Macromolecules
Cite This: Macromolecules 2019, 52, 4526−4533
Article
pubs.acs.org/Macromolecules

Ethynylsulfone-Based Spontaneous Amino-yne Click Polymerization: A Facile Tool toward Regio- and Stereoregular Dynamic Polymers

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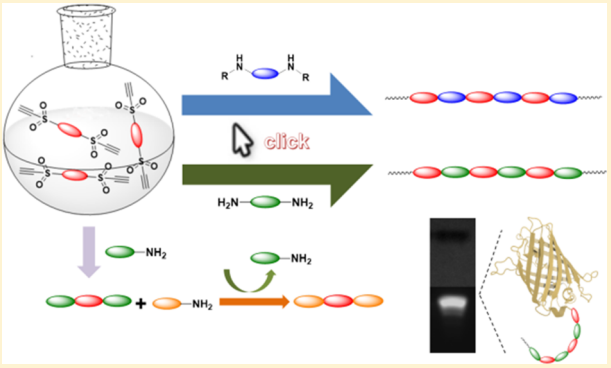
Supporting Information

ABSTRACT: Development of efficient polymerizations is crucial for polymer science from which polymeric materials with versatile properties could be produced. In this work, a new and efficient spontaneous amino-yne click polymerization is successfully established by using activated diynes of bis(ethynylsulfone)s. Compared with the ester-activated diynes, that is, dipropiolates, bis(ethynylsulfone)s could polymerize with all kinds of diamines including aliphatic and aromatic primary and secondary ones under very mild reaction conditions, and soluble and thermally stable poly(β-aminovinylsulfone)s (PAVSs) with high weight-average molecular weights (M_w up to 160,000) and excellent regio- and stereoregularity (the ratio of *E* isomers up to 100%) were obtained in high yields (up to 99%). Due to the strong electron-withdrawing ability of sulfonyl groups, the resultant PAVSs show a dynamic property and could undergo the amine exchange, which makes the polymers readily degrade upon addition of monoamines. Moreover, this highly efficient spontaneous amino-yne click reaction could be used to facilely label and decorate proteins. Thus, this work not only establishes a more efficient amino-yne click polymerization, which could be used to label bioconjugates, but also provides a novel strategy to construct regio- and stereoregular dynamic polymers.



INTRODUCTION

The click polymerization,[1] developed based on the click reaction and having the advantages of high efficiency, mild reaction conditions, excellent selectivity, environmental friendliness, atom economy, and so on,[2,3] has become a powerful tool for the synthesis of functional polymers. Among the established click polymerizations, the alkyne-based ones have drawn much attention, which could readily furnish linear and topological polymers with advanced properties and diverse applications.[4−21]

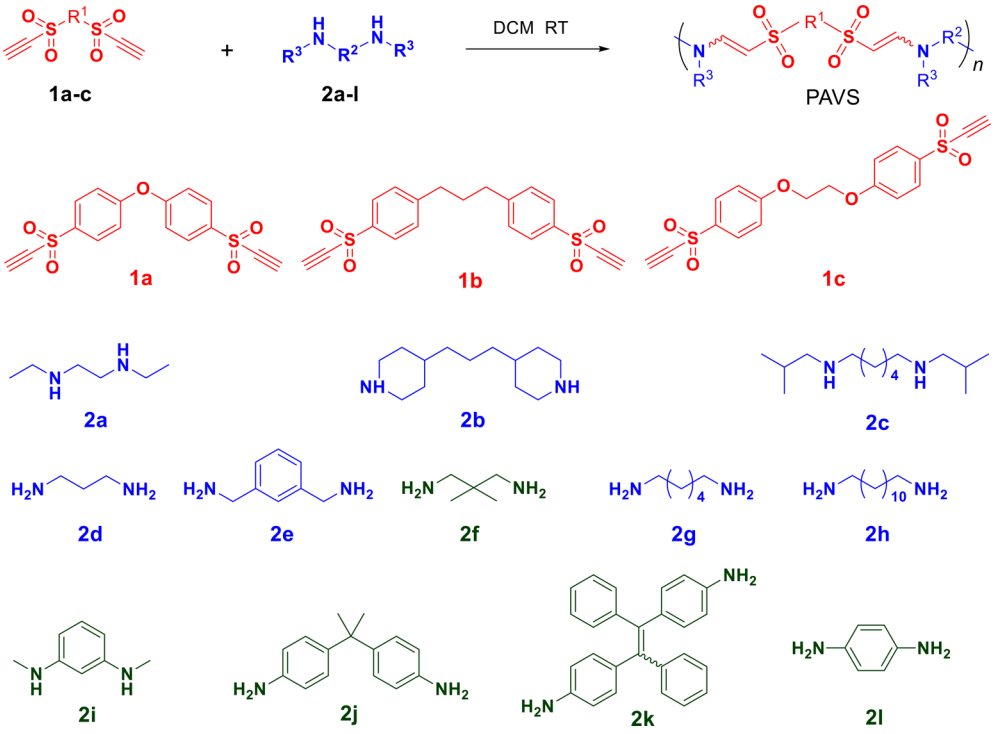
To date, the transition-metal,[22−29] organobase-catalyzed,[30−33] and metal-free and spontaneous[34,35] alkyne-based click polymerizations have been developed, among which the transition-metal-catalyzed alkyne-based click polymerization is well established. However, the metallic residues in the polymeric products can hardly be completely removed, which will cause cytotoxicity and deteriorate the electrooptical property of the products during their applications.[27,36] To solve this difficulty, the metal-free and spontaneous click polymerizations based on the activated monomer strategy or using unique monomers have been developed. For example, the ester or ketone group-activated alkynes could readily polymerize with azide monomers via a metal-free fashion, and regioregular polytriazoles were efficiently yielded.[37−40] Using the similar activated alkyne strategy, the organobase-catalyzed phenol-yne and spontaneous amino-yne click polymerizations have also recently been established by our groups.[41,42] Moreover, by employing aromatic alkynes, we also developed a spontaneous thiol-yne click polymerization, and regioregular poly(vinylene sulfide)s with high weight-average molecular weights (M_w) were obtained in excellent yields.[43]

These powerful click polymerizations have been used to prepare functional polymers, which have been applied in diverse areas.[44,45] For example, the spontaneous amino-yne click polymerization using dipropiolate and aliphatic secondary diamine as monomers could readily produce regio- and

Received: April 3, 2019
Revised: May 15, 2019
Published: June 11, 2019

DOI: 10.1021/acs.macromol.9b00670
Macromolecules 2019, 52, 4526−4533

Scheme 1. Syntheses of Poly(β-aminovinylsulfone)s by Spontaneous Click Polymerization of Bis(ethynylsulfone)s and Diamines



stereoregular poly(β-aminoacrylate)s with high M_w in high yields under very mild reaction conditions, and these polymers have been used in optoelectronic and biological fields.[46−49]

Nonetheless, the stereoregularity of the polymers decreased when the dipropiolates polymerized with aliphatic primary diamines under the same conditions although they still propagated in a spontaneous way. In addition, the reaction failed when the aromatic diamine monomers were used probably because the conjugation between the aromatic ring and amino groups reduces the electrophilic ability of the latter. Thus, it is envisaged that the increase in the electron-withdrawing ability of groups connected with ethynyl groups might make the alkyne monomer more reactive and could react with all kinds of amine monomers.

Following this idea, we designed and synthesized bis(ethynylsulfone) monomers in which the ethynyl groups were activated by stronger sulfonyl groups than the ester ones. The polymerization results show that these diynes could spontaneously polymerize with all kinds of diamines including aliphatic/aromatic primary/secondary ones to furnish regio- and stereoregular poly(β-aminovinylsulfone)s (PAVSs) under mild reaction conditions, suggesting that it is a new type of spontaneous amino-yne click polymerization.

Due to the strong electron-withdrawing ability of sulfonyl groups, the aminovinyl groups in the PAVSs possess the unique dynamic property and could realize the amine exchange, which will find broad application in diverse areas.[50−53] Notably, this spontaneous amine-yne click reaction could be facilely applied in labeling bioconjugates bearing amino groups by the functional ethynylsulfone derivatives.[54] Thus, this work not only broadens the scope of spontaneous amino-yne click polymerization but also provides a series of functional dynamic PAVSs that are potentially applicable in optoelectronic and biological fields.

RESULTS AND DISCUSSION

Polymerization. The activated diynes of bis(ethynylsulfone)s were prepared according to routes shown in Scheme S1, and the detailed procedures are given in the Supporting Information. Their structures were fully characterized, and satisfactory results were obtained. The diamine monomers, except for **2k**, which was synthesized according to our reported procedures (Scheme S2),[55] are commercially available.

Next, we used diyne **1a** and diamine **2a** as model monomers to optimize the polymerization conditions (Scheme S3 and Tables S1−S3). Given the high reactivity of **1a**, this polymerization could propagate spontaneously in dichloromethane (DCM) at room temperature. After the polymerization parameters were systematically studied, the optimal conditions were obtained, that is, the solvent is DCM, the monomer concentration is 0.5 M, the reaction time is 5 h, and the atmosphere is nitrogen, and P**1a**/**2a** with a M_w of 51,000 was furnished in excellent yield (99%).

Encouraged by above results, we applied these optimized reaction conditions to polymerize bis(ethynylsulfone)s **1** with different aliphatic/aromatic primary/secondary diamines **2** to investigate its universality and robustness (Scheme 1, Table 1, and Tables S4 and S5).

First, three aliphatic secondary diamines **2a−2c** were used to polymerize with bis(ethynylsulfone)s **1a−1c**, respectively. The results revealed that all the polymerizations were performed in a spontaneous fashion, and soluble PAVSs with high M_w (up to 160,000) and 100% *E* isomers were produced in high yields (up to 99%).

Second, five aliphatic primary diamines **2d−2h** with diverse structures were employed to polymerize with **1a−1c**. As expected, PAVSs with high M_w (up to 82,200) were obtained in high yields. Although the stereoregularity of some of them is

DOI: 10.1021/acs.macromol.9b00670
Macromolecules 2019, 52, 4526−4533

Table 1. Polymerization Results of Bis(ethynylsulfone)s 1a and Diamines 2d−2l[a]

entry	monomer	t (min)	yield (%)	M_w[b]	PDI[b]	E/Z[c]
1	**1a** + **2a**	300	99.2	51,000	2.13	100/0
2[e]	**1a** + **2b**	300	93.5	160,000	2.63	100/0
3[e]	**1a** + **2c**	20	94.1	75,100	2.72	100/0
4[d]	**1a** + **2d**	20	85.5	36,900	1.61	100/0
5[e]	**1a** + **2e**	5	94.0	53,600	2.26	97/3
6[e]	**1a** + **2f**	120	73.2	20,000	1.61	100/0
7	**1a** + **2g**	70	92.0	82,200	2.07	99/1
8	**1a** + **2h**	120	89.3	69,900	2.23	99/1
9	**1a** + **2i**	300	89.4	48,700	2.49	80/20
10	**1a** + **2j**	180	96.6	43,400	2.24	97/3
11	**1a** + **2k**	60	91.8	25,700	1.85	100/0
12[f]	**1a** + **2l**	5	74.2	7200	1.44	88/12

[a]Carried out in DCM at room temperature under nitrogen; [**1**] = [**2**] = 0.5 M. [b]Determined by gel permeation chromatography (GPC) using *N*,*N*-dimethylformamide (DMF) containing 0.05 M LiBr as an eluent on the basis of a linear poly(methyl methacrylate) (PMMA). [c]*E*/*Z*-isomeric unit ratio of the products determined by ^{1}H NMR. [d][**1**] = [**2**] = 0.1 M. [e][**1**] = [**2**] = 0.2 M. [f]Soluble part.

not 100%, it is still very high (the ratio of *E*-isomeric units in the polymers is in the range of 97−100%).

Third, we attempted to polymerize aromatic primary and secondary diamines with **1a**−**1c** to study the scope of this polymerization because dipropiolates are unable to react with them. Delightfully, PAVSs with high M_w (up to 48,700) and stereoregularity (the ratio of *E*-isomeric units in the polymers is in the range of 76−100%) could be obtained in high yields (up to 99%). The relatively poor stereoregularity of P**1a**/**2i** and P**1b**/**2i** is probably because the steric hindrance of **2i** is slightly higher than that of aromatic primary amines, such as **2k**. To our knowledge, this is the first example that the ethynyl groups could react with aromatic amines without any catalyst at room temperature.

The resultant PAVSs are soluble in highly polar organic solvents, such as *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO). They are also thermally stable. As shown in Figure S1, the temperatures for 5% weight loss of these polymers evaluated by the thermogravimetric analysis (TGA) are all above 220 °C.

Comparison of the Polymerization Results Using Bis(ethynylsulfone)s and Dipropiolates as Monomers. To elaborate the reactivity of our newly designed bis(ethynylsulfone)s, ester-activated diyne of dipropiolate **3** was synthesized and subjected to polymerize with diamines. As shown in Scheme 2, Scheme S4, and Table S6, both **1a** and **3** could polymerize with aliphatic secondary diamine **2c**, and polymers with 100% *E* isomers were obtained. It is worth noting that both the M_w and yield of P**1a**/**2c** are better than those of P**3**/**2c**. Using aliphatic primary diamine **2d**, the polymerization results become different. The polymerization of **1a** and **2d** could produce PAVS with a 100% *E* isomer and high M_w (36,900) in 85.5% yield after only 20 min at room temperature. Whereas, the reaction of **3** and **2d** could furnish P**3**/**2d** with inferior stereoregularity (the ratio of *E* isomer: 83%) and lower M_w (17,200) in a lower yield (70.5%) even after 300 min.

Notably, bis(ethynylsulfone) **1a** could polymerize with aromatic secondary diamine **2i** and primary diamine **2k** in DCM, and polymers of P**1a**/**2i** and P**1a**/**2k** with high M_w (P**1a**/**2i**: 48,700, P**1a**/**2k**: 25,700) and good stereoregularity were obtained in good yields (P**1a**/**2i**: 89.4%, P**1a**/**2k**: 91.8%) after 300 and 60 min, respectively. As a sharp contrast, dipropiolate **3** could not react with any of aromatic diamines. These results further confirm the superiority of bis(ethynylsulfone)s over propiolates as the monomers in the amino-yne click polymerization.

Structural Characterization. The structures of PAVSs were characterized by FT-IR, and NMR spectroscopies and satisfactory analysis data corresponding to their expected structures were obtained. Given that different kinds of diamines were used for the polymerizations, model compounds **M1**, **M2**, and **M3** were designed and synthesized under the same reaction conditions (Scheme S5) to verify the repeating units in the resultant polymers.

The FT-IR and ^{1}H and ^{13}C NMR spectra of P**1a**/**2a**, **M2**, and their corresponding monomers **1a** and **2a** are given here as examples. In the FT-IR spectra of monomers (Figure S2), three peaks located at 3225, 2078, and 3300 cm^{-1} are readily assignable to the stretching vibration of ≡C—H and C≡C of **1a** and H—N of **2a**, respectively. These peaks disappeared in the spectra of P**1a**/**2a** and **M2**. Meanwhile, a new peak associated with the stretching vibration of C═C at 1617 cm^{-1} was observed, confirming the occurrence of polymerization. Similar analysis results were achieved in the FT-IR spectra of P**1a**/**2c**, P**1a**/**2h**, P**1a**/**2i**, and P**1a**/**2j** (Figure S3).

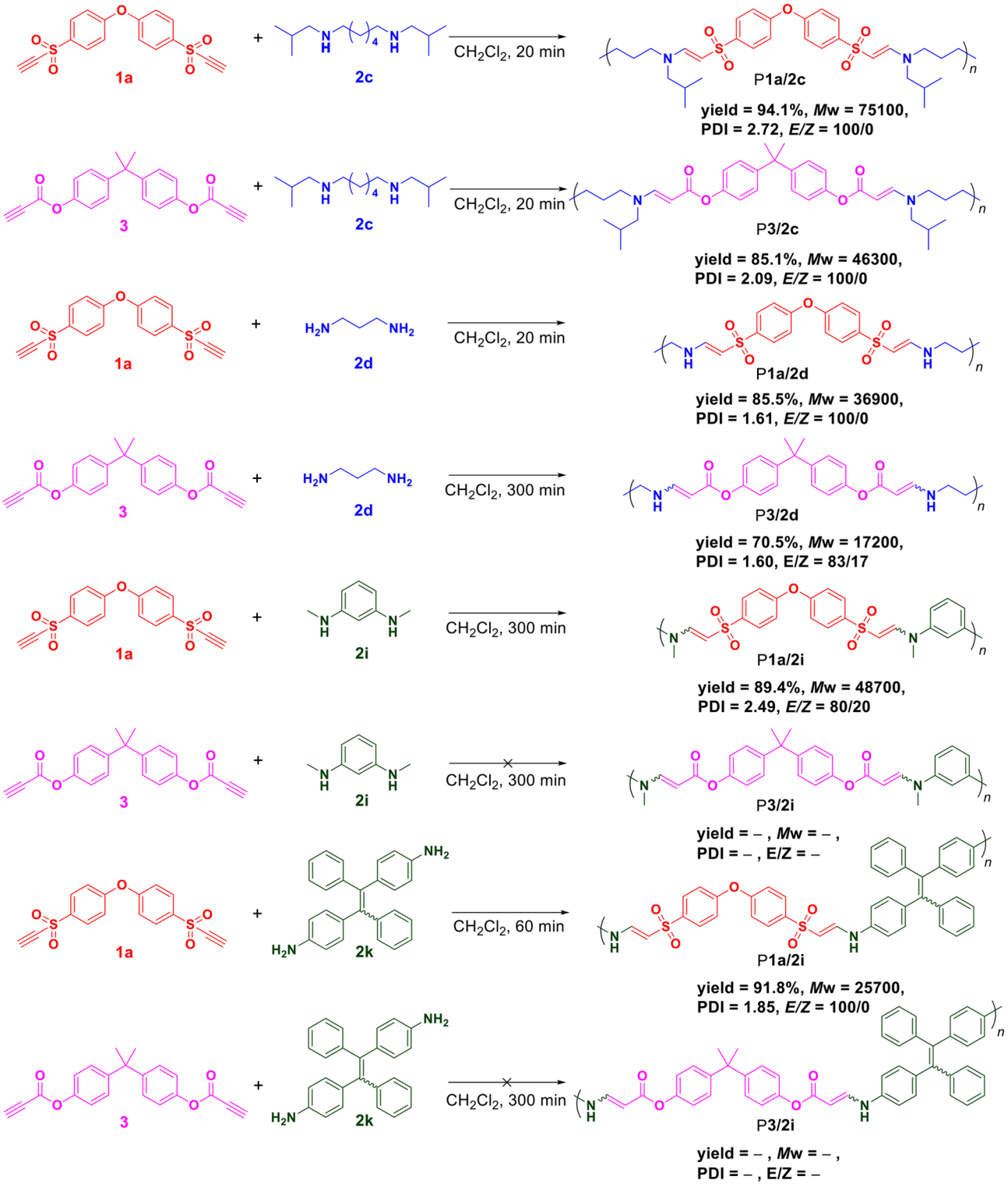
More detailed information about the polymer structures could be obtained through ^{1}H NMR spectral measurement. The ^{1}H NMR spectra of P**1a**/**2a**, **M2**, **1a**, and **2a** are shown here as an example (Figure 1). From the ^{1}H NMR spectra, we could observe that the typical ethynyl protons of diyne **1a** resonating at δ 3.51 and the CH_2 protons of **2a** resonating at δ 2.88, 2.69, 2.60, and 1.14 disappeared in the spectra of P**1a**/**2a** and **M2**. At the same time, two new peaks at δ 7.22 and 4.97, assignable to the resonance of the protons of vinyl groups adjacent to the amino and sulfonyl groups, along with another two new peaks assignable to the resonances of the CH_2 to amino groups at δ 3.28 and 3.13 appeared in the spectra of P**1a**/**2a** and **M2**. The coupling constant of protons of vinyl groups is recorded to be 13 Hz, indicative of the *E* isomers in P**1a**/**2a**. Meanwhile, no resonant peaks associated with *Z* isomers could be found in the spectra, indicating that the polymerization proceeds in a perfect regio- and stereoreselective fashion. Similarly, the polymers produced by the polymerization of **1a**−**1c** and aliphatic secondary diamines **2a**−**2c** all contain sole *E* isomers.

The ^{13}C NMR measurement further substantiates the conclusion drawn from above analyses. As shown in the ^{13}C NMR spectra of monomers **1a** and **2a**, model compound **M2**, and polymer P**1a**/**2a** in Figure S4, the ethynyl carbons of **1a** resonating at δ 82.19 and 80.33 are absent in the spectra of **M2** and P**1a**/**2a**. Moreover, the resonant peaks at δ 49.85, 44.48, and 15.59 in **2a** also disappeared in the spectra of the model compound and polymer. In addition, two new peaks assignable to the vinyl carbons were emerged at 149.53 and 91.52.

The ^{1}H and ^{13}C NMR spectra of four representative polymers, P**1a**/**2c**, P**1a**/**2h**, P**1a**/**2i**, and P**1a**/**2j**, shown in Figures S5 and S6 further provide an entire picture of the style of the polymerization. Similar results could be obtained from the ^{1}H NMR spectra of P**1a**/**2c** and P**1a**/**2h**. Whereas, in the spectra of P**1a**/**2i** and P**1a**/**2j**, very tiny resonant peaks belonging to the protons of vinyl groups could be observed at δ 4.61 and 5.16 with a coupling constant of 8 Hz, suggestive of

DOI: 10.1021/acs.macromol.9b00670
Macromolecules 2019, 52, 4526−4533

Scheme 2. Polymerizations of Bis(ethynylsulfone) 1a and Dipropiolate 3 with Diamines 2c, 2d, 2i, and 2k and Their Results



the existence of the *Z* isomers in these polymers small. Moreover, the ^{13}C NMR spectra of P**1a**/**2c**, P**1a**/**2h**, P**1a**/**2i**, and P**1a**/**2j** can also fit their corresponding structures.

Dynamic Nature of *β*-Aminovinylsulfonyl Groups. During the course of experiments, we occasionally found that there existed an amine exchange in the resultant polymers when bis(ethynylsulfone)s polymerized with primary amines, suggestive of the dynamic nature of the formed *β*-aminovinylsulfonyl groups. To better demonstrate the dynamic nature, we used model compounds **M1** and **M3** and aliphatic amine **17** to verify the amine exchanging process. As shown in Scheme 3, when 5 equal molar of **17** was reacted with **M1** in THF at 60 °C for 12 h, the latter was completely transferred to **18** as confirmed by the ^{1}H NMR analysis (Figures S7 and S8), confirming the occurrence of the dynamic amine exchanging process. Moreover, the efficiency of these processes achieved

DOI: 10.1021/acs.macromol.9b00670
Macromolecules 2019, 52, 4526−4533

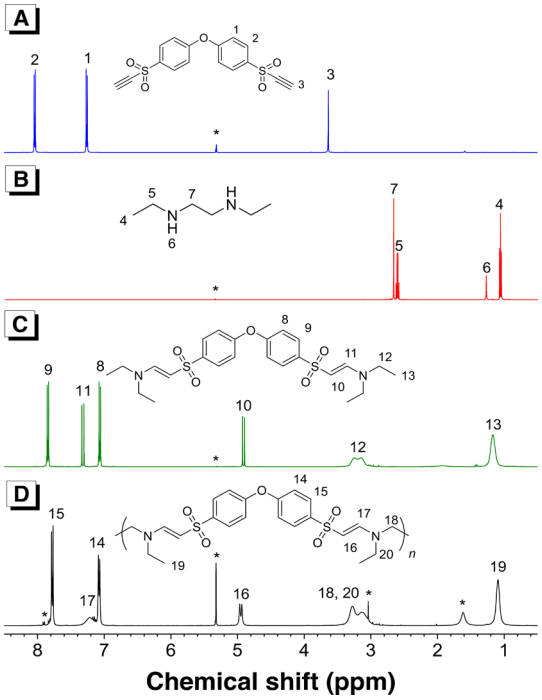


Figure 1. ^{1}H NMR spectra of (A) monomer **1a**, (B) monomer **2a**, (C) model compound **M2**, and (D) polymer P**1a**/**2a** in CD_2Cl_2. The solvent peaks are marked with asterisks.

approximately 100% because the reaction may accompany with the volatilization of ethylamine byproducts, which makes the reaction prefer to generate product **18**.

It is worth noting that similar amine exchanging processes were observed for the reaction of aliphatic amine **15** and aromatic amine **19** with **M1** under the same conditions (Scheme S6 and Figures S9−S14) as well as the reaction of **17** with **M3** in DCM at room temperature for 24 h. These results unambiguously confirm the existence of amine exchanging processes of the *β*-aminovinylsulfonyl groups.

This amine exchanging process might perform via the plausible mechanism shown in Scheme S7. First, due to the strong electron-withdrawing ability of sulfonyl groups, the aminovinyl bonds could change to C═N bonds via resonance, which are evidenced by the partial degradation of the polymers under acidic conditions (Figures S15 and S16). It is well-known that C═N is a dynamic bond and could undergo a process of reversible addition and fragmentation reaction. As a result, the new C═N bond would form after the addition of another amine with the destruction of the former C═N. At last, a new product can be obtained via the resonance process of the first step.

Degradation of PAVSs. By taking advantage of the dynamic property of *β*-aminovinylsulfonyl moieties, we studied the degradation of the PAVSs. As shown in Figure 2A, P**1a**/**2d** and P**1a**/**2j** were gradually degraded as indicated by the decrease of M_w values after addition of 10 equal molar of ethylamine and aniline within 8 h. Afterward, the M_w values of the polymers remained almost unchanged. To investigate the degradation dynamics of P**1a**/**2d**, the degraded products were extracted from the system with an interval of 2 h.

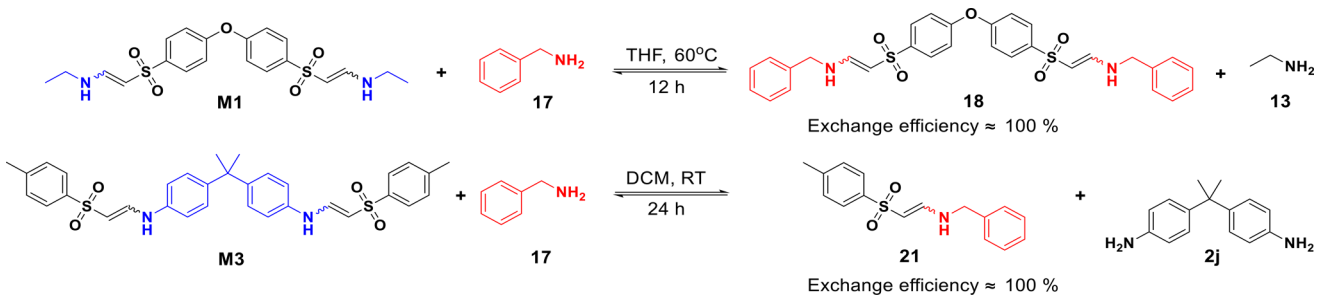
After working up, the products were measured by ^{1}H NMR. From the ^{1}H NMR spectra of degraded products (Figure 2B−2G), we could find that a new triplet peak appeared at *δ* 1.06 with prolonging the degradation time. This peak is readily assignable to the resonance of the methyl group of the degraded product that derived from ethylamine through dynamic amine exchange. These results suggest that the PAVSs are dynamic polymers, which provide a useful platform to derive polymers with multiple functions.

Bioconjugate Labeling. Given that most of the bioconjugates contain amino groups and the high reactivity of ethynylsulfonyl groups toward all kinds of amine groups, we employed our developed spontaneous amino-yne click reaction to label bioconjugates, such as secondary antibody (IgG) and bovine serum albumin (BSA) (the experimental details are given in the Supporting Information). As illustrated by the agarose gel electrophoresis (Figure 3A,C), compared to the native IgG, the bright fluorescence signal and an enhancement of M_w could be observed after addition of **1a** and **2k** to its aqueous solution. Notably, no fluorescence and M_w increase were detected when IgG was mixed with **2k** only. These results suggest that the fluorescent **2k** was successfully conjugated with IgG by the reaction of ethynylsulfonyl groups of **1a**. Moreover, due to the aggregation-induced emission (AIE) feature of **2k**, the detection of IgG was realized with relatively high sensitivity compared to the colorimetric methods. Similar labeling results were achieved when BSA was treated with **1a** and **2k** under the same reaction conditions (Figure 3B,D). These results not only verify that the reaction of ethynylsulfonyl groups with primary amine is successfully applied in biomacromolecule labeling to form functional bioconjugates but also offer a powerful strategy for biomedicine researches.

■ CONCLUSIONS

In summary, new kinds of activated diynes of bis-(ethynylsulfone)s in which the ethynyl groups are activated by the sulfonyl groups were rationally designed and facilely

Scheme 3. Syntheses of *β*-Aminovinylsulfone Derivatives of 18 and 21 via Amine Exchanges from M1 and M3, Respectively



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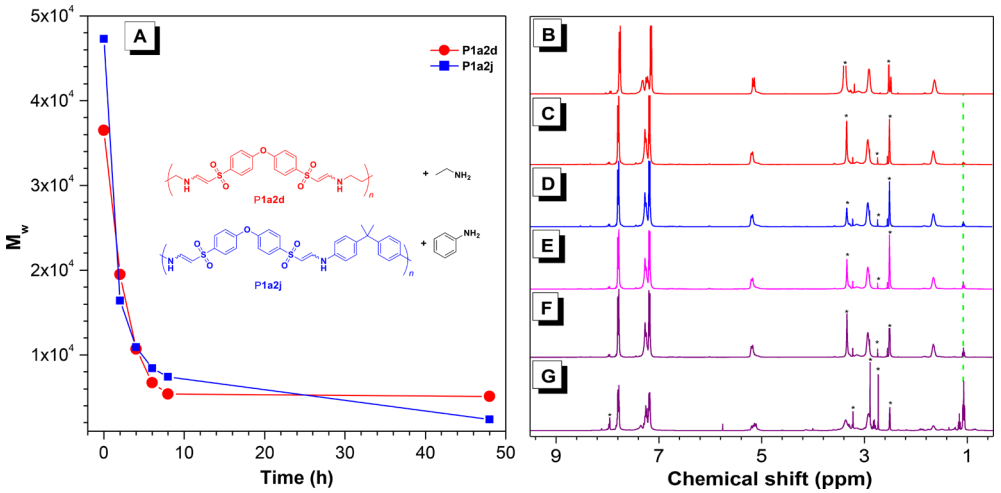

Figure 2. (A) Changes of weight-average molecular weights (M_w) of P1**a**/**2d** and P1**a**/**2j** vs degradation time after addition of primary amines. ^{1}H NMR spectra of P1**a**/**2d** after degradation for (B) 0, (C) 2, (D) 4, (E) 6, (F) 8, and (G) 48 h in DMSO-d_6. The solvent peaks are marked with asterisks.

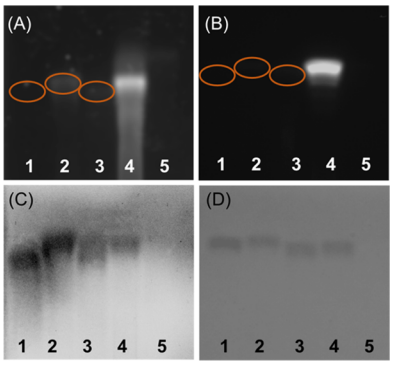

Figure 3. Agarose gel images recorded for (1) lgG, (2) lgG-**1a**, (3) lgG-**2k**, (4) lgG-P**1a**/**2k**, and (5) P**1a**/**2k** under (A) UV irradiation and (C) white light as well as those for (1) BSA, (2) BSA-**1a**, (3) BSA-**2k**, (4) BSA-P**1a**/**2k**, and (5) P**1a**/**2k** under (B) UV irradiation and (D) white light.

synthesized. By using these activated diynes, a new kind of spontaneous amino-yne click polymerization was successfully established, and regio- and stereoregular PAVSs with high M_w (up to 160,000) were obtained in high yields (up to 99%). Different from the ester-activated diynes of dipropiolates, which could only polymerize with aliphatic amines, bis(ethynylsulfone)s could polymerize with all kinds of diamines including aliphatic/aromatic primary/secondary ones with higher efficiency in a spontaneous fashion. Due to the strong electron-withdrawing ability of sulfonyl groups, the β-amino-vinylsulfonyl moieties have dynamic properties, which make the resultant PAVSs degradable via amine exchange upon addition of monoamines within 8 h. Moreover, taking advantage of the high reactivity of ethynylsulfonyl groups toward all kinds of amines, the spontaneous amino-yne click reaction could be used to facilely label biomacromolecules to form functional bioconjugates. Thus, this work not only establishes a new kind of amino-yne click polymerization but also provides a novel strategy to construct regio- and stereoregular dynamic polymers with excellent degradation ability.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.9b00670.

Experimental detail, reaction condition optimization, polymerization results, structural characterization data, amines exchanging data, and protein labeling data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21788102, 21525417, and 21490571), the National Program for Support of Top-Notch Young Professionals, the Natural Science Foundation of Guangdong Province (2016A030312002), the Fundamental Research Funds for the Central Universities (2015ZY013), and the Innovation and Technology Commission of Hong Kong (ITC-CNERC14S01).

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