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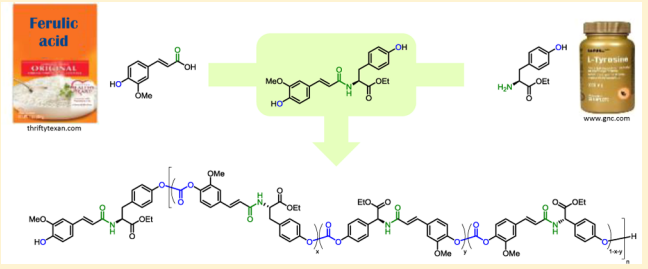
Poly(carbonate−amide)s Derived from Bio-Based Resources: Poly(ferulic acid-*co*-tyrosine)

Amandine Noel, Yannick P. Borguet, Jeffery E. Raymond, and Karen L. Wooley*

Departments of Chemistry and Chemical Engineering and the Laboratory for Synthetic-Biologic Interactions, Texas A&M University, College Station, Texas 77842-3012, United States

Supporting Information

ABSTRACT: Ferulic acid (FA), a bio-based resource found in fruits and vegetables, was coupled with a hydroxyl-amino acid to generate a new class of monomers to afford poly(carbonate−amide)s with potential to degrade into natural products. L-Serine was first selected as the hydroxyl-amino partner for FA, from which the activated *p*-nitrophenyl carbonate monomer was synthesized. Unfortunately, polymerizations were unsuccessful, and the elimination product was systematically obtained. To avoid elimination, we revised our strategy and used L-tyrosine ethyl ester, which lacks an acidic proton on the α position of the ethyl ester. Four new monomers were synthesized and converted into the corresponding poly(carbonate−amide)s with specific regioselectivities. The polymers were fully characterized through thermal and spectroscopic analyses. Preliminary fluorescent studies revealed interesting photophysical properties for the monomers and their corresponding poly(carbonate−amide)s, beyond the fluorescence characteristics of L-tyrosine and FA, making these materials potentially viable for sensing and/or imaging applications, in addition to their attractiveness as engineering materials derived from renewable resources.



INTRODUCTION

Polymers are pervasive throughout all aspects of the modern age and, as described by Rolf Mülhaupt, "without polymers, modern life would be impossible because polymers secure the high quality of life and serve as pacemakers for modern technologies".[1] Consequently, the urge to find renewable resources to reduce consumption of fossil fuel feedstocks, decrease the use of energy intensive products, and solve recycling and/or degradation issues has led to the investigation of biopolymers. Additionally, the increase in fuel costs observed over the past 30 years[2] dictates a transition to polymeric precursors that do not rely expressly on fossil fuels. However, the full life cycle assessment of most bio-based polymers is not well reported, and a focus on the environmental impacts of biopolymers will be necessary.[3] As unrecycled polymers end up in the oceans (estimated 5 billion kg per year),[4] water-degradable polymers such as polycarbonates that degrade into carbon dioxide and diols[5] represent a reasonable class of materials to investigate further.

Polycarbonates are mainly used where toughness, high optical transparency, and solvent resistance are required. Although more stable toward hydrolysis than their polyester counterparts, polycarbonates are able to degrade in water and are, thus, considered as aqueous degradable materials.[6] Strategies for the use of renewables in polycarbonates include polycondensation of feedstock products such as aliphatic diols,[7] ring-opening polymerization of 6-membered cyclic carbonates,[8] epoxides and carbon dioxide-based systems,[9,10] polycondensation of cereal-based products such as 1,4:3,6-isosorbide,[11] and natural phenols to afford copolymers.[12] Noteworthy, biorenewable-based polycarbonates have found applications as powder coating agents[13] and as drug delivery vehicles.[14,15] Previous efforts from our lab have led to the synthesis of polycarbonates derived from both carbohydrates[16] and quinic acid.[17] In an effort to broaden the scope to natural products with biological activities, the present paper describes the synthesis and characterization of high value poly(carbonate−amide)s derived from rather inexpensive ferulic acid and a hydroxyl-amino acid.

It was hypothesized that bio-based poly(carbonate−amide)s derived from FA and a hydroxyl-containing amino acid would possess interesting mechanical properties arising from the rigid conjugated cinnamic acid core of FA and the H-bonding potential of the amino acid component, while also having the potential to undergo hydrolytic breakdown and lead to biologically beneficial byproducts and carbon dioxide. Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA) is a secondary metabolite of the biosynthesis of lignin, derived from phenylalanine and tyrosine via Shikimate pathway.[18] It is found in cereals (ca. 0.3 wt % in wheat bran), fruits, vegetables, and plant tissues. FA can be naturally found in its free form, as monomers, dimers, or polymers but also as esters formed by condensation with hydroxyl acids, alcohols, or saccharides or as

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amides formed by condensation with amines. Because of its antioxidant properties, FA exhibits a wide range of therapeutic effects such as anticancer, antidiabetic, cardio-protective, neuroprotective, and anti-inflammatory activities. It has also found use as a food preservative[18] and has shown antibacterial activity against Gram-negative and -positive bacteria, including the anthrax agent *B. subtilis*.[20] Moreover, FA has been incorporated into a biodegradable polymer as a pendant group to enhance antioxidant properties, specifically for tissue engineering applications.[21,22] Reports of polymers containing FA in the main chain include (co)polyesters,[4,23,24] poly(anhydride−ester),[25] poly(ether ester)s,[26,27] a methacrylic−FA copolymer,[28] and a polyamide.[29] To the best of our knowledge, no FA-based polycarbonates have been reported to date.

EXPERIMENTAL SECTION

Materials. All chemicals and reagents were used as received from Sigma-Aldrich Co or VWR International. *Caution*: special precautions should be taken when working with phosgene precursors, including diphosgene and triphosgene. They are highly toxic by inhalation and ingestion; use of personal protective equipment, including a respiratory mask, is recommended. Tetrahydrofuran (THF) and dichloromethane were purified by passage through solvent purification system (JC Meyer Solvent Systems) and used as dried solvents. Column chromatography was performed on a CombiFlash Rf4x (Teledyne ISCO) with RediSep Rf Column (Teledyne ISCO).

Characterization. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer. Chemical shifts were referenced to the solvent resonance signals. IR spectra were recorded on a Shimadzu IR Prestige attenuated total reflectance Fourier-transform infrared spectrometer (ATR-FTIR) and analyzed using IRsolution v. 1.40 software. Size exclusion chromatography (SEC) measurements were performed on a Waters Chromatography Inc. (Milford, MA) system equipped with an isocratic pump model 1515, a differential refractometer model 2414, and a four-column set of 5 μm Guard (50 × 7.5 mm), Styragel HR 4 5 μm DMF (300 × 7.5 mm), Styragel HR 4E 5 μm DMF (300 × 7.5 mm), and Styragel HR 2 5 μm DMF (300 × 7.5 mm) using DMF (0.05 M LiBr) as the eluent (1.00 mL/min) at 70 °C. Polymer solutions were prepared at a concentration of about 5 mg/mL and an injection volume of 200 μL was used. Data collection and analysis were performed with Empower 2 v. 6.10.01.00 software (Waters, Inc.). The system was calibrated with poly(ethylene oxide) standards (Polymer Laboratories, Amherst, MA) ranging from 106 to 174 000 Da, and an additional internal calibration based on the oligomeric fraction was also realized (Supporting Information, Methods to Monitor the Polymerizations). Glass transition temperatures (T_g) and melting points (m_p) were measured by differential scanning calorimetry (DSC) on a Mettler-Toledo DSC822 (Mettler-Toledo, Inc., Columbus, OH) under N_2. Measurements of T_g were recorded with a heating rate of 15 °C/min, and those for m_p were recorded with a heating rate of 10 °C/min. The measurements were analyzed using Mettler-Toledo Stare v.10.00 software. Thermogravimetric analysis (TGA) was performed under an Ar atmosphere using a Mettler-Toledo model TGA/DSC 1, with a heating rate of 10 °C/min.

UV/vis measurements were acquired on a Shimadzu UV-2550 spectrophotometer. All steady-state emission, excitation, and 3 D spectra were obtained with a Horiba FluoroMax4 with automatic polarizers. Measurements were performed in DMF in matched quartz cuvettes with path lenghts of 1 cm.

Synthesis of (*E*)-*N*-(Feruloyl)-L-tyrosine (8). To a solution of tyrosine ethyl ester hydrochloride (1.57 g, 6.39 mmol) in CH_2Cl_2 (23 mL) were added ferulic acid (1.97 g, 6.39 mmol) and HOBt (863.3 mg, 6.39 mmol). The reaction was cooled down at 0 °C, and Et_3N (2.7 mL, 19.17 mmol) and EDCI (992 mg, 6.39 mmol) were added. The reaction was stirred at room temperature overnight. To the mixture was added a saturated aqueous solution of $NaHCO_3$, and the crude product was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was removed, and the crude product was purified by flash chromatography 0% to 100% of AcOEt in hexane over 40 min (80 g silica cartridge). The solvent was removed to give the desired product as a white foam (1.65 g, 4.28 mmol, 67%). FTIR (ATR) υ_{max} (cm^{-1}): 3600−3150, 1726, 1667, 1514. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.54 (d, J = 15.5 Hz, 1 H), 7.28 (d, J = 0.9 Hz, 1 H), 7.04−6.93 (m, 4 H), 6.89 (dd, J = 8.1, 0.9 Hz, 1 H), 6.78−6.73 (m, 2 H), 6.29−6.24 (m, 2 H), 6.07 (br s, 1 H), 4.99 (dtd, J = 6.7, 5.7, 1.0 Hz, 1 H), 4.21 (q, J = 7.2, 2 H), 3.88 (s, 3 H), 3.16 (dd, J = 14.1, 5.7 Hz, 1 H), 3.08 (dd, J = 14.1, 5.7 Hz, 1 H), 1.29 (t, J = 7.2, 3 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 172.0 (C), 166.0 (C), 155.3 (C), 147.6 (C), 146.7 (C), 142.1 (CH), 130.4 (2 CH), 127.3 (C), 127.0 (C), 122.5 (CH), 117.2 (CH), 115.5 (2 CH), 114.7 (CH), 109.6 (CH), 61.7 (CH_2), 55.9 (CH_3), 53.5 (CH), 37.2 (CH_2), 14.2 (CH_3) ppm. MS (ESI$^+$) m/z (%) 386.2 (100, [M + H]$^+$). ESIHRMS calcd for $C_{21}H_{24}NO_6$ (M+H) 386.1604; found 386.1609; m_p = 70 °C.

Synthesis of Ethyl (*S*)-2-Amino-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (10). To a solution of L-tyrosine ethyl ester chlorohydrate (5.4 g, 22.0 mmol) in THF (110 mL) were added DMAP (536.8 mg, 4.4 mmol), Et_3N (9.2 mL, 65.9 mmol), and TBDMSCl (8.3 g, 54.9 mmol). The reaction was stirred at reflux for 3 h. After cooling down at room temperature, the mixture was filtered and the filtrate was purified by flash chromatography 0% to 100% of AcOEt in hexane over 40 min (80 g silica cartridge). The solvent was removed to give the desired product as a colorless oil (5.8 g, 17.9 mmol, 81%). FTIR (ATR) υ_{max} (cm^{-1}) 1732, 1510. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.04 (d, J = 8.4 Hz, 2 H), 6.76 (d, J = 8.4 Hz, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.66 (dd, J = 7.7, 5.5 Hz, 1 H), 3.00 (dd, J = 13.7, 5.5 Hz, 1 H), 2.81 (dd, J = 13.7, 7.7 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.97 (s, 9 H), 0.18 (s, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 175.1 (C), 154.5 (C), 130.2 (2 CH), 129.8 (C), 120.1 (2 CH), 60.9 (CH_2), 55.9 (CH), 40.4 (CH_2), 25.7 (3 CH_3), 18.2 (C), 14.2 (CH_3), −4.4 (2 CH_3) ppm. MS (ESI$^+$) m/z (%) 324.2 (100, [M + H]$^+$). ESIHRMS calcd for $C_{17}H_{30}NO_3Si$ (M+H) 324.1995; found 324.2004.

Synthesis of Ethyl (*S*,*E*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)-phenyl)-2-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)-propanoate (11). To a solution of **10** (5 g, 15.5 mmol) in CH_2Cl_2 (77 mL) were added ferulic acid (5 g, 15.5 mmol) and HOBt (2.1 g, 15.5 mmol). The reaction was cooled down at 0 °C and Et_3N (4.3 mL, 31.0 mmol) and EDCI (2.4 g, 15.5 mmol). The reaction was stirred at room temperature overnight. To the mixture was added a saturated aqueous solution of $NaHCO_3$ and the crude product was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was removed under vacuum, and the crude product was purified by flash chromatography 0% to 50% of AcOEt in hexane over 50 min (120 g silica cartridge). The solvent was removed to give the desired product as a yellow foam with 10% of **10** (6.39 g, 12.8 mmol, 83%). FTIR (ATR) υ_{max} (cm^{-1}) 3500−3150, 1732, 1657, 1593. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) ^{1}H δ: 7.53 (d, J = 15.6 Hz, 1 H), 7.05−6.94 (m, 5 H), 6.88 (d, J = 8.4 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.25 (d, J = 15.6 Hz, 1 H), 6.19 (d, J = 7.8 Hz, 1 H), 4.96 (dt, J = 7.8, 5.7 Hz, 1 H), 4.17 (qd, J = 7.0, 1.8 Hz, 2 H), 3.88 (s, 3 H), 3.16−3.08 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.96 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.8 (C), 165.6 (C), 154.6 (C), 147.6 (C), 146.8 (C), 141.7 (CH), 130.3 (2 CH), 128.5 (C), 127.0 (C), 122.4 (CH), 120.0 (2 CH), 117.4 (CH), 114.8 (CH), 109.5 (CH), 61.5 (CH_2), 55.8 (CH_3), 53.4 (CH), 37.1 (CH_2), 25.6 (3 CH_3), 18.1 (C), 14.1 (CH_3), −4.5 (2 CH_3) ppm. MS (ESI$^+$) m/z (%) 500.2 (100, [M + H]$^+$); ESIHRMS calcd for $C_{27}H_{38}NO_6Si$ (M+H) 500.2468; found 500.2453; m_p = 47 °C.

Synthesis of Ethyl (*S*,*E*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)-phenyl)-2-(3-(3-methoxy-4-(((4-nitrophenoxy)carbonyl)oxy)-phenyl)acrylamido)propanoate (12). A solution of **11** (2.07 g, 4.14 mmol) and pyridine (3.1 mL, 6.2 mmol) in CH_2Cl_2 (12.5 mL) was added dropwise to a solution of *p*-nitrophenyl chloroformate (1.69 g, 8.28 mmol) in CH_2Cl_2 (25.1 mL). The reaction was stirred at room temperature for 7 h. Water was added, and the crude was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was removed under vacuum. The residue was purified by flash chromatography on a silica cartridge (80 g, hexane/AcOEt 0 to 50%

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over 30 min). The desired product was obtained as a yellow foam (1.95 g, 2.93 mmol, 71%). FTIR υ_{max} (cm^{-1}) 1784, 1738, 1624, 1509. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 8.30 (d, J = 9.2 Hz, 2 H), 7.57 (d, J = 15.5 Hz, 1 H), 7.48 (d, J = 9.2 Hz, 2 H), 7.21 (d, J = 8.7 Hz, 1 H), 7.15−7.09 (m, 2 H), 6.98 (d, J = 8.4 Hz, 2 H), 6.75 (d, J = 8.4 Hz, 2 H), 6.37 (d, J = 15.5 Hz, 1 H), 6.22 (d, J = 7.8 Hz, 1 H), 4.96 (dt, J = 7.8, 5.6 Hz, 1 H), 4.19 (qd, J = 7.1, 2.6 Hz, 2 H), 3.93 (s, 3 H), 3.21−3.05 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.96 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.7 (C), 164.8 (C), 155.4 (C), 154.7 (C), 151.0 (C), 150.2 (C), 145.5 (C), 140.55 (C), 140.50 (CH), 134.5 (C), 130.3 (2 CH), 128.4 (C), 125.4 (2 CH), 122.3 (CH), 121.6 (2 CH), 121.0 (CH), 120.8 (CH), 120.1 (2 CH), 111.5 (CH), 61.6 (CH_2), 56.1 (CH_3), 53.4 (CH), 37.1 (CH_2), 25.6 (3 CH_3), 18.1 (C), 14.2 (CH_3), −4.5 (2 CH_3) ppm; MS (ESI^+) m/z (%) 665.3 (100, $[M + H]^+$). ESIHRMS calcd for $C_{34}H_{41}N_2O_{10}Si$ (M + H) 665.2530; found 665.2519; m_p = 56 °C.

Synthesis of Ethyl (*E*)-(3-(3-Methoxy-4-(((4-nitrophenoxy)-carbonyl)oxy)phenyl)acryloyl)-L-tyrosinate (13). To a solution of **12** (1.74 g, 2.74 mmol) in CH_2Cl_2 (13.7 mL) was added dropwise $BF_3{\cdot}OEt_2$ (0.69 mL, 5.48 mmol). The reaction was stirred at room temperature for 23 h. A saturated solution of $NaHCO_3$ was added, and the crude was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was removed under vacuum. The residue was purified by flash chromatography on a silica cartridge (120 g, hexane/AcOEt 0 to 100% over 40 min). The desired product was obtained as a white foam (1.28 g, 2.33 mmol, 85%). FTIR (ATR) υ_{max} (cm^{-1}) 3300−3150, 1782, 1732, 1661, 1514. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 8.27 (d, J = 9.2 Hz, 2 H), 7.52 (d, J = 15.6 Hz, 1 H), 7.45 (d, J = 9.2 Hz, 2 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.11 (br s, 1 H), 7.03−7.02 (m, 2 H), 6.95 (d, J = 8.4 Hz, 2 H), 6.72 (d, J = 8.4 Hz, 2 H), 6.51 (d, J = 7.9 Hz, 1 H), 6.37 (d, J = 15.6 Hz, 1 H), 4.96 (dt, J = 8.0, 5.7 Hz, 1 H), 4.23−4.16 (m, 2 H), 3.86 (s, 3 H), 3.13 (dd, J = 14.1, 5.7 Hz, 1 H), 3.03 (dd, J = 14.1, 6.2 Hz, 1 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.9 (C), 165.5 (C), 155.5 (C), 155.3 (C), 150.9 (C),150.3 (C), 145.5 (C), 140.9 (C), 140.5 (CH), 134.3 (C), 130.3 (2 CH), 127.0 (C), 125.3 (2 CH), 122.3 (CH), 121.6 (2 CH), 120.74 (CH), 120.67 (CH), 115.5 (2 CH), 111.6 (CH), 61.8 (CH_2), 56.0 (CH_3), 53.7 (CH), 37.0 (CH_2), 14.1 (CH_3) ppm. MS (ESI^+) m/z (%) 551.2 (100, $[M + H]^+$). ESIHRMS calcd for $C_{28}H_{27}N_2O_{10}$ (M + H) 551.1666; found 551.1654.

Synthesis of AA′AA′ Polymer from 13. To a solution of **13** (702 mg, 1.27 mmol) in pyridine (0.42 mL) was added dropwise triethylamine (0.36 mL, 2.55 mmol). The mixture was stirred at room temperature for 5 h and was quenched with a saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and dried over Na_2SO_4, and the solvent was removed. The mixture was solubilized in CH_2Cl_2, precipitated into MeOH three times, and dried under vacuum to give the desired product as a yellowish solid which follows A′AAA′, AA′A′A, AA′AA′ patterns in 22/15/63 proportions (389.5 mg, 0.94 mmol, 74%). DMF SEC: M_n = 5.8 kg mol^{-1}, $Đ$ = 1.43. FTIR (ATR) υ_{max} (cm^{-1}) 3400−3200, 1778, 1736, 1661, 1624, 1508. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.61−7.51 (m, 14 H), 7.23−7.20 (m, 98 H), 6.43−6.23 (m, 28 H), 5.00 (br s, 14 H), 4.23−4.14 (m, 28 H), 3.87 (br s, 42 H), 3.27−3.13 (m, 28 H), 1.32−1.10 (m, 42 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.5 (14 C), 165.1 (14 C), 152.0 (3.1 $C(O)_{A'AAA'}$), 151.3 (8.8 $C_{AA'AA'}$), 151.22 (5.2 $C_{AAA'A'}$), 151.16 (8.8 $C(O)_{AA'AA'}$), 150.7 (2.1 $C(O)_{AA'A'A}$), 150.2 (8.8 $C_{AA'AA'}$), 150.0 (5.2 $C_{AAA'A'}$) 141.1, 141.0, 140.9 (14 CH + 14 C), 134.2, 134.1, 134.0 (28 C), 130.52, 130.49 (28 CH), 122.6 (8.8 $CH_{AA'AA'}$), 122.5 (5.2 $CH_{AAA'A'}$), 120.94, 120.89, 120.8 (28 CH), 120.6 (14 CH), 111.5 (5.2 $CH_{AAA'A'}$), 111.4 (8.2 $CH_{AA'AA'}$), 61.7 (14 CH_2), 56.1 (14 CH_3), 53.3 (14 CH), 37.2 (14 CH_2), 14.2 (14 CH_3) ppm. T_g = 134 °C; T_p = 350 °C.

Synthesis of Ethyl (*S*,*E*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)-phenyl)-2-(3-(4-((chlorocarbonyl)oxy)-3-methoxyphenyl)-acrylamido)propanoate (14). To a solution of **11** (532.5 mg, 1.07 mmol) in CH_2Cl_2 (12 mL) were added diphosgene (79 μL, 0.66 mmol) and a catalytic amount of activated charcoal. The solution was cooled to −45 °C, and *N*,*N*-dimethylaniline (0.24 mL, 1.92 mmol) was added dropwise. The reaction was allowed to stir at −45 °C and then warmed slowly to room temperature and reacted overnight. The salts and activated charcoal were removed by filtration, and the solvent was removed under vacuum. The product was purified by flash chromatography (24 g, 0% to 50% of AcOEt in hexane over 20 min) to lead to a white foam (492.8 mg, 0.88 mmol, 82%). FTIR (ATR) υ_{max} (cm^{-1}): 1790, 1738, 1659, 1632, 1510. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.57 (d, J = 15.6 Hz, 1 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.13−7.06 (m, 2 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.75 (d, J = 8.4 Hz, 2 H), 6.36 (d, J = 15.6 Hz, 1 H), 6.12 (d, J = 7.7 Hz, 1 H), 4.96 (dt, J = 7.7, 5.6 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.91 (s, 3 H), 3.14 (dd, J = 5.6, 2.6 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.97 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.6 (C), 164.7 (C), 154.8 (C), 150.7 (C), 148.9 (C), 141.5 (C), 140.4 (C), 135.0 (CH), 130.4 (2 CH), 128.3 (C), 122.1 (CH), 121.3 (CH), 120.7 (CH), 120.1 (2 CH), 111.5 (CH), 61.6 (CH_2), 56.1 (CH_3), 53.4 (CH), 37.1 (CH_2), 25.6 (3 CH_3), 18.2 (C), 14.2 (CH_3), −4.4 (2 CH_3) ppm.

Synthesis of AA′AA′ Polymer from 14. In the glovebox, a mixture of **14** (198 mg, 0.35 mmol) and AgF (89.4 mg, 0.70 mmol) was prepared. Then outside of the glovebox, acetonitrile (0.14 mL) and pyridine (0.56 mL) were added. The mixture was ventilated with a cartridge containing NaOH to quench fumes of phosgene. The reaction mixture was stirred at room temperature for 15 min and was quenched with a saturated solution of $NaHCO_3$. The mixture was solubilized in DMF, filtered through a pad of Celite, then precipitated out into MeOH three times, and dried under vacuum to give the desired product as a white solid which follows A′AAA′, AA′A′A, AA′AA′ patterns in 5/5/90 proportions (80.9 mg, 0.20 mmol, 57%). DMF SEC: M_n = 8.3 kg mol^{-1}, $Đ$ = 2.08. FTIR (ATR) υ_{max} (cm^{-1}): 3300−3200, 1789, 1737, 1659, 1622, 1510. ^1H NMR spectrum (500 MHz, d_6-DMSO) δ: 8.67−8.47 (m, 20 H), 7.57−7.12 (m, 160 H), 6.72 (d, J = 15.9 Hz, 20 H), 4.68−4.54 (m, 20 H), 4.18−3.98 (m, 40 H), 3.89 (br s, 60 H), 3.20−2.86 (m, 40 H), 1.35−0.94 (m, 60 H) ppm. ^{13}C NMR spectrum (125 MHz, d_6-DMSO) δ: 171.5 (20 C), 164.9 (20 C), 151.7 (2 $C(O)_{A'AAA'}$), 150.94 (16 $C_{AA'AA'}$), 150.88 (4 $C_{AAA'A'}$), 150.8 (16 $C(O)_{AA'AA'}$), 150.4 (2 $C_{AA'A'A}$), 149.4 (20 C), 140.1 (20 C), 138.8 (20 CH), 135.5 (16 $C_{AA'AA'}$), 135.4 (4 $C_{AAA'A'}$), 134.5 (16 $C_{AA'AA'}$), 134.4 (4 $C_{AAA'A'}$), 130.4 (32 $CH_{AA'AA'}$), 130.3 (8 $CH_{AAA'A'}$), 122.7 (20 CH), 122.1 (20 CH), 121.0 (8 $CH_{AAA'A'}$), 120.8 (32 $CH_{AA'AA'}$), 120.3 (20 CH), 111.8 (20 CH), 60.6 (20 CH_2), 56.05 (20 CH_3), 53.8 (20 CH), 36.1 (20 CH_2), 14.0 (20 CH_3) ppm. T_g = 129 °C, T_p = 337 °C.

Synthesis of Diethyl 2,2′-(((2*E*,2′*E*)-3,3′-((Carbonylbis(oxy))-bis(3-methoxy-4,1-phenylene))bis(acryloyl))bis(azanediyl))-(2*S*,2′*S*)-bis(3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-propanoate) (15). To a solution of **11** (1.1 g, 2.2 mmol) and 4-nitrophenyl chloroformate (225.2 mg, 1.1 mmol) in CH_2Cl_2 (2.2 mL), at room temperature was added Et_3N (0.46 mL, 3.3 mmol). The reaction was stirred at room temperature overnight. The solvent was removed under vacuum. The residue was purified by flash chromatography on a silica cartridge (40 g, hexane/AcOEt 0 to 60% over 30 min). The desired product was obtained as a white foam (657.8 mg, 0.64 mmol, 58%, brm: 84%). FTIR (ATR) υ_{max} (cm^{-1}): 1782, 1732, 1667, 1508. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.54 (d, J = 15.6 Hz, 2 H), 7.20 (d, J = 8.7 Hz, 2 H), 7.08−7.05 (m, 4 H), 6.99 (d, J = 8.4 Hz, 4 H), 6.75 (d, J = 8.4 Hz, 4 H), 6.37 (d, J = 7.1 Hz, 2 H), 6.36 (d, J = 15.6 Hz, 2 H), 4.95 (dt, J = 7.9, 5.8 Hz, 2 H), 4.18 (qd, J = 7.1, 2.3 Hz, 4 H), 3.90 (s, 6 H), 3.18−3.01 (m, 4 H), 1.26 (t, J = 7.1 Hz, 6 H), 0.96 (s, 18 H), 0.16 (s, 12 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.4 (2 C), 154.7 (2 C), 151.2 (2 C), 150.7 (C), 141.0 (2 C), 140.7 (2 CH), 134.1 (2 C), 130.3 (4 CH), 128.4 (2 C), 122.5 (2 CH), 120.7 (2 CH), 120.6 (2 CH), 120.0 (4 CH), 111.5 (2 CH), 61.5 (2 CH_2), 56.0 (2 CH_3), 53.5 (2 CH), 37.0 (2 CH_2), 25.6 (6 CH_3), 18.1 (2 C), 14.1 (2 CH_3), −4.5 (6 CH_3) ppm. MS (ESI^+/MALDI) m/z (%) not detected.

Synthesis of Ethyl (*S*)-3-(4-(λ-Oxidanyl)phenyl)-2-((*E*)-3-(4-(((4-((*E*)-3-(((*S*)-1-ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-carbonyl)oxy)-3-methoxyphenyl)acrylamido)propanoate (16). To a solution of **15** (4.76 g, 4.93 mmol) in CH_2Cl_2 (25 mL) was added dropwise $BF_3{\cdot}OEt_2$ (2.5 mL, 19.7 mmol). The reaction was

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stirred at room temperature for 23 h. A saturated solution of $NaHCO_3$ was added, and the crude was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was removed under vacuum. The residue was purified by flash chromatography on a silica cartridge (4 g, hexane/AcOEt 0 to 100% over 15 min). The desired product was obtained as a white foam (2.55 g, 3.2 mmol, 65%). FTIR (ATR) υ_{max} (cm^{-1}): 3600−3100, 1784, 1738, 1661, 1614, 1512. ^1H NMR spectrum (500 MHz, d_8-THF) δ: 8.18 (s, 2 H), 7.53 (d, J = 15.6 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 1.8 Hz, 2 H), 7.17 (d, J = 8.2 Hz, 2 H), 7.12 (dd, J = 8.2, 1.8 Hz, 2 H), 6.97 (d, J = 8.4 Hz, 4 H), 6.66−6.59 (m, 6 H), 4.83 (dt, J = 8.0, 6.3 Hz, 2 H), 4.11 (q, J = 7.1 Hz, 4 H), 3.88 (s, 6 H), 3.05 (dd, J = 13.9, 6.3 Hz, 2 H), 2.96 (dd, J = 13.9, 6.7 Hz, 2 H), 1.20 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, d_8-THF) δ: 172.2 (2 C), 165.3 (2 C), 157.3 (2 C), 152.3 (2 C), 151.1 (C),141.8 (2 C), 140.0 (2 CH), 135.6 (2 C), 130.8 (4 CH), 127.9 (2 C), 123.0 (2 CH), 122.4 (2 CH), 120.7 (2 CH), 115.7 (4 CH), 112.4 (2 CH), 61.3 (2 CH_2), 56.01 (2 CH_3), 54.5 (2 CH), 37.7 (2 CH_2), 14.3 (2 CH_3) ppm. ^1H NMR spectrum (500 MHz, d_6-DMSO) δ: 9.24 (s, 2 H), 8.48 (d, J = 7.7 Hz, 2 H), 7.44−7.37 (m, 4 H), 7.34 (d, J = 8.2 Hz, 2 H), 7.21 (dd, J = 8.4, 1.8 Hz, 2 H), 7.02 (d, J = 8.5 Hz, 4 H), 6.74 (d, J = 15.8 Hz, 2 H), 6.66 (d, J = 8.5 Hz, 4 H), 4.52 (ddd, J = 8.8, 7.7, 5.8 Hz, 2 H), 4.06 (q, J = 7.1 Hz, 4 H), 3.91 (s, 6 H), 2.95 (dd, J = 13.9, 5.8 Hz, 2 H), 2.86 (dd, J = 13.9, 8.8 Hz, 2 H), 1.13 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR spectrum (125 MHz, d_6-DMSO) δ: 171.7 (2 C), 164.8 (2 C), 156.0 (2 C), 150.9 (2 C), 150.4 ($C(O)_{AA'A'A}$),140.1 (2 C), 138.6 (2 CH), 134.5 (2 C), 130.0 (4 CH), 127.0 (2 C), 122.7 (2 CH), 122.3 (2 CH), 120.3 (2 CH), 115.1 (4 CH), 111.9 (2 CH), 60.5 (2 CH_2), 56.1 (2 CH_3), 54.2 (2 CH), 36.2 (2 CH_2), 14.0 (2 CH_3) ppm. MS (ESI^+/APCI/MALDI) m/z not detected.

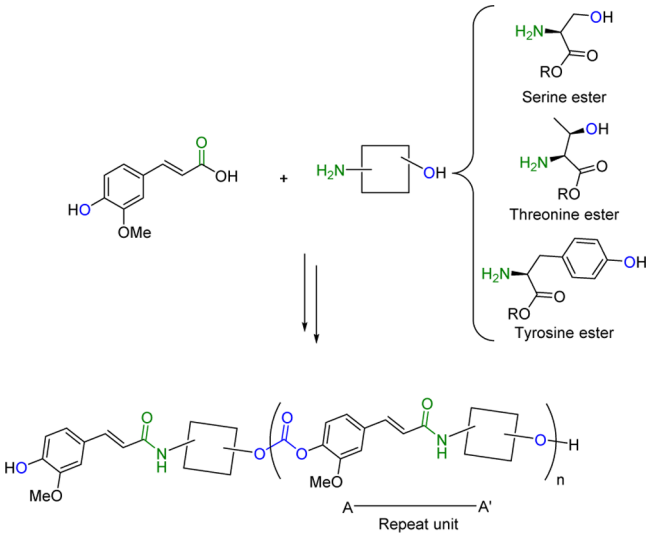
Synthesis of A′AAA′A′AAA′ Polymer from 16. To a solution of **16** (122.1 mg, 0.15 mmol) in pyridine (0.60 mL) at 0 °C was added dropwise diphosgene (21 μL, 0.17 mmol). The mixture was ventilated with a cartridge containing NaOH to quench fumes of phosgene. The reaction mixture was stirred at room temperature for 2 h and was quenched with a saturated solution of $NaHCO_3$. The product was an orange gel which was solubilized in warm DMF/DMSO mixture and precipitated out into MeOH three times and dried under vacuum to give the desired product as a white/yellowish solid which follows an AAA′A′ pattern (91.3 mg, 0.11 mmol, 73%). DMF SEC: M_n = 18.6 kg mol^{-1}, $Đ$ = 2.06. FTIR (ATR) υ_{max} (cm^{-1}): 3400−3200, 1776, 1736, 1667, 1625, 1601, 1504. ^1H NMR spectrum (500 MHz, d_6-DMSO) δ: 8.60 (d, J = 7.6 Hz, 45 H), 7.42 (d, J = 15.6 Hz, 45 H), 7.41−7.24 (m, 315 H), 7.24−7.17 (m, 45 H), 6.72 (d, J = 15.8 Hz, 45 H), 4.61 (q, J = 7.8 Hz, 45 H), 4.06 (q, J = 6.8 Hz, 90 H), 3.90 (s, 135 H), 3.14−2.95 (m, 90 H), 1.11 (t, J = 7.1 Hz, 135 H) ppm. ^{13}C NMR spectrum (125 MHz, d_6-DMSO) δ: 171.5 (45 C), 164.9 (45 C), 151.7 (23 $C(O)_{A'AAA'}$), 150.9 (45 C), 150.4 (22 $C(O)_{AA'A'A}$), 149.4 (45 C), 140.1 (45 C), 138.8 (45 CH), 135.4 (45 C), 134.5 (45 C), 130.3 (90 CH), 122.7 (45 CH), 122.1 (45 CH), 121.0 (90 CH), 120.3 (45 CH), 112.0 (45 CH), 60.6 (45 CH_2), 56.08, 56.06 (45 CH_3), 53.8 (45 CH), 36.1 (45 CH_2), 14.0 (45 CH_3) ppm. T_g = 130 °C, T_p = 343 °C.

Synthesis of the Random Polymer from 8. To a solution of **8** (70.3 mg, 0.18 mmol) in pyridine (0.34 mL) at 0 °C was added dropwise diphosgene (12 μL, 0.10 mmol). The mixture was ventilated with a cartridge containing NaOH to quench fumes of phosgene. The reaction mixture was stirred at room temperature for 15 h and was quenched with a saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and dried over Na_2SO_4, and the solvent was removed under vacuum. The brown film formed was solubilized in CH_2Cl_2, precipitated into MeOH three times, and dried under vacuum to give the desired product as a brownish solid which follows AA′A′A, A′AAA′, AA′AA′ patterns in 37/23/40 proportions (35.4 mg, 0.086 mmol, 48%). During the reaction, a yellow solid part was formed, insoluble in CH_2Cl_2, $CHCl_3$, pyridine, DMF, DMSO, acetone, and H_2O even after sonication and heating. This insoluble fraction could not be analyzed and consequently may explain the lower yield observed. DMF SEC: M_n = 14.8 kDa, $Đ$ = 2.57. FTIR (ATR) υ_{max} (cm^{-1}): 3400−3200, 1778, 1732, 1666, 1628, 1504. ^1H NMR spectrum (500 MHz, $CDCl_3$) δ: 7.53 (br d, J = 15.0 Hz, 36 H), 7.22−6.93 (m, 238 H), 6.47−6.22 (m, 72 H), 5.04−4.93 (m, 36 H), 4.18 (br q, J = 7.2, 6.5 Hz, 72 H), 3.86 (br s, 108 H), 3.28−3.11 (m, 72 H), 1.42- 1.02 (m, 108 H) ppm. ^1H NMR spectrum (500 MHz, d_6-DMSO) δ: 8.60 (br d, J = 7.7 Hz, 36 H), 7.47−7.15 (m, 252 H), 6.76−6.65 (m, 72 H), 4.64−4.57 (m, 36 H), 4.10−4.01 (m,72 H), 3.89 (br s, 108 H), 3.17−2.93 (m, 72 H), 1.11 (br t, J = 7.1 Hz, 108 H) ppm. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ: 171.5 (36 C), 165.1 (36 C), 152.0 (8.3 $C(O)_{A'AAA'}$), 151.3 (14.4 $C_{AA'AA'}$), 151.1 (21.6 $C_{AAA'A'}$), 150.7 (14.4 $C(O)_{AA'AA'}$), 150.2 (13.3 $C(O)_{AA'A'A}$), 150.0 (36 C), 141.1, 141.0, 140.9 (36 CH + 36 C), 134.1, 134.0 (72 C), 130.52, 130.49 (72 CH), 122.6 (14.4 $CH_{AA'AA'}$), 122.5 (21.6 $CH_{AAA'A'}$), 120.94, 120.89, 120.8 (72 CH), 120.6 (36 CH), 111.4 (21.6 $CH_{AAA'A'}$), 61.8 (36 CH_2), 56.1 (21.6 $CH_{3AAA'A'}$), 56.0 (14.4 $CH_{3AA'AA'}$), 53.3 (36 CH), 37.2 (36 CH_2), 14.2 (36 CH_3) ppm. ^{13}C NMR spectrum (125 MHz, d_6-DMSO) δ: 171.4 (34 C), 165.9 (34 C), 151.6 (8.3 $C(O)_{A'AAA'}$), 150.93 (14.4 $C_{AA'AA'}$), 150.87 (21.6 $C_{AAA'A'}$), 150.8 (14.4 $C(O)_{AA'AA'}$), 150.3 (13.3 $C(O)_{AA'A'A}$), 149.4 (36 C), 140.1 (36 C), 138.7 (36 C), 135.5 (14.4 $C_{AA'AA'}$), 135.4 (21.6 $C_{AAA'A'}$), 134.44 (14.4 $C_{AA'AA'}$), 134.38 (21.6 $C_{AAA'A'}$), 130.4 (28.8 $CH_{AA'AA'}$), 130.3 (43.2 $CH_{AAA'A'}$), 122.6 (36 CH), 122.1 (36 CH), 121.0 (43.2 $CH_{AAA'A'}$), 120.8 (28.8 $CH_{AA'AA'}$), 120.3 (36 CH), 111.9 (21.6 $CH_{AAA'A'}$), 111.8 (14.4 $CH_{AA'AA'}$), 60.6 (36 CH_2), 56.1 (36 CH_3), 53.8 (36 CH), 36.1 (36 CH_2), 14.0 (36 CH_3) ppm. T_g = 135 °C, T_p = 343 °C.

RESULTS AND DISCUSSION

We envisioned that the poly(carbonate−amide)s could be synthesized readily either by copolycondensation of a diol with a phosgene derivative or by homopolycondensation of an AB monomer obtained by prior conversion of one of the alcohol groups to an activated carbonate or chloroformate. The required diol monomer would first be obtained by coupling FA to a hydroxyl-containing amino acid by means of a peptidic bond (Scheme 1). This approach would enable degradation to occur via two distinct pathways: aqueous hydrolysis of the carbonate bond and enzymatic cleavage of the amide bond.[30] Among the naturally occurring amino acids, serine, with its more reactive primary alcohol, was expected to be the most attractive coupling partner, followed by threonine, which contains a less reactive secondary alcohol, and finally tyrosine, which features a phenolic functionality that could lead to solubility issues for high molecular weight polymers.

Scheme 1. Peptidic Coupling between FA and Protected Hydroxyl-Amino Acids



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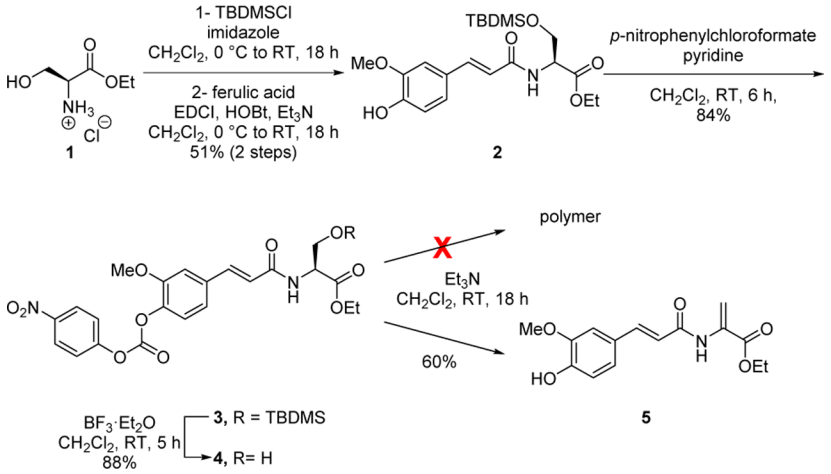
Scheme 2. Synthesis of the Activated AB Monomer 4 and Attempted Polymerization, with Instead the Product from Elimination Being Formed



First Strategy: FA–Serine Poly(carbonate–amide) Precursor. An AB monomer activated as a *p*-nitrophenyl carbonate **4** was initially designed, as the polymerization of similar species has been reported in the literature.[31] This monomer was preferred to its more reactive chloroformate analogue because the synthesis of the latter requires the manipulation of phosgene derivatives.

The monomer synthesis began from the commercially available L-serine, which was protected as its ethyl ester. The esterification resulted in **1** (92%).[32] This protection step was necessary to selectively convert the hydroxyl group to a silyl ether derivative and also for the later selective amidation with ferulic acid (Scheme 2). The TBDMS protecting group is cleavable under mild acidic conditions and was chosen for its stability under basic conditions used in the following steps. A peptidic coupling of this intermediate with ferulic acid generated **2** in two steps (51%). The structure was confirmed by the presence of a signal attributed to the quaternary carbon peak of the amide by ^{13}C NMR (165.8 ppm) and by FTIR (1658 cm^{-1}) spectroscopies. The *p*-nitrophenyl carbonate **3** was synthesized in 84% yield by reaction of the phenol with *p*-nitrophenyl chloroformate in the presence of pyridine. Subsequent deprotection by boron trifluoride provided the activated AB monomer **4** (88%). Formation of the carbonate link in **3** and **4** was confirmed by both ^{13}C NMR (150.3 ppm) and FTIR (1778, 1784 cm^{-1}) spectroscopies. A doublet of triplets at 2.49 ppm by ^{1}H NMR spectroscopy, as well as a broad band around 3200–3400 cm^{-1} by FTIR spectroscopy, confirmed the presence of a free alcohol in **4**. Experimental details are reported in the Supporting Information.

Unfortunately, rather than undergoing polymerization, **4** led to an elimination product **5** upon treatment with base. No reaction occurred during our first attempt at polymerizing monomer **4** in the presence of pyridine, and the starting material was recovered unchanged. The use of a stronger base, triethylamine, did not lead to a polymer either. Instead, the elimination product **5** was obtained. Further details confirming the structure of the former compound are presented in the Supporting Information.

Alternatively, the introduction of the activated *p*-nitrophenyl carbonate on the primary alcohol of the serine residue was not attempted. We reasoned that the presence of such an electron-withdrawing group would most likely enhance the acidity of the proton on the α-carbon of the amino acid residue, favoring the elimination pathway. Therefore, the choice of the hydroxyl-amino acid was reconsidered.

Second Strategy: FA–Tyrosine Poly(carbonate–amide) Precursors. Tyrosine was selected over threonine in order to avoid any possible side reaction on the α-carbon of the amino acid residue in the activated monomer. In an attempt to minimize the toxicity of the products potentially released during degradation of the polymers, the commercially available L-tyrosine ethyl ester, which would generate ethanol upon hydrolysis, was used as a starting building block (rather than use of a methyl ester that would generate methanol). Interestingly, the natural amides (*E*)-*N*-(feruloyl)-L-tyrosine methyl ester **6** and *tert*-butyl ester **7** have already been synthesized and tested biologically (Figure 1).[33] A stronger

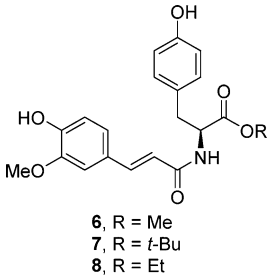


Figure 1. Structures of the known **6**, **7**, and the new **8**.

antioxidant effect was revealed for the more sterically hindered *tert*-butyl ester when compared with the methyl ester, and both surpassed ferulic acid in lipid peroxidation assays.[33] The anticipated hydrolytic degradation product of a FA–tyrosine-based poly(carbonate–amide) system, (*E*)-*N*-(feruloyl)-L-tyrosine ethyl ester **8** (Figure 1), may, therefore, present a bioactivity similar to its methyl and *tert*-butyl counterparts. Based upon this strategy, a series of four monomers were synthesized, having functionalities installed that would allow for condensation polymerization via carbonate formation and including regiochemistries that would produce either head-to-tail, tail-to-head-to-head-to-tail, or random sequences in the resulting poly(carbonate–amide)s.

BA′ Monomers: Targeting an AA′AA′ (Head-to-Tail) Polymer Regiochemistry. A monoactivated BA′ monomer

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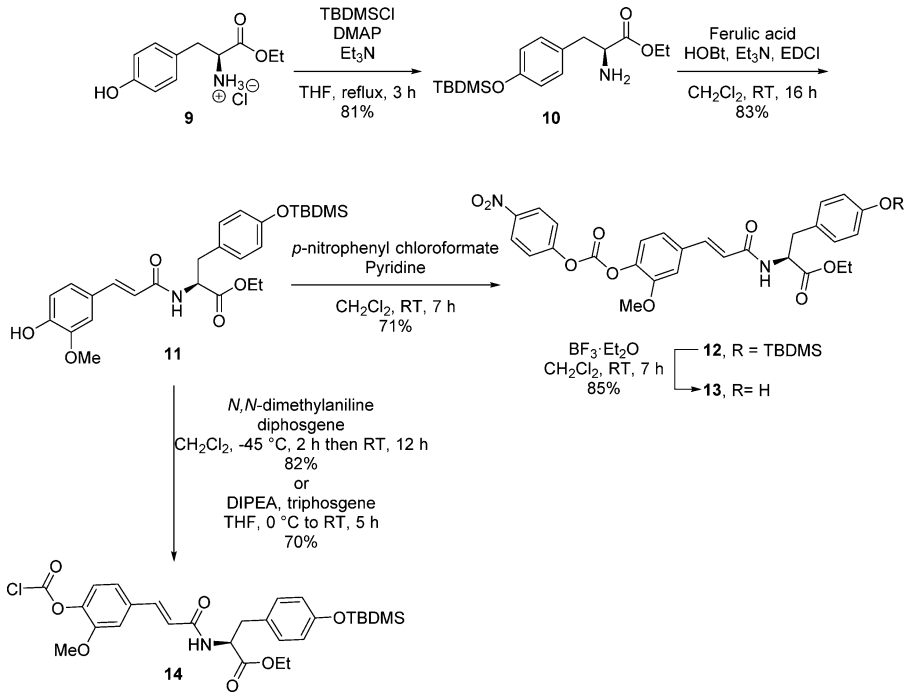
Scheme 3. Synthesis of BA′ Monomers Activated with *p*-Nitrophenyl Carbonate (13) and Chloroformate (14) Functionalities



was initially designed in order to synthesize a regioregular AA′AA′ (head-to-tail) polymer, where A is the phenol of FA, A′ is the phenol of tyrosine, and B is an activated carbonate or chloroformate derivative of the FA phenol. The *p*-nitrophenyl carbonate BA′ monomer **13** was targeted first using the same synthetic pathway as described above for **4**. The phenol group of the tyrosine ethyl ester hydrochloride **9** was protected with TBDMSCl, resulting in **10** (81%).[34] A peptidic coupling between **10** and FA generated **11** (83%). The free alcohol of **11** was activated to a *p*-nitrophenyl carbonate **12** in the presence of pyridine (71%). Finally, the deprotection of **12** under mild conditions afforded the activated BA′ monomer **13** in high yield (85%). ^{13}C NMR and FTIR spectroscopies confirmed both the formation of the carbonate and the deprotection of the phenol group (Scheme 3).

Polymerizations were conducted in the presence of a base to generate the nucleophilic phenoxide group. Optimization of the experimental conditions was performed through variation of the solvents (CH_2Cl_2 and pyridine), the initial monomer concentration (1 M, 3 M), the base (Et_3N, pyridine, DIPEA, DMAP or a mixture), the reaction times (5 to 72 h), and temperatures (rt, 50 °C, 95 °C). The outcomes of the reactions were evaluated in terms of the final degree of polymerization (DP_n), as determined by SEC. The reliability of the number-average molecular weights (M_n) determined against PEO calibration was confirmed by comparison with the M_n obtained from a relative calibration performed from the oligomeric fraction contained in the crude polymerization mixture (Table S1, see details in Supporting Information). Also, chain-end functionalization of the polymers with reactive capping agents (allylchloroformate and furfuryl isocyanate) and their subsequent analysis by ^{1}H NMR spectroscopy gave further support to the DP_n values that are reported and also revealed that the primary component of the system is an acyclic polymer (see details in Supporting Information). Despite parametrization, all the reactions resulted in polymers with DP_n values limited to a range of 15−20, according to SEC and ^{1}H NMR spectroscopic measurements. One of the samples was further characterized by ^{13}C NMR spectroscopy to obtain insight into the regioselectivity of the polymerizations. Surprisingly, the analysis of the spectrum showed evidence of the formation of all three possible regioisomers (head-to-tail, head-to-head, tail-to-tail) in the isolated polymer (*vide infra*), instead of the expected AA′AA′ (head-to-tail) regiospecificity as implied by monomer design. The poor regioselectivity and the limited DP_n achieved can plausibly be explained by the release of a *p*-nitrophenolate, which may act as an additional nucleophile able to attack the polymeric carbonyl-based backbone and promote exchange reactions or by the insufficient difference in the leaving group ability of *p*-nitrophenol and the FA phenol.

In an attempt to minimize regiorandomness and achieve higher DP_n, the alcohol **11** was converted to the more reactive chloroformate **14** by reaction with either diphosgene,[35] which gave the best yield (82%), or triphosgene[36] (70%) (Scheme 3). Despite the lower yield, triphosgene was preferred because of its ease of use. The presence of a chloroformate functionality in **14** was confirmed by ^{13}C NMR (148.9 ppm) and FTIR (1790 cm^{-1}) spectroscopies. Interestingly, this new BA′ monomer, designed to generate a polymer with higher regioregularity and molecular weight, was obtained in only three synthetic steps. The polymerization was then triggered by the deprotection of the phenol silyl ether, which generated the propagating nucleophile in a single sequence.

Several sources of fluoride such as tetrabutylammonium fluoride, potassium fluoride, cesium fluoride, and silver fluoride were evaluated for the deprotection of the silyl ether to the phenolate. Among them, silver fluoride, which drove the reaction by precipitation of silver chloride, was the most promising and afforded oligomers. The screening of solvents (pyridine, pyridine/CH_3CN, THF/CH_3CN, or CH_3CN) revealed the necessity of both CH_3CN (AgF solubility) and pyridine (polymer solubility) to achieve polymerization. The use of 2 equiv of AgF proved necessary to obtain high DP_n values, whereas higher loadings complicated the purification

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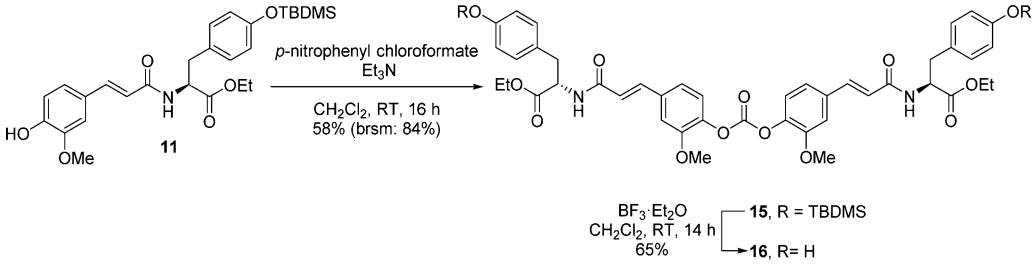
Scheme 4. Synthesis of the A′AAA′ Monomer as the Dimer 16 from 11



process. Although no effect of the reaction temperature (rt vs 60 °C) was observed, a marked effect of the initial monomer concentration was noticed. In dilute media (0.1 M) only small oligomers were formed (Supporting Information, Table S3, entry 1) while some precipitate was noticeable at 0.5 M (entry 3), and the reaction mixture almost instantaneously crashed out of solution at even higher concentration (0.75 M, entry 4). A kinetic study was performed at an intermediate concentration of 0.5 M (entries 5−8). After 1.5 h, a polymer of M_n = 11.1 kg mol^{-1} ($Đ$ = 1.92) was extracted with a low yield (14%) from the heterogeneous reaction mixture. Reduction of the reaction time down to 15 min facilitated the work-up and led to a polymer of M_n = 8.3 kg mol^{-1} ($Đ$ = 2.08, DP_n = 20) with a decent yield (56%). The corresponding polymers exhibited a high degree of AA′AA′ (head-to-tail) regioselectivity as inferred from ^{13}C NMR spectroscopic measurements.

A′AAA′ Monomer: Targeting an A′AAA′A′AAA′ (Tail-to-Head-to-Head-to-Tail-to-Tail-to-Head-to-Head-to-Tail) Regioregular Polymer, Abbreviated as AAA′A′. With the AA′AA′ polymer in our hands, we then sought to synthesize the AAA′A′ polymer with a high regioselectivity by polycondensation of the dimeric monomer **16**. The A′AAA′ monomer **16** was obtained from **11** by dimerization, using *p*-nitrophenyl chloroformate as an activating reagent, followed by deprotection of the phenol groups under mild conditions (Scheme 4). The initial formation of the carbonate bond between the two FA subunits in **16** was performed because of the potentially lower reactivity of the corresponding phenols during the polymerization process (steric hindrance of the *o*-methoxy group). Also, this strategy allowed for ready attribution of the peak at 150.4 ppm to the carbonate in an A′AAA′ sequence in the ^{13}C NMR spectrum, which is necessary to quantify the relative ratio of regioisomers in the polymers.

The desired AAA′A′ polymer was obtained by polycondensation of the diphenol **16** with a phosgene derivative. A first set of experiments performed in pyridine, which acted as a base and solvent, revealed that neat diphosgene was more effective at promoting polycondensation than was triphosgene. Optimization of the reaction conditions, such as the initial monomer concentration, the diphosgene feed ratio, and the reaction time, led to the isolation of a high molecular weight AAA′A′ polymer of M_n = 18.0 kg mol^{-1} ($Đ$ = 2.06, DP_n = 44) in 2 h with 74% yield (Supporting Information, Table S4). Detailed ^{13}C NMR spectroscopic analyses revealed the presence of only two signals attributed to carbonate groups (150.4 and 151.7 ppm for the FA−FA carbonate of the monomer A′AAA′ and the newly established tyrosine−tyrosine carbonate AA′A′A sequences, respectively) which confirmed the high regioselectivity of the AAA′A′ polymer (Figure 2).

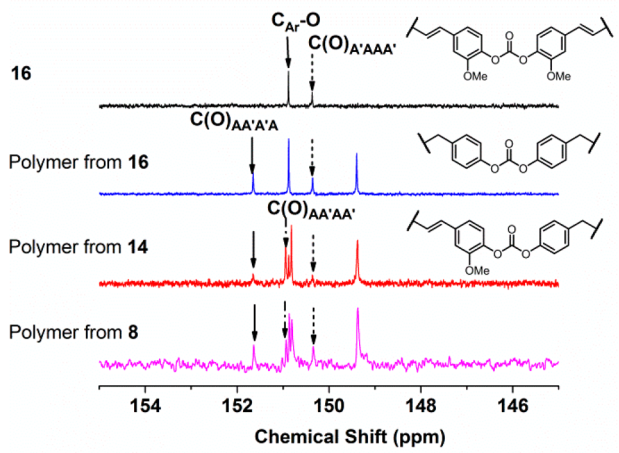
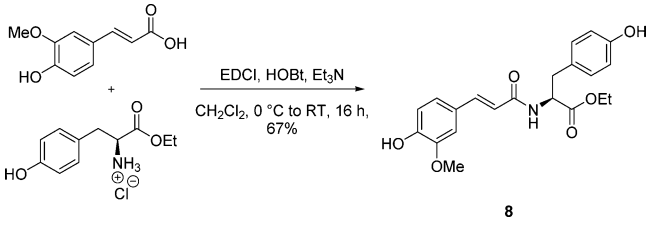


Figure 2. ^{13}C NMR attribution of carbonyl carbons corresponding to the carbonate functionalities of the FA−FA coupling A′AAA′ in monomer **16** (black), the newly established tyrosine−tyrosine couplings AA′A′A of the resulting polymer (blue), the predominance of FA−tyrosine couplings AA′AA′ from the polymerization of **14** and all three types of carbonate carbonyls from the random couplings of FA and tyrosine groups during the polymerization of **8**.

AA′ Monomer: Straightforward Access to a Regiorandom Polymer. In order to fully realize a FA-*co*-tyrosine strategy for the generation of bio-derived poly(carbonate−amide)s, it was of interest to develop a shorter monomer synthesis. The so-called AA′ monomer **8** was obtained in only one step (67%) by peptidic coupling of commercially available FA and L-tyrosine ethyl ester hydrochloride (Scheme 5). The formation of the amide linkage in **8** was confirmed by spectroscopic characterization.

Scheme 5. Synthesis of the AA′ Monomer 8



Polymerization conditions were based on those employed during the polymerization of monomer **16**; modifying the diphosgene equivalency, the global concentration and the reaction time, a polymer of M_n = 14 kg mol^{-1} ($Đ$: 2.57, DP_n = 34) was obtained (47%) (Supporting Information, Table S5). The relative ratio of the three types of carbonates, having tyrosine−tyrosine, FA−FA, and tyrosine−FA couplings,

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Table 1. Characterization of the Polymers Synthesized

entry	polymer	$M_{n,PEO}$[a] (kg mol^{-1})	$M_{n,OLIGO}$[b] (kg mol^{-1})	$(DP_n)_{SEC}$[b]	$Đ$	T_g[c] (°C)	T_p[d] (°C)	yield (%)	proportion AA′A′A:A′AAA′:AA′AA′[d]
1	AA′AA′ from **13**	5.5	5.8	14	1.43	134	350	74	22:15:63
2	AA′AA′ from **14**	8.5	8.3	20	2.08	129	337	57	5:5:90
3	AAA′A′	17.7	18.6	44	2.06	130	343	73	50:50:0
4	random	14.6	14.8	34	2.57	135	343	48	37:23:40

[a]Determined by SEC (DMF, 0.05 M LiBr) using PEO standards. [b]Determined by SEC (DMF, 0.05 M LiBr) using oligomer calibration. [c]Determined by DSC. [d]Determined by TGA. [e]Determined by ^{13}C NMR spectroscopy.

AA′A′A, A′AAA′, and AA′AA′ sequences, respectively, present in the polymer was found to be 37:23:40, as determined by the integration of the ^{13}C NMR signals of the carbonate carbonyl carbon (Figure 2). It is clear that the AA′A′A and AA′AA′ sequences are more prevalent than the A′AAA′ sequence in the regiorandom polymer sample. This lack of true regiorandomness could be rationalized by a lower reactivity of the phenolic group from the FA subunit *vs* the one from the tyrosine residue during polycondensation because of a higher steric hindrance. A summary of the properties of this regiorandom polymer is provided Table 1, entry 4.

Thermal Analysis. The thermal stability of all four polymers has been assessed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (Table 1). The nominal difference observed in the glass transition temperature (129 °C < T_g < 135 °C) and the first derivative TGA peak (337 °C < T_p < 351 °C) for each of the polymers under investigation reveals that the thermal properties were not influenced by the regiochemistry. The thermal stability of a representative polymer sample (AA′AA′ polymer from **13**) was compared to the monomer (**8**)/multimer (**16**) and the starting materials (Figure 3). As expected, the AA′ and A′AAA′

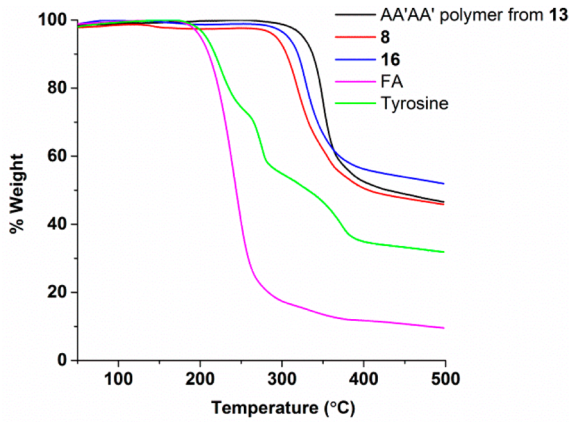

Figure 3. Thermogravimetric analysis of AA′AA′ polymer from **13**, AA′ monomer **8**, A′AAA′ monomer **16**, FA, and tyrosine.

monomers (**8** and **16**, respectively) were less thermally stable than the polymer (318 and 328 °C, respectively) and more stable than the L-tyrosine ethyl ester (224, 276, and 375 °C) and FA (243 °C). High residual masses were observed at 500 °C for all polymers as well as for monomer **8** and multimer **16**. This stability may plausibly be explained by the formation of highly conjugated structures.

Fluorescence Properties. Fluorescent properties of FA and tyrosine have been investigated in the past, and these compounds have been used as probes for assessing intermolecular interactions[37,38] as well as FA proportion and disposition in food.[39] A recent study of tyrosine's three-dimensional emission spectra provided a way to distinguish tyrosine from tryptophan, which can find applications in the analysis of deep sea chemistries.[40] Because of these fluorescent properties in the starting materials (Supporting Information, Figures S4 and S5), a comparison of absorbance, excitation, and emission spectra of the AA′ monomer **8** and the random polymer was obtained, revealing a shift in the maximum wavelength in the emission spectra from 394 nm (**8**) to 427 nm (random polymer from **8**) (Figure 4). These initial results displayed a variation in the fluorescence properties of the monomer and the polymer. This red-shift to a material that is suited to 350 nm excitation and 430 nm emission regimes makes the emissivity of the random polymers viable for their immediate use as imaging agents, employing one of the most common imaging modalities in microscopy (DAPI filter set).[41]

CONCLUSIONS

The design and synthesis of a poly(carbonate−amide) based on FA, a renewable and biocompatible resource present in fruits and vegetables, has been reported. In order to generate a poly(carbonate−amide) by polycondensation, FA was coupled to a hydroxyl-amino acid via an amide link. An activated monomer based on the FA−L-serine couple was synthesized but failed to polymerize. Moving to an L-tyrosine partner led to the generation of an array of new FA−tyrosine monomers and copolymers. A good overall control of the regioselectivity of the resulting polymers was achieved by careful design of the monomers and led to the synthesis of poly(carbonate−amide)s possessing head-to-head, tail-to-tail, and head-to-tail sequences in a nearly regiospecific fashion. Additionally, a regiorandom poly(carbonate−amide) was generated from the easily synthesized AA′ monomer **8**. Although the glass transition and thermal degradation properties of the FA−tyrosine-based poly(carbonate-amide)s (T_g and T_p) were not significantly influenced by the regioselectivity or the chain length, preliminary results on the fluorescent properties showed a shift in the maximum of the excitation and emission spectra between the AA′ monomer **8** and the corresponding random polymer. Further fluorescence studies are underway to probe the imaging promise of this new class of bio-derived poly(carbonate−amide)s. It is envisioned that bio-based poly(carbonate−amide)s derived from FA and a hydroxyl-containing amino acid could potentially undergo hydrolytic breakdown and lead to biologically beneficial byproducts and carbon dioxide. Moreover, the rigidity of both FA and tyrosine subunits as well as the polar, hydrogen-bonding amide groups may lead to materials with enhanced mechanical properties. Degradation and mechanical properties testing experiments are underway. Specifically, applications would include engineering plastics, biomedical components, and other applications where mechanical strength and degradation are both desired.

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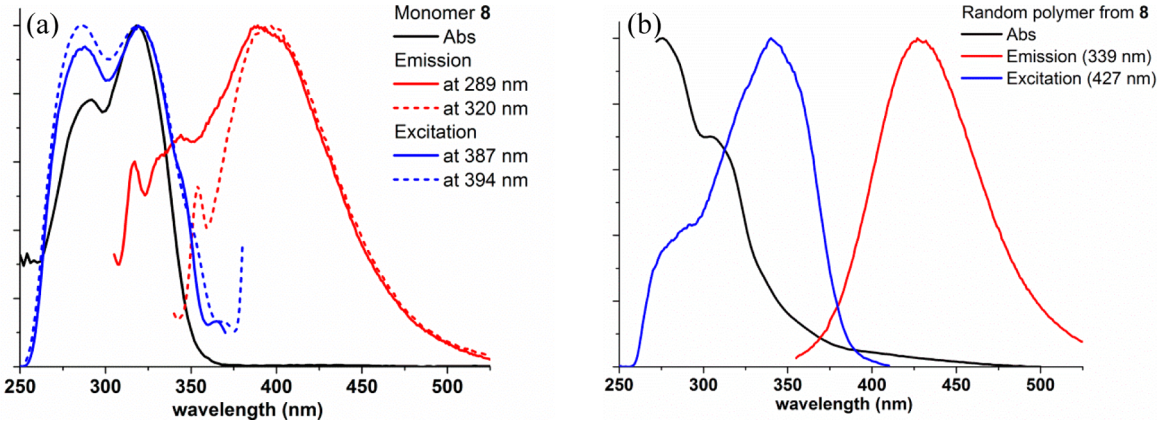

Figure 4. Absorbance, excitation, and emission spectra for (a) monomer **8** and (b) the corresponding regiorandom polymer.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental, characterization, and spectroscopic information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wooley@chem.tamu.edu (K.L.W.).

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

brsm, based on recovered starting material; DSC, differential scanning calorimetry; equiv, equivalent; DP_n, degree of polymerization; FA, ferulic acid; M_n, number-average molecular weights; NMR, nuclear magnetic resonance; PEO, poly(ethylene glycol); SEC, size-extrusion chromatography; TGA, thermogravimetric analysis.

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