Solvent-Free Mechanochemical Post-Polymerization Modification of Ionic Polymers

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Despite their superior stability and facile handling, ionic polymers have limited solubility in most organic solvents, restricting the range of substrates and reaction conditions to which they can be applied. To overcome this solubility issue, the present study presents a solvent-free mechanochemical reaction. Specifically, a post-polymerization modification of ammonium-functionalized polyether was demonstrated using a solvent-free vibrational ball-milling technique. The formation of imine bonds between the ionic polymer and an aromatic aldehyde led to the complete conversion to imine within 1 h without any bond breakage on the polymer backbone. The viability of this approach for a wide range of aldehydes was also evaluated, highlighting the potential of the mechanochemical post-polymerization modification of polymers that are inaccessible by conventional solution approaches.

Mechanochemistry is a chemical reaction that is induced by the direct application of mechanical energy. Mechanochemical reactions are typically fast,[1] can be conducted without a solvent,[2,3] and allow for the chemoselectivity to be adjusted via neat and liquid-assisted grinding.[4] As such, mechanochemical approaches have been widely employed in many areas of synthetic chemistry.[5–7] Though mechanical force is often associated with destructive aspect in polymer science, including particle size reduction and chain breaking, mechanochemical approaches have recently received significant attention for the synthesis of polymers. For example, poly(phenylene vinylene) has been synthesized using Gilch polymerization via ball-milling,[8] while the polycondensation reaction between diamine and dialdehyde was successfully induced using planetary ball-milling.[9] Kim and co-workers recently demonstrated the

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mechanochemical ring-opening polymerization of lactide,[10] and Cho and Bielawski have shown that atom transfer radical polymerization is also possible via a mechanochemical reaction.[11]

The difference in the solubility of polymers and small molecules often impedes any reaction between the two. For example, the solubility of ionic polymers in most organic solvents is low, limiting the range of substrates and reactions with which they can be involved. In order to address this issue, a number of different approaches have been suggested, including multi-step reactions[12] and reactions with co-solvents.[13] Indirect approaches, such as the use of block copolymers[14] or functional groups,[15] to increase the solubility of polymers in organic solvents have also been proposed, but these are not optimal because the original polymer must be modified.

In this context, solvent-free mechanochemical post-polymerization modification (PPM) could address this challenge by bypassing the solubility issues.[16] The potential of mechanochemical PPM has been demonstrated previously, including the ω-functionalization of α-methoxy-functionalized poly(ethylene glycol) (mPEG) in the solid state[17] and thiol substitution in polynorbornene derivatives.[18] In addition, Ohn and Kim reported the PPM of the hydrophobic poly(4-vinyl benzaldehyde) with the ionic reactant ammonium carbonate,[19] while Moores and co-workers recently investigated the mechanochemical phosphorylation of cellulose nanocrystals, which have poor solubility in common organic solvents.[20]

Imine bond formation is usually conducted in organic solvents such as dichloromethane and tetrahydrofuran,[21,22] mostly commonly via the reaction between amines and aldehydes.[23] Replacing the amine with an ammonium salt as a substrate for imine bond formation represents a convenient means to access the amine group due to its higher stability in ambient conditions and facile handling.[24] However, while most of the ammonium salt dissolves in water, this impedes the imine bond reaction, which requires a dehydration step between the amine and aldehyde. To overcome this issue, the use of phase-transfer catalysts has been suggested, though this leads to a poor reaction and conversion rate.[25] Herein, we propose a solvent-free mechanochemical approach for the PPM of ammonium-functionalized polyether as a representative ionic polymer. The polyether was reacted with various aldehydes of different solubilities, resulting in a fast reaction rate with full conversion (Scheme 1).
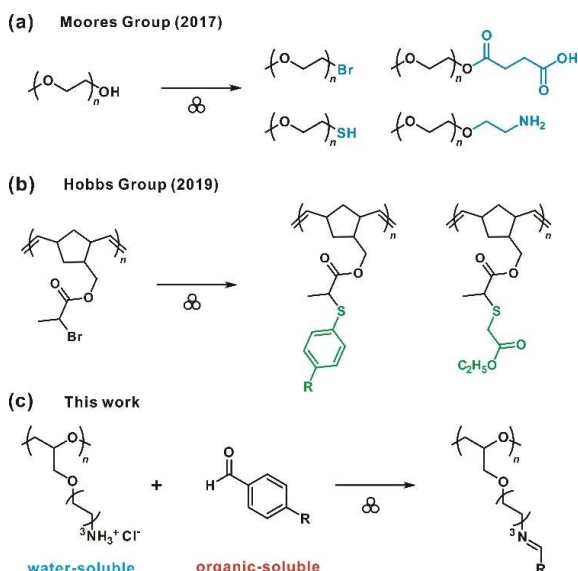
A model ionic polymer with a polyether backbone was selected for this study for the following two reasons: (1) high

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Scheme 1. Mechanochemical post-polymerization used to modify (a) *m*PEG,[17] (b) polynorbornene derivatives,[18] and (c) ammonium-functionalized polyether.

aqueous solubility and (2) limited chain scission during mechanochemical reactions. Polyether is a biocompatible polymer with ultrahigh water solubility, a stealth effect, and low immunogenicity.[26,27] For this reason, polyether derivatives are currently employed when high water solubility is required, such as for drug delivery systems[28,29] and hydrogels.[30,31] Moreover, it is known that a backbone scission is a commonly observed side reaction during the mechanochemical ball-milling of polymers, with the backbone scission rate proportional to the glass transition temperature (T_g) of the polymer.[32] Because the T_g of polyether is lower than that of polymers with a rigid carbon backbone,[33] the use of polyether could potentially ameliorate backbone scission.

Ammonium-functionalized polyether was synthesized using anionic ring-opening polymerization (AROP) with a novel epoxide monomer, azidohexyl glycidyl ether (AHGE), as reported previously by our group (Figure S1).[34] The polymerization of AHGE was conducted with the organic superbase *t*-BuP$_4$ using benzyl alcohol as an initiator in toluene at room temperature. The AROP of AHGE led to a conversion of over 99% for the monomers within 10 h, yielding P(AHGE)$_{20}$ with a highly controlled molecular weight and dispersity, as evidenced by ^{1}H NMR spectroscopy and size-exclusion chromatography
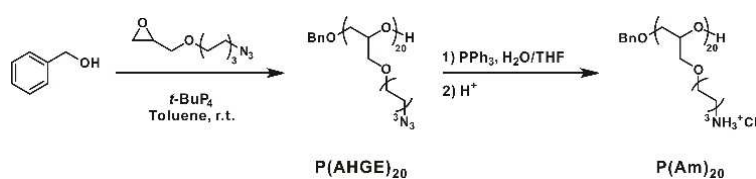
(SEC) (Table S1 and Figure S2). Subsequently, Staudinger reduction was performed using triphenylphosphine to transform the azide functionalities along the polymer backbone to the ammonium moiety P(Am)$_{20}$ (Scheme 2).

The prepared ammonium-functionalized polyether P(Am)$_{20}$ was then subjected to a mechanochemical reaction with benzaldehyde to form imine bonds. In this study, we used the high-speed vibratory ball mill MM400 (Restch) with a 10-mL stainless jar and 7-mm stainless balls. The P(Am)$_{20}$ was ground in the jar with benzaldehyde as a representative aldehyde and potassium carbonate at a frequency of 30 Hz for 1 h. The formation of the product was determined on the basis of ^{1}H NMR spectroscopy (Figure 1).

While it was not possible to accurately monitor the consumption of the starting polymer P(Am)$_{20}$ in D$_2$O due to the limited solubility of the imine product in water, subsequent analysis with both D$_2$O and CDCl$_3$ proved that the reaction underwent full conversion. First, the lack of a signal from the polymer in the ^{1}H NMR spectrum in D$_2$O confirmed that the P(Am)$_{20}$ had been fully consumed. In particular, the complete disappearance of the characteristic peak at 2.96 ppm corresponding to the protons adjacent to the ammonium group (Figure 1, peak a) confirmed the full conversion of this reaction. Furthermore, the distinct peak corresponding to the proton at the imine bond emerged at 8.23 ppm (Figure 1, peak b). The ratio of the peak integral between peak b and other peaks also confirmed the complete formation of imine bonds.

Once we confirmed the successful formation of the imine bonds, various mechanochemical parameters were optimized, including the number of balls, the applied frequency, and the reaction time (Table 1). Because the mechanical force in a ball-milling system is delivered via the friction of the metal balls, the number of balls and the frequency is directly correlated to the mechanical energy and mixing efficiency, resulting in greater impact per collision.

As expected, the conversion was higher as the number of balls[6] and frequency[35] increased (entries 1–4 and 6 in Table 1). 1 h was required for full conversion (entries 5 and 6). Interestingly, applying more mechanical force on the benzaldehyde-functionalized P(Im)$_{20}$ did not produce any signs of side reactions, such as imine bond breakage (entry 7). Based on these data, we concluded that this reaction was indeed affected by the mechanical force and could be controlled with various mechanochemical parameters.

Under the previously determined optimized conditions, the viability of this mechanochemical approach with other aldehydes was investigated (Scheme 3). Aldehydes with varying
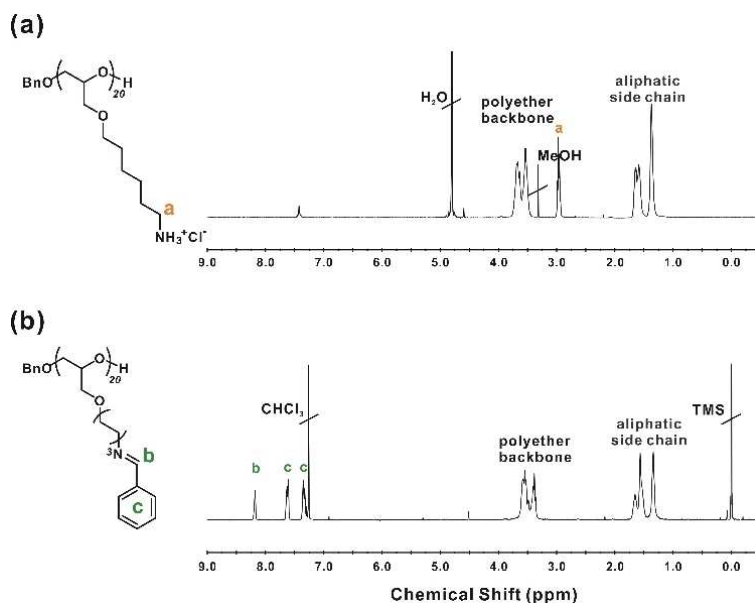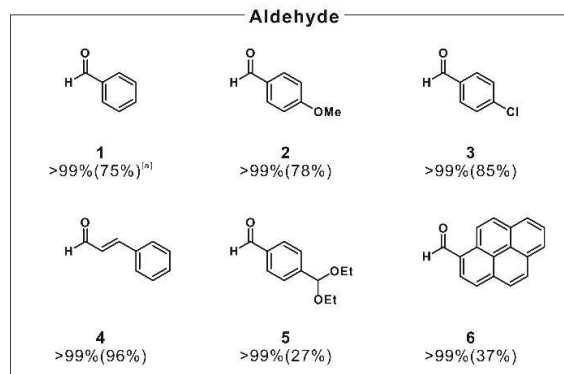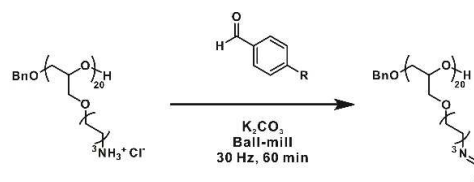

Scheme 2. Synthesis of ammonium-functionalized polyether using anionic ring-opening polymerization with AHGE, followed by the Staudinger reduction of P(AHGE)$_{20}$ to P(Am)$_{20}$.

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Figure 1. Mechanochemical imine formation of $P(Am)_{20}$ with the corresponding ^1H NMR spectrum of (a) $P(Am)_{20}$, and (b) imine formation with benzaldehyde $(P(Im)_{20})$. (a) is measured in D_2O, whereas (b) is measured in $CDCl_3$.

Table 1. Optimization of the mechanochemical parameters used in this study.[a]

Entry	Number of balls	Frequency [Hz]	t [min]	Conversion[b] [%]
1	1	30	60	58
2	2	30	60	>99
3	3	10	60	54
4	3	20	60	63
5	3	30	30	67
6	3	30	60	>99
7	3	30	120	>99

[a] Reaction conditions: $P(Am)_{20}$ (30.0 mg, 0.14 mmol of the ammonium group), benzaldehyde (29.6 mg, 0.28 mmol), and K_2CO_3 (38.6 mg, 0.28 mmol) milled in a ball mill (10-mL stainless jar, 7-mm stainless balls). [b] Conversion analysis using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene or toluene as an internal standard.

electronic properties (**2–6**) were evaluated in comparison to the representative benzaldehyde (**1**). Regardless of its electronic properties, all the selected aromatic aldehydes (**2**, **3**) displayed full conversion with a high isolated yield, including cinnamaldehyde (**4**), a well-known anticancer drug.[28] An aldehyde with a protecting acetal group remained intact (**5**), and 1-pyrenecarboxaldehyde (**6**), an aldehyde with a bulky moiety, also showed complete conversion. In the reaction with 1-pyrenecarboxaldehyde, it was interesting to note that all the reactants employed in this system (i.e., the polymer, base, and aldehyde) were solid, which cannot be achieved under conventional bulk conditions. Compounds **5** and **6** had a relatively low isolated yield compared to the other compounds because the product has a similar solubility to the aldehyde, limiting the isolation of the product via precipitation (Figures S3–S8). During the reaction, no signals for backbone breakage or side-chain degradation were detected (Table S1 and Figure S9). It is also of note that

Scheme 3. Mechanochemical post-polymerization modification of $P(Am)_{20}$ with various functional aldehydes. [a] Conversion calculated using ^1H NMR spectroscopy (isolated yield).

the product had a similar molecular weight dispersity to the original polymer, indicating that there were no side reactions between the chains.

The scalability of this approach was further examined in a large scale. When the reaction with 300 mg of $P(Am)_{20}$, which is 10 times larger than the original scale was performed, it was found that the reaction proceeded smoothly at a full conversion with 67% isolated yield. This poses a high potential in scalability of the current mechanochemical post-polymerization modifica-

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tions. In addition, the polymer with a higher degree of polymerization was evaluated in this study. Interestingly, while the P(Am)$_{70}$ showed a modest conversion of 45% in the reaction with **1** for 1 h, it displayed a full conversion under longer reaction time of 3 h (Figure S10).

Unlike the successful conversion of the aromatic aldehydes, mechanochemical imine formation using aliphatic aldehydes was not accessible. The stability of the imine group is strongly determined by the presence of proximal electron-rich species such as a double bond or an aromatic ring.[36] As such, the product after the reaction with aliphatic aldehyde was degraded immediately after the ball-milling, preventing proper analysis.

In order to further illustrate the advantages of mechanochemical modification, we conducted the identical reaction in hexane, dichloromethane, and methanol (Figure 2). These solvents were selected on the basis of the solubility of the polymer and aldehyde. Both reagents are insoluble in hexane, only the aldehyde is soluble in dichloromethane, and both reagents are soluble in methanol. More polar solvents such as *N,N*-dimethylformamide and dimethylsulfoxide were insufficient to dissolve both reagents (Table S2). It was observed that the conversion rate after 6 h differed between the solvents, with a conversion rate of 7.1% in hexane, 24.0% in dichloromethane, and 81.0% in methanol. Even though both the polymer and aldehyde are soluble in methanol, full conversion could not be achieved even with a longer reaction time, highlighting the benefits of the proposed solvent-free mechanochemical approach.

In summary, we demonstrated successful solid-state imine bond formation using a solvent-free mechanochemical method. The ammonium moiety on the end of the aliphatic side chain of the polyether reacted with various types of aromatic aldehyde, producing stable imine bonds on the polymer side chains. The ball-milling technique allowed a green reaction without the

need for organic solvents, which have potential environmental concerns. It was confirmed that various ball-milling parameters influenced the reaction rate, while the applied mechanical force did not break the backbone or the side chain of the polymer. In addition, the imine bonds were successfully formed regardless of the electronic properties of the aromatic aldehydes. Unlike the solvent-phase reaction, the proposed mechanical reaction led to full conversion for a range of aldehydes. We anticipate that the proposed approach opens a new direction for the mechanochemical modification of polymers with limited solubility.

Acknowledgements

Conflict of Interest

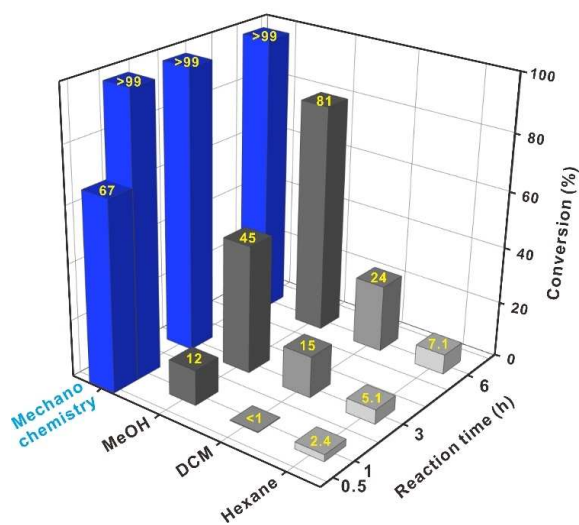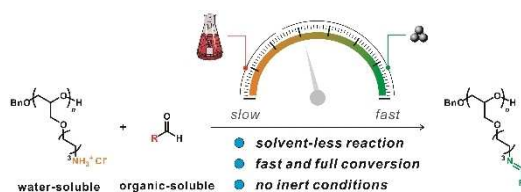The authors declare no conflict of interest.

Figure 2. Comparison of the post-polymerization modification of P(Am)$_{20}$ with 1-pyrenecarboxaldehyde via mechanochemistry and solvent-phase reactions in various reaction solvents. DCM: dichloromethane.

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Solvent-Free Mechanochemical Post-Polymerization Modification of Ionic Polymers

Mechanochemical modification: A solvent-free mechanochemical reaction is employed on reactants of different solubilities. The formation of imine bonds between a polyether with ammonium pendant groups and an aromatic aldehyde is induced via a vibrational ball-milling technique, leading to the fast and efficient production of imines in the pendant groups. Unlike the solvent-phase reaction, the proposed reaction leads to the rapid and full conversion of various aldehydes.