ACS Macro Letters

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Sequence Regulated Poly(ester-amide)s Based on Passerini Reaction

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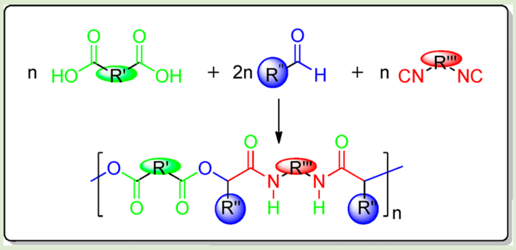
Supporting Information

ABSTRACT: Multicomponent polymerization based on Passerini reaction is described. Room temperature polymerization of dicarboxyl acid, monoaldehyde, and diisocyanide leads to the formation of a new type of sequence regulated poly(ester-amide)s in an efficient one-pot process. The polymerization was confirmed to be a stepwise mechanism, and the resulting polymers were characterized and determined to be linear polymers with a sequence regulated backbone repeating unit of ester–ester–amide–amide. When functional aldehydes were used, functional side groups could be easily introduced at the same time, providing a simple way for further modification.

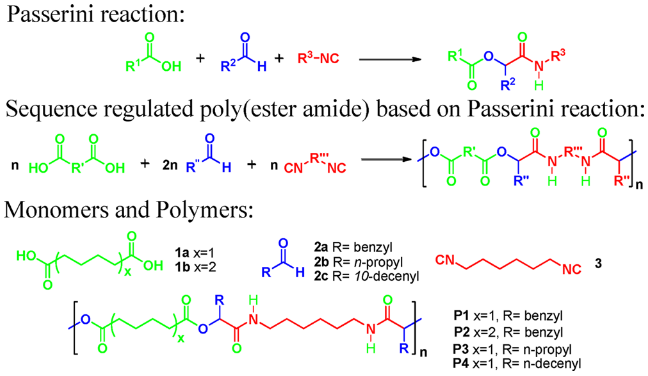


Multicomponent polymerization of a set of monomers is a general and efficient way to vary the polymer composition and, in turn, to regulate the polymer properties. Compared with nature systems, synthetic polymers from conventional copolymerizations have a low level of control, either in the polymer backbone or at the side chain.[1−4] For example, polycondensation of more than three monomers usually resulted in polymers with backbone microstructure heterogeneity of repeating units, while for copolymerization of vinyl monomers, control over the monomer sequence along the backbone is more difficult; even for a set of two monomers, the simplest alternating sequence can only be obtained by limited special monomer pairs. In this context, sequence control of synthetic polymers either in the backbone or side groups has recently emerged as an important research field in polymer science.[1−6] Inspired by the structures and functions of biomacromolecules like proteins and nucleic acids, it is highly anticipated that rational design and synthesis of sequence-defined polymers can create unprecedented properties of synthetic polymers.[7,8] The challenge remains to be the synthesis of sequence-regulated polymers from a set of monomers in a one-pot and efficient process.[9−15]

Isocyanide-based multicomponent reactions (IMCRs) are extremely powerful synthetic tools that can assemble three or more different components into one molecule in a one-pot process and have, therefore, been playing important roles in many fields.[16−24] Among the IMCRs, Passerini reaction, first described in 1921, an efficient atom-economical three component reaction, can afford an ester-amide linkage from a carboxylic acid, an aldehyde, and an isocyanide.[22] However, this highly efficient reaction has been overlooked for a long time in polymer synthesis; only until quite recently, the synthesis of dendrimers,[20] linear polyesters with tunable amide side chains,[23] and surface-triblock dendrimers by this reaction was reported.[24]

In this letter, we extended the use of Passerini reaction for preparing sequence-regulated poly(ester-amide) (Scheme 1).

Scheme 1. Synthetic Strategy of Sequence Regulated Poly(ester-amide) Based on Passerini Reaction



By employing a dicarboxylic acid, an aldehyde, and a diisocyanide, the sequential information (i.e., ester-amide sequence) formed from Passerini reaction can be incorporated into the structure of a polymer main chain at the same time to afford a sequence-regulated poly(ester–ester–amide–amide) in a one-pot process. To our knowledge, this methodology also offers an alternative to prepare modifiable biodegradable poly(ester-amide)s, each repeating unit of which contains two ester bonds followed by two amide linkages, as well as two functional side groups when functional aldehyde component is used.[25−30] In addition, compared with the conventional step-

Received: September 1, 2012
Accepted: October 18, 2012
Published: October 19, 2012

growth polymerization based on two component reactions, this conceptually new strategy also offers a simple way to control the average molecular weights (M_n) of polymers by tuning the relative molar ratio of the aldehyde, a monogroup component, to the diacid or diisocyanide.[31]

Herein, we designed and synthesized four kinds of sequence regulated polymers (**P1**−**P4**) from commercially available monomers (**1a**, **1b**, **2a**−**c**, and **3**). They are different in chain length of repeating unit (**P1** and **P2**), and side groups (**P1**, **P3**, and **P4**), respectively. Polymerization kinetics and M_n control were examined in the process of preparing **P1**.

First, we carried out the polymerization of **1a** + **2a** + **3** (molar ratio 1:2:1, [**1a**] = 1.0 M) in CH_2Cl_2 at 30 °C. The initially heterogeneous reaction mixture became homogeneous after 2 h, with a viscosity increase of the solution, indicating the formation of polymers. We followed the polymerization kinetics by ^1H NMR and gel permeation chromatography (GPC) measurements (Figure 1). Oligomers were obtained after 15 min, with the monomer conversion being 54%. The conversion of monomers reached over 98% after 2 h, together with a continuous increase of M_n. At this stage, the viscosity of the solution was so high that it is hard to have effective stirring by a magnetic stirrer. The M_n increased exponentially at the later stage of the polymerizations, as shown in Figure 1b, which is consistent with the conventional step-growth polymerizations.

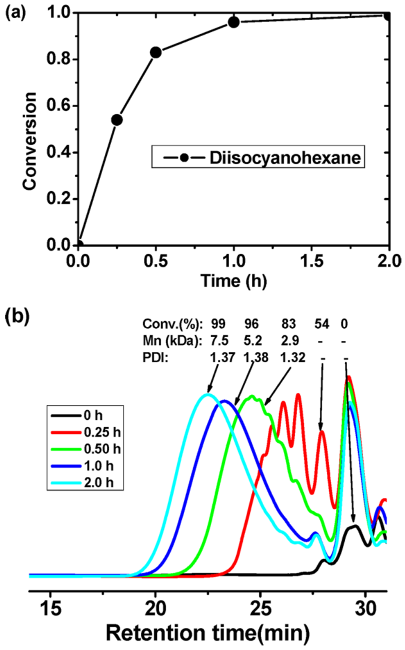


Figure 1. Kinetics study for the polymerization of **1a** + **2a** + **3**. [**1a**] = 1.0 M; [**1a**]:[**2a**]:[**3**] = 1:2:1. The polymerization was performed in CD_2Cl_2 at 30 °C: (a) time−conversion plot; (b) GPC traces.

Next, to demonstrate the new feature of M_n control in this multicomponent polymerization, **1a**, **2a**, and **3** were polymerized in different molar ratios (1:2*r*:1, $r \leq 1$, [**1a**] = [**3**] = 1.0 M) for 36 h to ensure a full conversion of **2a**. The M_n and polydispersity index (PDI) of the polymers were obtained. We found that M_n is directly dependent on *r* (Figure 2): increasing *r* resulted in the increase of M_n, and high molecular weight polymer can only be obtained when *r* is close to 1. As in conventional step polymerizations,[31] we derived an equation to calculate the M_n in this polymerization system: $M_n = M(1 + r)/(1 + r - 2rp)$, where *M* is the average molecular weight of the starting components, *r* is the molar equivalent of **2a** to **3**, *p* is the extent of reaction of **2a**. The calculated M_n is very close to the measured values. Thus, we can easily adjust the polymer molecular weight by using different amount of the monogroup component.

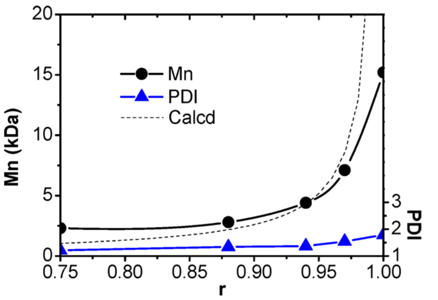


Figure 2. Control the M_n of polymers by tuning the relative molar ratio of the aldehyde to the diacid or diisocyanide. The polymerization was performed in CH_2Cl_2 at 30 °C. *r* is the molar equivalent of **2a** to **3**.

Various conditions were then examined for the synthesis of **P1** and the results are summarized in Table 1. In all cases, polymers with moderate to high molecular weights were obtained. In general, by increasing the concentrations of the three components (entries 1−4), both the yields and the M_n of **P1** increased. However, when the monomer concentration was 2.0 M, the polymer yield was high, but M_n of **P1** was lower than that obtained at 1.5 M. We rationalized this to the high viscosity of the polymerization system, which prevented further polymerization. Considering the high yield and low PDI after precipitation in ethyl ether, we deduced that the inevitable ring-forming side reactions rarely occurred. Solvents also affect the polymerization (entries 2 and 5−9). When performed in aprotic solvents (CH_2Cl_2, $CHCl_3$, and toluene), relative high yields and high M_n of **P1** were obtained, which was in agreement with the general Passerini reaction.[16−19] The successful polymerization in methanol suggests that hydroxyl groups do not affect the polymerization. The polymerization in toluene was also conducted at 60 °C (entry 10), but polymers with low molecular weight were obtained in low yield. Particularly, considering the aqueous medium effects on multicomponent reactions, we presumed water would increase the polymerization rate, in addition to the environmental advantages.[32,33] Unfortunately, phase separation was observed in about 10 min, which hindered further polymerization, resulting in low yield and M_n of the final polymers (**P1**, see entry 8 in Table 1, **P3** and **P4**, see Figures S1 and S2).

One typical **P1** sample was characterized by ^1H NMR, ^{13}C NMR spectra, and the matrix-assisted laser-desorption-ionization time-of-flight mass (MALDI-TOF-MS; Figures 3 and 4). In the ^1H NMR spectrum, all the protons corresponding to the proposed repeating unit of poly(ester-amide) that should be generated via the expected efficient Passerini reaction are clearly observed, and the integrations of these peaks further confirmed the integrity of the polymer structure. However, end groups are hardly differentiated due to overlapping of peaks, therefore, the absolute M_n is hard to determine. In addition, the ^{13}C NMR spectrum is also consistent with the proposed **P1** structure. More accurately, the MALDI-TOF-MS spectrum of **P1** consisted of a series of peaks, each separated by 522 Da intervals, which was very close to the formula weight of the

Table 1. Multicomponent Polymerization Based on Passerini Reaction

entry	monomers	solvent	conc.[a] (M)	T (°C)	t (h)	yield[c] (%)	M_n[d] (kDa)	PDI[d]
1	**1a** + **2a** + **3**	CH_2Cl_2	0.5	30	36	67	4.4	1.35
2	**1a** + **2a** + **3**	CH_2Cl_2	1.0	30	36	86	8.1	1.47
3	**1a** + **2a** + **3**	CH_2Cl_2	1.5	30	36	94	15.2	1.79
4	**1a** + **2a** + **3**	CH_2Cl_2	2.0	30	36	97	8.9	1.53
5	**1a** + **2a** + **3**	$CHCl_3$	1.0	30	36	73	5.8	1.34
6	**1a** + **2a** + **3**	THF	1.0	30	36	67	4.4	1.35
7	**1a** + **2a** + **3**	CH_3OH	1.0	30	36	52	4.7	1.44
8	**1a** + **2a** + **3**	H_2O	1.0	30	7[b]	44	2.6	1.25
9	**1a** + **2a** + **3**	toluene	1.0	30	7[b]	77	12.0	1.74
10	**1a** + **2a** + **3**	toluene	1.0	60	7[b]	71	6.6	1.54
11	**1b** + **2a** + **3**	CH_2Cl_2	1.0	30	36	88	6.6	1.51
12	**1a** + **2b** + **3**	CH_2Cl_2	1.0	30	36	81	3.6	1.45
13	**1a** + **2c** + **3**	toluene	1.0	30	36	76	6.2	1.33

[a] Here shows the concentration of dicarboxylic acids, which is equal to the concentration of diisocyanides. The concentration of aldehydes is double in molar ratio. [b] Phase separation was observed both in water and toluene. [c] Determined after precipitation in ethyl ether and vacuum dryness (30 °C, 12 h). [d] Measured by GPC in THF.

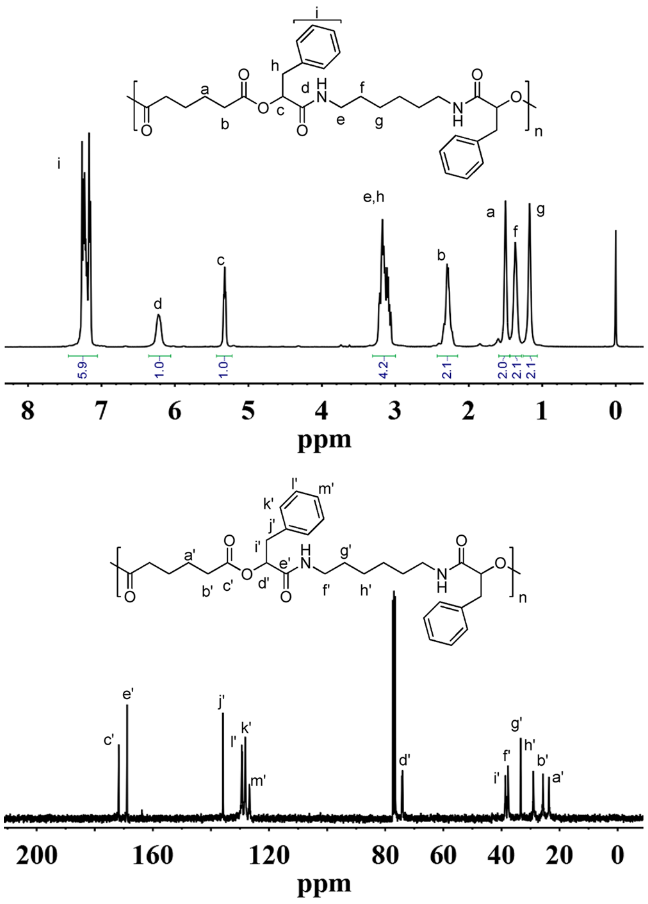


Figure 3. ^1H and ^{13}C NMR spectra of **P1** (Table 1, entry 2, M_n = 8.1 kDa, PDI = 1.47).

repeating unit. The molecular weights obtained from individual peaks were close to the polymers with dicarboxylic acid and carboxylic acid–isocyanide end groups. These results further confirmed the precise structure of **P1**. The thermal properties of **P1** were also examined by thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC; Figures S3 and S4). Depending on the molecular weight, **P1** can be stable up to 275 °C, above which slow decomposition occurred. The onset decomposition temperature of **P1** increased with the molecular weight. **P1** was amorphous and exhibited T_gs ranging from 43 to 50 °C as the molecular weight increased from 8.9 to 15.2 kDa, no melting temperature was observed as in other biodegradable ploy(ester-amide)s.[29]

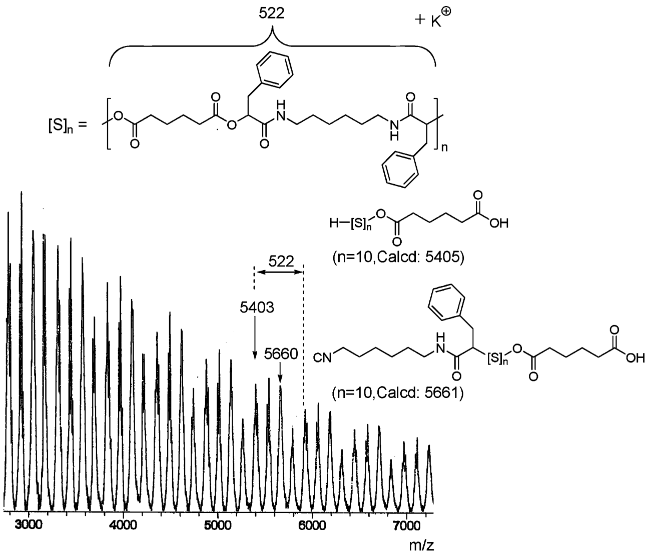


Figure 4. MALDI-TOF-MS spectra of **P1** (Table 1, entry 2, M_n = 8.1 kDa, PDI = 1.47).

Based on the above results, we extended this strategy for the synthesis of **P2–4** by using different dicarboxylic acid or aldehyde, and polymers with relatively high yields and expected structures were obtained (Table 1, entries 11–13; Figures S6 and S7).

The simple and efficient postmodifications of side chain double bonds in **P4** with the well-known thiol-ene click chemistry was further demonstrated (Figure S8).[34,35] A mixture of 1-dodecanethiol and **P4** was irradiated with 365 nm UV light in the presence of a trace amount of photoinitiator (2,2-dimethoxy-2-phenylacetophenone, DMPA). Complete disappearance of the double bonds was observed after 12 h, and precipitation in *n*-pentane and characterization of the product by ^1H NMR measurement confirmed the expected structure, indicating the efficient modification (Figure S8).

In summary, we have demonstrated a new example of multicomponent polymerization to synthesize polymers with a sequence-regulated repeating unit in polymer backbones. This was fulfilled by a one-pot process of dicarboxylic acids, aldehydes, and diisocyanide based on Passerini reaction. Furthermore, we have shown two important features of the polymerization: the sequential information was transferred to the polymer main chain, affording a new type of poly(ester-amide); functional side groups could be easily introduced to the polymers. The easy availability of monomers together with the advantage of functional group tolerance offers many possibilities for constructing a variety of new polymer architectures with this synthetic strategy. We are currently working on functionalization of the polymer side groups in a more complex sequence-regulated manner.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, formula deriving, and Figures S1–S8. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the National Natural Science Foundation of China (No. 21090351) and 973 Project (2011CB201402).

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