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Article

Synthesis and Comprehensive Characterization of Amino Acid-Derived Vinyl Monomer Gels

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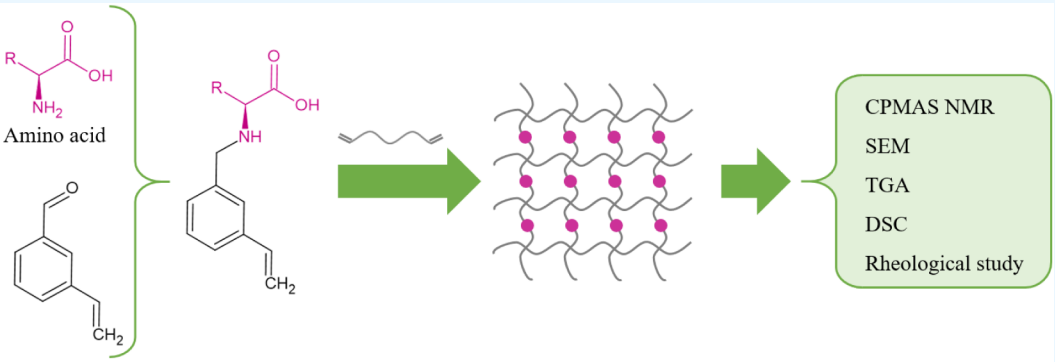

ABSTRACT: In this study, we report an easy synthetic pathway to vinyl monomers derivatized with amino acids. Tyrosine-, phenylalanine-, tryptophan-, leucine-, and methionine-based monomers were synthesized, and their polymerization in the presence of cross-linking agents led to the formation of amino acid-based gels. The nature of cross-linker, the time of polymerization, and the type of initiation (photopolymerization or thermopolymerization) were investigated. The obtained gels were characterized using a combination of thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), rheology, scanning electron microscopy (SEM), and solid-state nuclear magnetic resonance (NMR) spectroscopy. These novel amino acid-based gels could find applications in various areas such as drug delivery, biosensing, and biotechnology.

INTRODUCTION

Polymer gels have been used in various fields of science due to their numerous properties, and they can be natural or synthetic.[1] Gels made from natural polymers, such as cellulose, collagen, or chitosan, often present biocompatibility, biodegradability, or biological activity to the detriment of mechanical strength.[2] On the other side, synthetic polymer gels such as poly(ethylene glycol), poly(vinyl alcohol), poly(methyl methacrylate), and polyurethanes can have better mechanical strength and stability but generally do not exhibit bioactivity.[3] That is why, there is a growing interest in including biological moieties to synthetic chains, in order to gather qualities from both sides.[4]

Over the past few years, amino acids have received an increasing interest as biomaterials for functional polymers.[5,6] Due to the variety of functional groups present in amino acids and their general biocompatibility,[7] they are looked upon in the fields of drug delivery,[8,9] tissue engineering,[10] and regenerative medicine.[11,12] Amino acid-based polymers can also display interesting properties such as fluorescence,[13] chiral recognition,[8] or pH-responsive characteristics[14] that make them of particular interest in the development of biosensors.[15]

Although the use of nonmodified amino acids as monomers in peptide-like polymers can provide good biodegradability,[16] it is sometimes of interest to use more stable and resistant materials since the amide bond in peptide-like polymers is sensitive to the change in pH, temperature, oxido-reductive compounds, or enzymatic activity. Polymer chains made from monomers linked with C−C bonds through free radical polymerization are very stable and resistant to physicochemical changes in the media. So, it appears interesting to modify amino acid with vinylic moieties,[17,18] grafted either on the N-terminal ($-NH_2$) or on the C-terminal (COOH) end, which would then provide monomers with both amino acid functionality and C−C bond stability when polymerized.

The copolymerization with cross-linking agents allows the formation of robust reticulated networks resulting in the formation of gels with good mechanical strength.[19] These polymer networks present better mechanical, thermal, and chemical stability than their non-cross-linked counterparts.

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Although covalent cross-linking significantly increases the stability of the gels, it leaves enough reactivity for them to show interesting properties such as volume-phase transition when exposed to variation in conditions like temperature, pH, solvent, and more.[20]

In this study, we report an easy synthetic route for the fabrication of amino acid-based vinylic monomers, their reticulated polymerization into solid gels, and the characterization of those gels by SEM, TGA, DSC, rheology, and solid-state NMR.

MATERIAL AND METHODS

Reagents. L-Tyrosine, L-phenylalanine, L-tryptophan, L-methionine, L-leucine, 3-vinylbenzaldehyde, sodium hydroxide (NaOH), sodium borohydride ($NaBH_4$), azobis-(isobutyronitrile) (AIBN), and acetic acid were all purchased from Sigma-Aldrich and used as received. Methanol (MeOH), ethanol (EtOH), and diethyl ether were purchased from Carlo Erba and used as received. Ethylene glycol dimethacrylate (98%, 90−110 ppm monomethyl ether hydroquinone) (EGDMA) and 3-(acryloyloxy)-2-hydroxypropyl methacrylate (200 ppm monomethyl ether hydroquinone, 350 ppm BHT as an inhibitor) (AHPMA) were purchased from Sigma-Aldrich and purified on neutral alumina before use. $(CD_3)_2SO$ was purchased from Eurisotop and used as received.

Monomer Synthesis. The synthetic protocol is inspired by the one reported by Narita and Akiyama.[21] Schematic representations of the reaction are presented in Figure 1. In

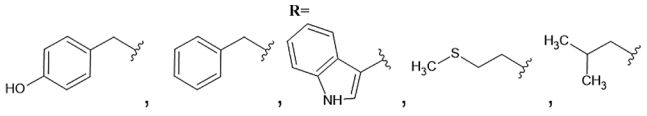
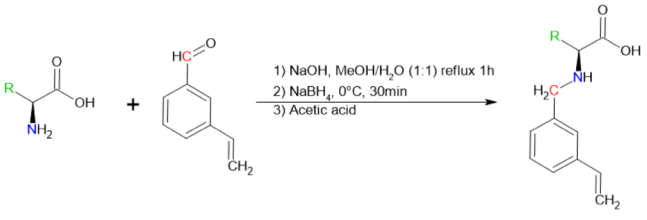


Figure 1. Reductive amination of 3-vinylbenzaldehyde and amino acids.

a typical experiment, 7.5 mmol of amino acid, 0.6 g of sodium hydroxide, and 7.7 mmol of 3-vinylbenzaldehyde were solubilized in 35 mL of a mixture of 1:1 water/methanol. The mixture was refluxed for 1 h before cooling to 0 °C after which 0.6 g of sodium borohydride was added and agitated for 30 min. Acetic acid was slowly added until the isoelectric point of the amino acid was reached. The white powder that precipitated was filtered and washed with water and then with diethyl ether. The solid was dried and stored at room temperature. Structure and purity were confirmed by NMR spectroscopy. Mass of the products was confirmed by mass spectrometry (MS).



Polymerization Protocol. 0.8 mmol of monomer, 2.4 mmol of cross-linker, and 0.3 mmol of AIBN were solubilized in 5 mL of a mixture (2:3) of 1 M NaOH aqueous solution and ethanol. The mixture was degassed by bubbling with argon for 30 min at 0 °C. The polymerization was initiated by UV (365 nm) irradiation at 0 °C or by heating as described in Table 1. The obtained gels were stored in excess of solvent.

Table 1. Synthesis Conditions of the Studied Gels

polymer	monomer	cross-linker	solvent (mL)	initiation
	0.8 mmol	2.4 mmol	5 mL	0.3 mmol AIBN
P1	**1**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P2	**2**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P3	**3**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P4	**4**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P5	**5**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P-Mix	equimolar mixture of **1** to **5**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P1-AHPMA	**1**	AHPMA	(2:3) 1 M NaOH/EtOH	UV 5 h
P4-T	**4**	EGDMA	(2:3) 1 M NaOH/EtOH	60 °C overnight
P2-2h	**3**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 2 h
P2-8h	**3**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 8 h
P2-14h	**3**	EGDMA	(2:3) 1 M NaOH/EtOH	UV 14 h

Instruments and Analysis. ^1H and ^{13}C NMR spectroscopy of monomers was performed on a JEOL JNM-ECZR 500 MHz spectrometer to confirm structure and purity. Monomers were solubilized in $(CD_3)_2SO$.

MS analysis were performed on Thermo Fisher Scientific LCQ Fleet by direct infusion of acidic aqueous solutions of monomers.

SEM analysis was performed using a JEOL JSM IT800 SHL microscope operating at 3 kV. Samples were rinsed with neutral water and ethanol mixture to eliminate sodium hydroxide and then left to dry on the support. The samples were subjected to a platinum metallization step prior to analysis to limit charge accumulation and diminish noise.

TGA measurements were carried out employing a Mettler Toledo ATG/DSC 3+ instrument with a temperature ramp from ambient to 600 °C at a rate of 10 °C/min. TGA is classically used in polymer analysis to study thermal stability.[22]

DSC was conducted using a Netzsch DSC Sirius 3500 instrument to determine the glass transition. Aging was performed by heating up to 250 °C, cooling down to −50 °C, isothermal at −50 °C for 90 min, and then heating up to 70 °C and then up to 150 °C.

Solid-state NMR spectroscopy was used to confirm polymerization and the absence of free monomers.[23] The analysis was performed on a Bruker Avance 400 III HD spectrometer operating at 9.4 T. Samples were packed into 4 mm zirconia rotors and analyzed at 295 K. Proton magic angle spinning (^1H MAS) experiments were conducted utilizing the depth pulse sequence with a recycle delay of 5 s. Additionally, ramped cross-polarization (CP) was observed at ^1H. ^{13}C NMR spectra were acquired with a recycle delay of 3 s and a contact time of 2 ms. For samples with higher gelatinous content, a multiple ramped CP pulse sequence was preferred, with a recycle delay of 1.5 s, a contact time of 2 ms, and 4 CP loops separated by a delay of 1 s. Chemical shifts were referenced to tetramethylsilane (TMS).

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Rheological measurements were carried out using a NETZSCH Kinexus Pro+ rheometer equipped with a 4 cm striated parallel plate geometry, with additional measurements performed by utilizing a 1 mm gap between the plates. The experiments were conducted at a constant temperature of 25 °C. Additional rheological studies during polymerization were conducted at 0 °C using an Anton Paar MCR 302 rheometer equipped with a 25 mm diameter mobile setup and irradiated at a wavelength of 365 nm and an irradiation intensity on the order of 20 mW/cm^2.

RESULTS AND DISCUSSION

Obtaining the amino acid-based vinylic monomer was fairly simple, with a two-step, one-pot synthesis procedure. The focus remained on hydrophobic amino acid in this work, as the resulting monomers precipitate when the pH of the isoelectric point is reached and are therefore easily purified. The yield ranged between 50 and 70% depending on the amino acid, with great purity that could be achieved with only minimal purification, through a series of aqueous and organic washing steps that permitted the elimination of organic and inorganic residues. Monomers derived from tyrosine, phenylalanine, tryptophan, methionine, and leucine were obtained (Figure 2).

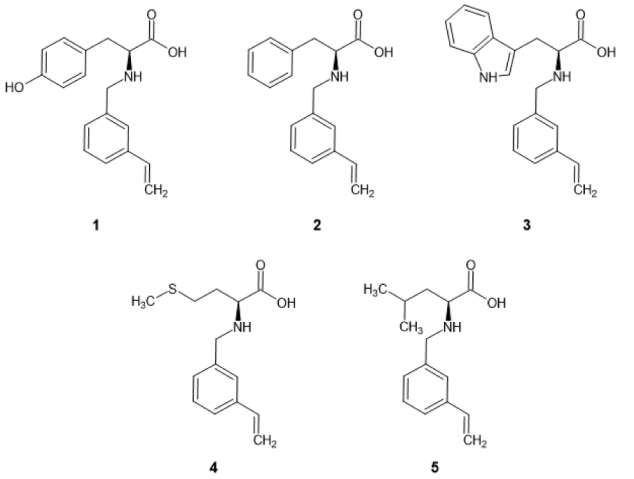

Figure 2. Structures of the vinyl monomers derived from tyrosine (**1**), phenylalanine (**2**), tryptophan (**3**), methionine (**4**), and leucine (**5**).

Structures were confirmed by the NMR spectra. The signals of the vinylic part can be found on all five monomers: H_{trans}, H_{cis}, and H_{gem} of the alkene at, respectively, around 6.7, 5.8, and 5.3 ppm, four aromatic protons around 7.5 ppm, and two diastereotopic protons around 3.9 and 3.8 ppm. The signals corresponding to the amino acid part were also found, and complementary ^{13}C NMR was performed to confirm the structure. Complete attribution of each individual monomer is detailed in Figures S1−S10.

The type of polymerization process used here includes five main components: monomers, a cross-linker, a polymerization initiator, an initiation mode, and a solvent system. Finer tuning can also be taken into consideration, such as the stirring rate, time of reaction, or temperature. For each parameter, there could be a large number of variations, but we chose to narrow our study around a few of them. Structures of both cross-linkers used are illustrated in Figure 3.

The obtained gels are solid, transparent, and colorless to yellowish and can display the presence of bubbles as shown in Figure 4. It can be noted that under similar conditions, the homopolymerization of EGDMA did not yield a solid gel but instead resulted in a white suspension (Figure S11). Using styrene as a monomer did not lead to the formation of a solid gel either. This indicates that the formation of a gel under these conditions is intrinsically linked to the presence of the amino acid moieties in the monomers.

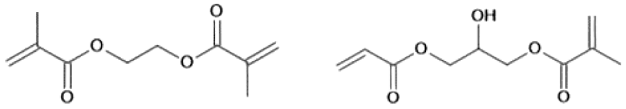

Figure 3. Structures of the cross-linkers EGDMA (left) and AHPMA (right).

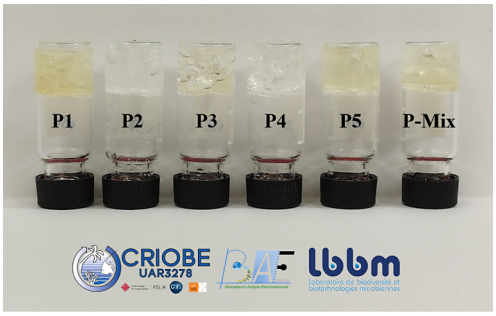

Figure 4. Picture of gels samples. From left to right, **P1**, **P2**, **P3**, **P4**, **P5**, and **P-Mix**.

Gels were stored at 4 °C in an excess of solvent to reach swelling equilibrium before further treatment for characterization.

Solid-State NMR. The solid-state NMR spectra obtained for the polymers present broadened peaks with chemical shifts consistent with bound monomers, with little to no presence of fine peaks indicative of unbound monomers. This strongly suggests the successful covalent incorporation of monomers within the polymer matrix. Variations in synthesis conditions, such as thermal or photoinitiation, duration of irradiation, or change in cross-linkers, do not seem to influence this incorporation, indicating robustness of the polymerization process (Figures S12−S19).

TGA. The thermal profile of the various polymers shows only one thermal degradation around 420 °C. While monomers exhibit multistage degradation, these distinct stages are not visible in the degradation behavior of polymers (Figures S31−S36). This supports the idea that the presence of free monomers within the polymer matrix is minimal as indicated by solid-state NMR results. Additionally, it suggests that the functional groups susceptible to degradation in the free monomeric state maintain their integrity upon polymerization, further confirming the robustness of the polymerization process in preserving functional moieties. However, while materials present good thermal stability, it is important to consider operating within a temperature range compatible with the solvents used to maintain swelling. This consideration ensures the preservation of the desired structural integrity and functionality required for their intended applications.

SEM. On SEM imaging, each polymer sample presents comparable structural features, characterized by a combination of smooth and granulated morphologies, as shown in Figure 5. Additional images are provided in Figures S20−S30.

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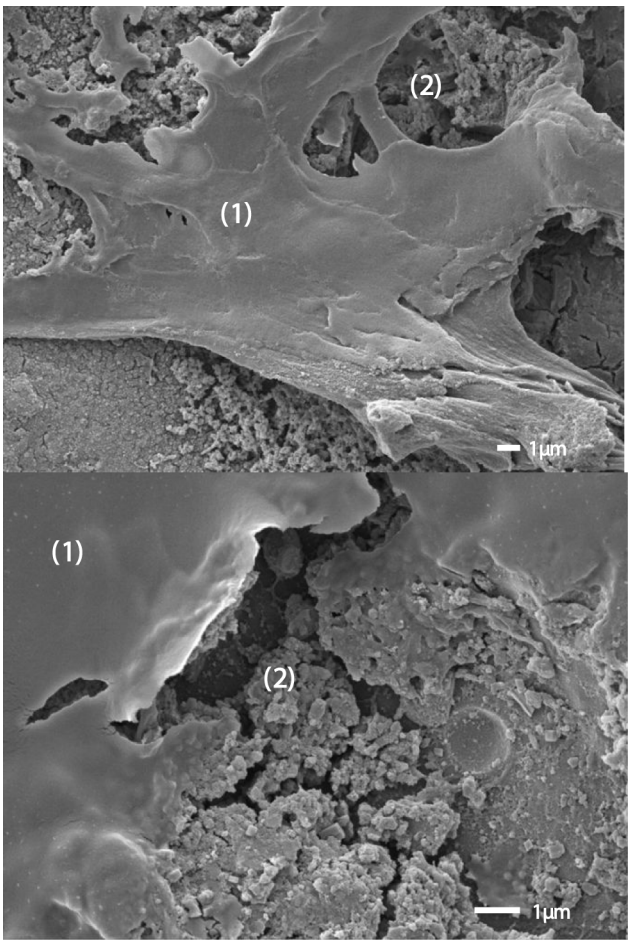

Figure 5. SEM images of **P2** (top) and **P-Mix** (bottom) presenting both smooth (1) and granulated (2) morphologies.

DSC. DSC analysis of the gels presents two changes in the slope of the cooling curve, around 100 and −10 °C, respectively (Figure S37). To confirm that these changes in the curve are glass transitions, preliminary aging of the gels was carried out before new DSC analysis. Aged gels show only one change in the slope between 0 and 10 °C depending on the gel, which can be attributed to greater certainty to a glass transition (Figure 6). The existence of a unique glass transition indicates that gels are statistical polymers and not block polymers and reflects a degree of homogeneity between monomer and cross-linker distribution within the polymer matrix.

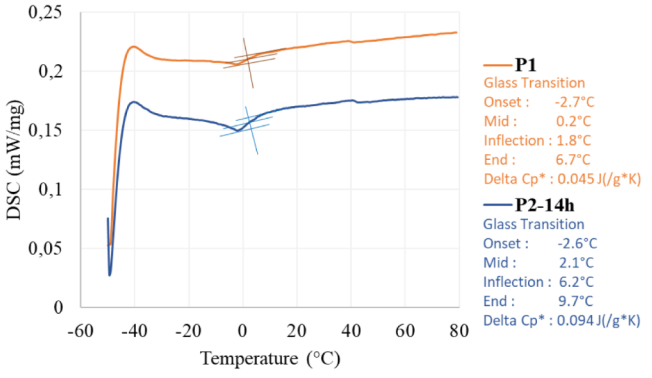

Figure 6. DSC of gels **P1** and **P2-14h** after aging.

Rheological Studies. The elasticity of the polymer is strongly influenced by the nature of the functional monomer. It can be noted that the polymer resulting from a mixture of all five monomers in equimolar proportions does not exhibit the average elasticity of polymers made from each monomer individually (Figure 7). The difference in moduli measured

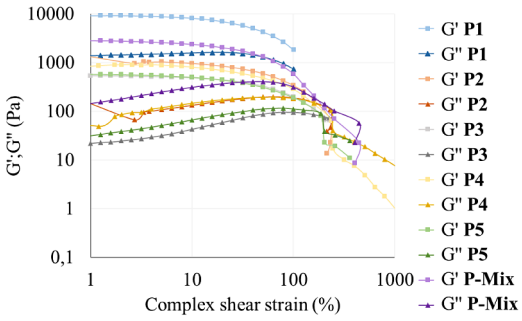

Figure 7. Storage modulus (G') and loss modulus (G'') of gels **P1**, **P2**, **P3**, **P4**, **P5**, and **P-Mix** when exposed to increasing complex shear strain.

reflects a more elastic gel obtained with EGDMA cross-linker than with AHPMA (Figure 8). AHPMA provides a slightly

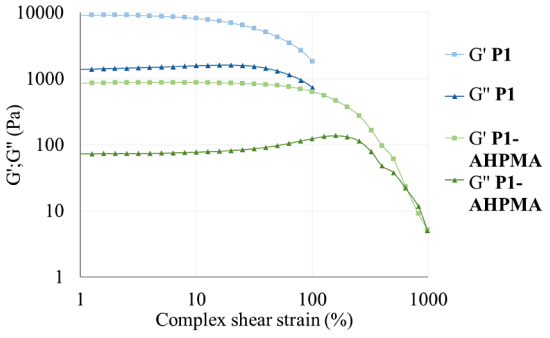

Figure 8. Storage modulus (G') and loss modulus (G'') of gels **P1** and **P1-AHPMA** when exposed to increasing complex shear strain.

greater resistance to strain. The gel synthesized through thermopolymerization is more elastic than the one obtained by photopolymerization, but both display the same resistance to strain (Figure 9).

A measurement of the moduli during polymerization was performed to monitor the gelation process (Figure 10). Three phases could be observed. Before irradiation, measurement of

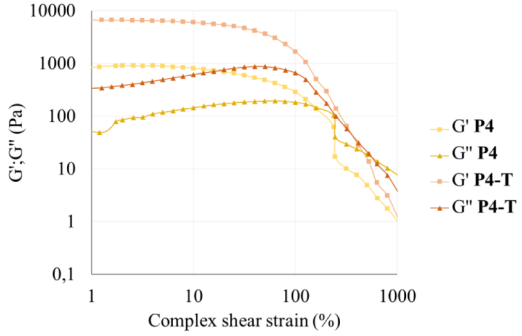

Figure 9. Storage modulus (G') and loss modulus (G'') of gels **P4** and **P4-T** when exposed to increasing complex shear strain.

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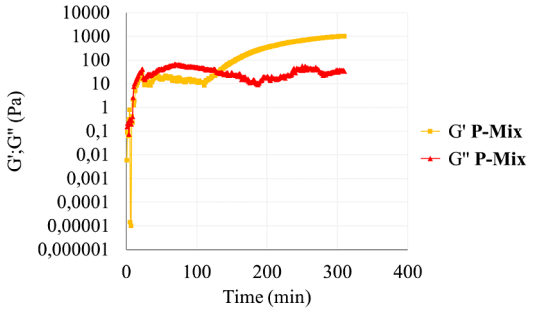

Figure 10. Storage modulus (G') and loss modulus (G'') of gel **P-Mix** evolution over time during polymerization. Irradiation began after 10 min of measurement.

the moduli is chaotic due to the very liquid nature of the solution. Irradiation is started after 10 min of measurement, and quickly after, a phase transition to a viscous liquid ($G'' > G'$) could be observed. After about 2 h of irradiation, a transition to an elastic solid ($G' > G''$) was visible and appeared fairly stable after 5 h of irradiation.

CONCLUSION

In conclusion, our study focused on the synthesis and characterization of novel amino acid–based gels derived from tyrosine, phenylalanine, tryptophan, leucine, and methionine monomers. An easy synthetic pathway was optimized to graft vinyl moieties onto these amino acids. Through a systematic comparison of the formed polymers, including a gel with an equimolar ratio of each monomer, we investigated the influence of cross-linker nature, polymerization time, and initiation type. Characterization techniques, including TGA, DSC, rheology, SEM, and solid-state NMR, were employed to assess the nature and properties of the synthesized gels. They showed that these derived amino acid monomers could be successfully incorporated into gels with interesting robustness. Further research into optimizing their properties and exploring specific application scenarios could unlock their full potential in various fields, such as drug delivery, biosensing, and biotechnology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05246.

Figures S1–S10: monomers ^{1}H and ^{13}C NMR spectra (pages S2–S11); Figure S11: image of EGDMA homopolymer (page S12); Figures S12–S19: solid-state NMR CPMAS spectra of monomers and gels (page S13–S17); Figures S20–S30: SEM images of gels (pages S18–S23); Figures S31–S36: TGA measurement of monomers and gels (pages S24–S26); Figure S37: DSC analysis of gels (pages S27) (PDF)

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Author Contributions

#C.B. performed all experiments and treatment and analysis of the results and wrote the manuscript. A.Z. performed the first synthesis experiments. G.F. and C.C.B. designed and directed the project and contributed to funding acquisition, supervision, writing of the review, and editing.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

TGA, Thermogravimetric analysis; DSC, differential scanning calorimetry; NMR, nuclear magnetic resonance; SEM, scanning electron microscopy; AIBN, azobis(isobutyronitrile); EGDMA, ethylene glycol dimethacrylate; AHPMA, 3-(acryloyloxy)-2-hydroxypropyl methacrylate; UV, ultraviolet; MS, mass spectrometry

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