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Efficient Multicomponent Postpolymerization Modification Based on Kabachnik-Fields Reaction

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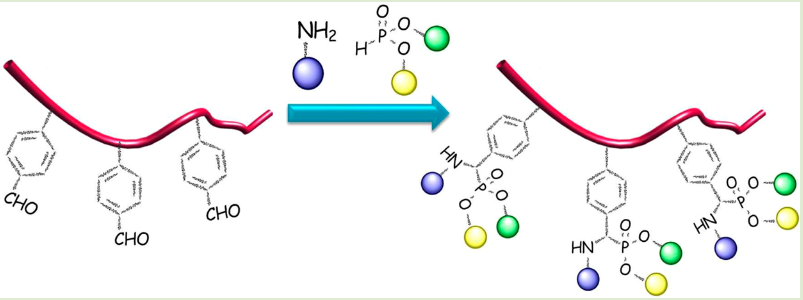
Supporting Information



ABSTRACT: A Kabachnik-Fields postpolymerization modification reaction (KF-PMR) was conducted on poly(4-vinyl benzaldehyde) (poly(St-CHO)) with amines and phosphites. Successful KF-PMR was demonstrated by precise structural analysis of the obtained polymers and kinetic investigation of the KF-PMR processes, making it a powerful tool for postpolymerization modifications that lead to α-amino phosphonates as side groups.

Since the discovery of the Strecker reaction, an artificial preparation of amino acids via a three-component reaction of amines, aldehydes (or ketones), and hydrogen cyanide, the chemistry of multicomponent reactions (MCRs) has been widely and extensively explored. A number of various MCRs have been discovered, which include the Biginelli reaction, the Gewald reaction, the Hantzsch reaction, the Kabachnik–Fields reaction, the Mannich reaction, the Passerini reaction, and the Ugi reaction, to mention a few.[1] The application scope of MCRs has been expanded to target not only construction of organic frameworks but also integration with a combinatorial approach, that is, a library synthesis. Especially, the marriage of MCRs and combinatorial synthesis has innovated pharmaceutical chemistry by boosting diversification of organic molecules to discover new structural candidate for drugs.

Meanwhile, MCRs have also found their way into polymer chemistry, not only to accelerate the synthetic access of diverse functional polymers but also to construct new polymer architectures.[2,3] Pioneering work in this field was reported by the group of Meier[4] and the group of Li.[5] They showed that the Passerini three-component reaction (Passerini-3CR) can be employed for conducting postpolymerization modification reactions on polymers featuring carboxylic acids with isocyanides and aldehydes as reactants as well as a polycondensation under step-growth conditions among dialdehydes, dicarboxylic acids, and isocyanides. Furthermore, the Passerini-3CR was found to be a very powerful synthetic strategy to produce functionalized polymers.[5−7] For example, the striking efficiency of the Passerini-3CR was further employed for a dendrimer synthesis by Rudick.[8] In addition to Passerini-3CR, the Ugi four-component reaction (Ugi-4CR) had been utilized to prepare functional monomers and polymer architectures.[9,10] Despite above-mentioned fruitful possibilities of MCRs in polymer chemistry, an intrinsic and inevitable drawback of the Passerini-3CR and the Ugi-4CR is the mandatory use of isocyanides in these reactions. As already stated by Ugi, isocyanides possess "horrible" odors, which had suppressed the chemistry of isocyanides.[11] In this context, polymer chemists have been exploring MCRs suitable for polymer synthesis based on nonisocyanide chemistry.[12−16] For example, the group of Choi as well as our group independently showed the successful utilization of Cu(I)-catalyzed three component reaction between sulfonyl azides, terminal alkynes, and amines (CuMCR) for constructing defined polymeric structures.[15,16]

To further enrich the synthetic MCR portfolio for polymer chemistry, we turned our attention to the Kabachnik-Fields reaction between aldehydes, amines, and phosphites because Kabachnik-Fields reactions proceed with high reactivity and selectivity.[17] Although Tao et al. demonstrated a concurrent Kabachnik-Fields reaction and RAFT polymerization in a one-pot process, the applicability of Kabachnik-Fields reaction with high molecular weight compounds has not been studied in detail.[13] Hence, in the present study we now aim to examine and precisely investigate the Kabachnik-Fields reaction with high molecular weight compounds.

In this study, we describe the structural assignment and a library synthesis of functional polymers via Kabachnik-Fields

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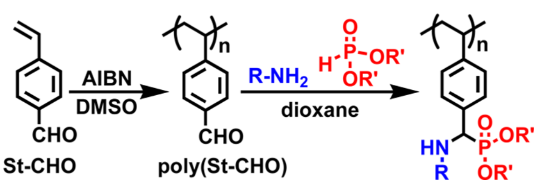
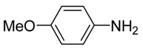
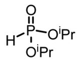
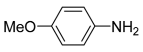
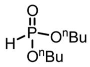
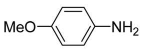
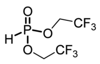
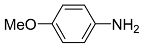
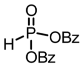
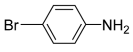
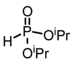
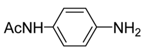
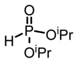
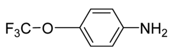
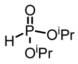
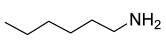
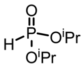
postpolymerization modification reaction (KF-PMR) and insights into the reaction mechanism for KF-PMR (Scheme 1).

Scheme 1. Schematic Representation of Kabachnik-Fields Postpolymerization Modification Reaction on Poly(4-vinyl benzaldehyde) (Poly(St-CHO))



To establish a versatile reaction platform, the Kabachnik-Fields postpolymerization modification reaction (KF-PMR) had to be optimized. In order to achieve this, poly(4-vinyl benzaldehyde) (poly(St-CHO), M_n = 42000) was prepared by free radical polymerization of 4-vinyl benzaldehyde (St-CHO) in DMSO. First, a KF-PMR was conducted in 1,4-dioxane in the presence of a large excess of *p*-anisidine and diisopropyl phosphite at 80 °C for 8 h (Table 1, run 1). As confirmed by the ^{1}H NMR spectrum of the obtained polymer (Figure 1), practically 100% conversion of aldehyde groups of the starting polymer was achieved. IR measurements of polymers before and after the KF-PMR revealed that the band at 1699 cm^{-1} owing to C═O stretching of aldehyde groups clearly disappeared (Figure S-1), confirming the practically quantitative conversion of aldehyde moieties. A SEC trace of the polymer after the KF-PMR revealed that the reaction system did not involve any detectable decomposition or cross-linking of the polymer chains. Neither high molecular weight shoulders nor peaks had been detectable after the KF-PMR (Figure S-2).

Table 1. Kabachnik-Fields Postpolymerization Reactions Starting from Poly(St-CHO)[a]

run	amine	phosphite	generation of amino-phosphonate (conv. of CHO) (%) [b]
1		 $\mathrm{H{-}P(=O)(O^iPr)(O^iPr)}$	> 99 (> 99)
2		 $\mathrm{H{-}P(=O)(O^nBu)(O^nBu)}$	94.1 (> 99)
3		 $\mathrm{H{-}P(=O)(OCH_2CF_3)(OCH_2CF_3)}$	83.6 (98.0)
4		 $\mathrm{H{-}P(=O)(OBz)(OBz)}$	95.0 (> 99)
5		 $\mathrm{H{-}P(=O)(O^iPr)(O^iPr)}$	> 99 (> 99)
6		 $\mathrm{H{-}P(=O)(O^iPr)(O^iPr)}$	> 99 [c] (> 99 [c])
7		 $\mathrm{H{-}P(=O)(O^iPr)(O^iPr)}$	> 99 (> 99)
8		 $\mathrm{H{-}P(=O)(O^iPr)(O^iPr)}$	63.6 (96.4)

[a] 1,4-Dioxane as a solvent; initial aldehyde concentration was adjusted to be 1.5 mol·L^{-1}; Ar atmosphere; $[\mathrm{CHO}]_0/[\mathrm{amine}]_0/[\mathrm{phosphite}]_0$ was adjusted to be 1/3/6; the reaction was conducted for 8 h. [b] The chemical compositions of the recovered polymers were determined by ^{1}H NMR measurements in $CDCl_3$. [c] The chemical compositions of the recovered polymers were determined by ^{1}H NMR measurements in CD_3OD.

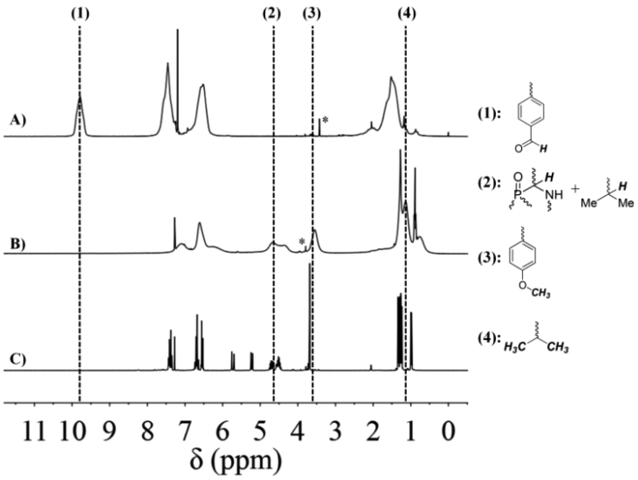


Figure 1. ^{1}H NMR spectra in $CDCl_3$ of poly(St-CHO) (A), the obtained polymer by Kabachnik-Fields reaction on poly(St-CHO) with *p*-anisidine and diisopropyl phosphite (B, run 1 in Table 1), and the model monomer St-AP (C). The symbol (*) refers to peaks owing to residual solvents.

In order to provide a direct evidence that the reaction proceeded via the Kabachnik-Fields reaction among the amines, phosphites, and the polymeric aldehydes, ^{1}H NMR measurements of the obtained polymers (run 1) were conducted and the results are shown in Figure 1. First, a sharp peak at 9.8 ppm owing to the aldehyde proton of poly(St-CHO) clearly disappeared and a peak at 3.5 ppm appeared, owing to the methyl protons of *p*-anisidine (Figure 1B). This shows that the aldehyde group of poly(St-CHO) was completely consumed and the *p*-anisidine was incorporated via the KF-PMR. In addition, peaks ranging from 4.1 to 5.0 ppm and from 0.5 to 1.4 ppm appeared, owing to the diisopropyl and benzyl protons (Figure 1B). Thus, not only amines, but also phosphites, were integrated in the obtained polymer. In order to eliminate a possibility of concurrent side reactions, a detailed analysis using model compounds was further carried out. For comparison and verification of the successful reaction processes, the Kabachnik-Fields reaction with low molecular weight model compounds was monitored by using ^{1}H NMR measurements. The Kabachnik-Fields reaction between the corresponding monomeric structure of the polymer, namely, 4-vinyl benzaldehyde (St-CHO), *p*-anisidine, and diisopropyl phosphite, was conducted in $CHCl_3$ to afford a model monomeric compound, diisopropyl [(4-methoxyphenyl)amino-4-vinylphenyl-methyl]-phosphonate (St-AP). As shown in Figure 1C, the benzyl proton and isopropyl methine protons of St-AP were observed in the region ranging from 4.4 to 4.8 ppm. In addition, methyl proton of the *p*-anisidine was observed at 3.7 ppm. These results gave a good agreement with the ^{1}H NMR spectrum of the obtained polymer by KF-PMR. In order to provide a direct evidence that phosphite moiety was integrated via KF-PMR, ^{31}P NMR spectra of the obtained polymer and the model monomer (St-AP) were recorded (Figure S-3). As shown in Figure S-3, in the ^{31}P NMR spectrum of the obtained polymer, a sharp peak at 21.3 ppm was observed, which was in a good agreement with the peak of St-AP observed at 20.8 ppm. Thus, the facile utilization of the Kabachnik-Fields reaction as a successful postpolymerization modification process was demonstrated by using model reactions and compounds.

To show the direct applicability of KF-PMR, a library of functional polymers was synthesized with varying amine and phosphite functionalities. As shown in Table 1, amines and phosphites with diverse functionalities could be successfully installed with high efficiency. In general, aromatic amines yielded quantitatively the α-amino phosphonates, while aliphatic amines resulted in lower conversions. It is worth noting here that the model monomer (St-AP) could not be polymerized in 1,4-dioxane at 80 °C with AIBN as a radical initiator, probably owing to steric hindrance and hydrogen abstraction of the α-amino phosphonate unit of St-AP. This clearly shows the advantage of KF-PMR to prepare polymeric α-amino phosphonates, which cannot be prepared by direct polymerization of the corresponding monomers.

Next, detailed kinetic investigations of the KF-PMR were carried out. Figure 2 shows a kinetic evolution of the chemical compositions of the obtained polymers after KF-PMR on poly(St-CHO) in 1,4-dioxane at 80 °C with 3 equiv of *p*-anisidine and 6 equiv of diisopropyl phosphite. The fraction of α-amino phosphonate moieties increased with increasing reaction time and reached >99% within 6 h. Along with the clear increase in α-amino phosphonate moiety generated by KF-PMR, the fraction of imine moieties decreased contrastively and disappeared also within 6 h. Noteworthy, aldehyde groups were consumed almost immediately (less than 15 min). These kinetic behaviors were also supported by IR kinetic measurements and are summarized in Figure S-4. These results on kinetics clearly indicated that (1) the imination of poly(St-CHO) with aromatic amines was a extremely fast process and the chemical equilibrium between aldehyde and imine largely shifted toward imine formation in spite of the fact that the generated water was not removed from the reaction mixture and (2) thus the rate-limiting step was the addition of phosphite moieties to the generated polymeric imines. In this context, in order to further confirm the reaction mechanism of KF-PMR, kinetic studies of the effects of reactant concentrations were conducted. The concentration of amines had no effects on KF-PMR conversions and only 5% excess of amine to aldehydes was enough to achieved practically quantitative conversion (Figure S-5). In a clear contrast to the amine component, an obvious concentration dependence was observed for the phosphite component (Figure S-6). To be precise, the composition of amino phosphonate of the obtained polymers by KF-PMR was decreased to 87.4% in the presence of 2.0 equiv of diisopropyl phosphite and 71.5% in the presence of only 1.05 equiv of diisopropyl phosphite, whereas a large excess of phosphite (>6 equiv) resulted in a practically quantitative conversion of aldehydes to amino phosphonate moieties. Thus, the following conclusions about the reaction mechanism of KF-PMR can be drawn and are depicted in Scheme 2: (1) The reaction rate of KF-PMR on poly(St-CHO) was solely dependent on the concentration of phosphites and (2) the necessary amount of amines could be reduced down to only 5% excess against aldehyde groups, making it an ideal candidate for employing a variety of amines in PMRs.

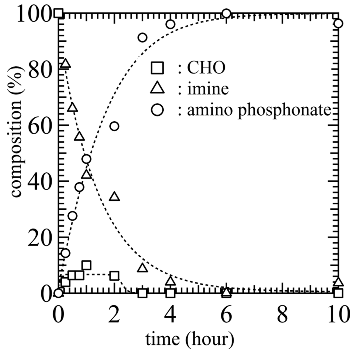
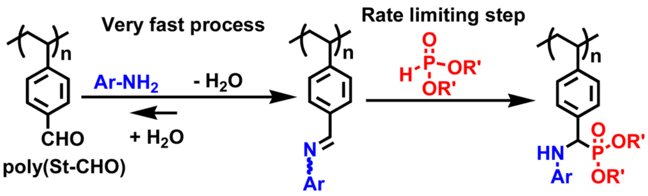


Figure 2. Kinetic plot for the Kabachnik-Fields reaction on poly(St-CHO) with *p*-anisidine and diisopropyl phosphite (line; guidance). Reaction conditions are as followings; 1,4-dioxane as a solvent; initial aldehyde concentration was adjusted to be 1.5 mol·L^{-1}; Ar atmosphere; $[CHO]_0/[amine]_0/[phosphite]_0$ was adjusted to be 1/3/6. The chemical compositions of the recovered polymers were determined by ^{1}H NMR measurements in $CDCl_3$.

Scheme 2. Schematic Representation of a Reaction Mechanism of KF-PMR



In conclusion, we have successfully established a new PMR protocol that allows installation of two different functionalities per single repeating unit with high efficiency and wide range of functionalities. Insight into mechanism of KF-PMR revealed that the imine formation reaction was fast and the chemical equilibrium between aldehyde and imine largely shifted toward imine formation for aromatic amines and aromatic aldehyde even in the presence of water and the rate determining step was the addition of phosphites. All in all, the Kabachnik-Fields reaction is a suitable reaction for the postpolymerization modification of polymers, which shows the advantages of attachment of amines in practically equivalent amounts in a MCR without the need for a metal catalyst. The properties of the resulting α-amino phosphonates as side groups are additionally highly interesting and are currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and the ^{1}H NMR spectra of obtained polymers are listed. 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

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