

Monomer **8** was synthesized with an L-leucine methyl ester branch to further study the synthesis of polymers containing pendant amino acid moieties. This monomer was polymerized as described above to form polymer **16**, which possesses an $\bar{M}_n$ = 26 100 g/mol as determined

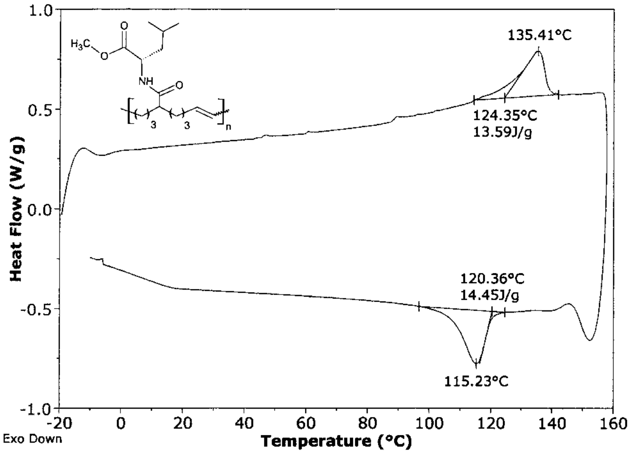

Figure 2. DSC trace of polymer **16**.

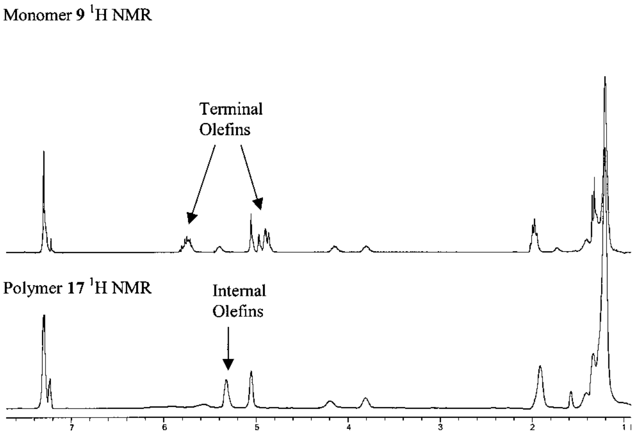

Figure 3. ^{1}H NMR of the monomer **9** and polymer **17** ($CDCl_3$).

by GPC. This polymer is semicrystalline and has a T_m = 135 °C and, like polymer **15**, appears to form a strong film (Figure 2).

Since an amino group is more reactive toward protein binding than a carboxylic acid group, monomer **9** was synthesized with a *N*-carbobenzyloxy (CBZ) protecting group on the terminal amine. This protecting group should be easily removed during the hydrogenation of the polymer backbone with Pd/C. Monomer **9** was polymerized to polymer **17** using a 100:1 ratio of monomer **9** to catalyst **1.** This resulted in another apparently strong film-forming polymer with a $\bar{M}_n$ = 21 000 g/mol. Figure 3 shows the ^{1}H NMR spectra of monomer **9** and polymer **17**. The formation of an internal olefin at 5.4 ppm, as well as the disappearance of the external olefins at 4.9 and 5.75 ppm, typical for ADMET polymerization, is evident by the comparison of the two spectra. Polymer **17** has the potential ability to facilitate the attachment of peptide sequences to polyolefin materials.

Conclusion. The first ADMET polymerization of α,ω-dienes bearing amino acid moieties yielding semicrystalline materials has been described. This method permits the exact placement of amino acid functionality within the polymer chain or as a pendant group along the polymer backbone, which lays the groundwork for the placement of specific peptide sequences into polymers via ADMET chemistry. The branched polymers are strong film-forming materials, and it is noteworthy that the unsaturated branched polymers **14** and **15** have T_m values as high as 135 °C. Circular dichroism and tensile strength studies currently are being pursued, as is the impact of exhaustive hydrogenation on the polymers.

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