Superbase-enabled anionic polymerization of poly(alkyl cyanoacrylate)s: achieving well-defined structures and controlled molar masses

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Abstract

Poly(alkyl cyanoacrylate)s (PACAs) find extensive use as adhesives in engineering and medicine. However, their high reactivity often leads to wide molar mass dispersity and uncontrolled chain-end functionalities. Achieving precise polymer structures is crucial, particularly for medical applications to prevent oligomer toxicity. The conventional anionic polymerization of cyanoacrylates initiated by water results in high molar mass dispersities ($Đ$) and low end-group functionalities. Nonetheless, under specific conditions, anionic polymerization holds the potential for controlling the molar mass and $Đ$ of PACAs. Here, we demonstrate the synthesis of well-defined PACAs by employing minute quantities (1%) of superbases to activate a functional thiophenol (PhSH) initiator. This strategy enables the attainment of adjustable molecular weights ($M_n > 20$ kg mol^{-1}) and moderate dispersities ($Đ < 1.4$) for homopolymers and block copolymers. The selective initiation by thiophenol is confirmed through ^{1}H DOSY NMR analysis. Furthermore, the controlled homo- and copolymerization of ACA derivatives highlights the remarkable performance of the superbase in conjunction with PhSH.
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Keywords: cyanoacrylate; anionic polymerization; superbases; phosphazene; super glue

INTRODUCTION

The excellent adhesion properties of poly(alkyl cyanoacrylate)s (PACAs) make them a popular 'super glue'.[1–4] The two electron-withdrawing groups (ester and cyano) are responsible for their outstanding reactivity and tendency to undergo fast polymerization.[3, 5, 6] This feature makes ACAs one of the rare monomer types able to be polymerized by an anionic polymerization (AP) mechanism in the presence of water.[7, 8] For commercial super glues, the moisture in the air is sufficient to initiate their polymerization. Also, aqueous emulsion polymerization of ACA was reported to produce high-molar-mass PACAs due to the fast propagation rates.[9–11] The US Food and Drug Administration-approved ACA instantly polymerizes in contact with blood and is widely used as a tissue adhesive for external as well as internal wounds, as it has been reported to be biodegradable.[12–17] PACAs are not only excellent adhesive materials, but were also found to be very promising polymer matrices as electrolytes for lightweight high-voltage batteries.[18, 19] PACAs also attracted attention in drug delivery and medical imaging as they were reported to pass the blood–brain barrier.[9, 17, 20, 21]

However, well-defined polymers are required to understand structure–property relations and to ensure biocompatibility for drug delivery. The toxicity of PACAs depends on the degree of polymerization as oligomers were found to be toxic.[14, 22] Thus, narrow $Đ$ and adjustable molecular weights would be desirable. However, high definition is difficult to achieve with these highly reactive ACA monomers. AP is one of the superior methods for the preparation of well-defined polymers. The AP of ACAs was widely investigated in the search for controlled polymerization conditions.[5, 23–28] Numerous studies can be found about the effect of pH on the AP of ACAs in solution and emulsion.[7, 8, 10, 29] Nonionic nucleophiles such as phosphines and amines as initiators form zwitterions as the propagating species.[5, 24, 30–32] Zwitterionic polymerizations have shown near-ideal kinetics resulting in narrowly distributed high-molar-mass polymers. However, PACAs with end-group functionalities would open up doors to new applications in medicine and fabrication. Selective initiation

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with functional moieties has to be investigated more extensively to achieve controlled AP of ACAs with tailored functionalities.

In the study reported here, we investigated the use of superbases as organocatalysts for the controlled polymerization of ACAs with a nucleophilic initiator, namely thiophenol. Superbases are renowned for their ability to facilitate rapid proton exchange and have been extensively employed as activators in diverse polymerization processes.[33–36]

Furthermore, we developed a custom-designed polymerization reactor utilizing polytetrafluoroethylene (PTFE) material (Fig. 1). The design of this reactor serves the purpose of minimizing water adsorption on the reactor surface and mitigating undesired initiation reactions that may occur through Si–OH groups on glass surfaces.[5] By reducing moisture interference, we achieved higher control over the AP of ACAs within an inert gas environment. This improved control offers promising prospects for exploring various polymer architectures incorporating biodegradable PACA segments.

MATERIALS AND METHODS
Chemicals
All solvents and chemicals were purchased from common suppliers (TCI, Sigma-Aldrich, Acros, Roth, Fischer Scientific, Fluka) and used without further purification unless particularly noted. Deuterated solvents for NMR measurements were purchased from Deutero GmbH (Kastellaun, Germany) and used without special processing. Deuterated tetrahydrofuran (THF-d_8) was dried over molecular sieves (4 Å). n-Butyl cyanoacrylate (BCA) was kindly supplied by Henkel Ireland Ltd (Loctite) and contains hydroquinone as stabilizer. N-Hexyl cyanoacrylate (HCA) was purchased from Cuantum (Barcelona, Spain). UHU® super glue was the source for ethyl 2-cyanoacrylate (ECA). THF for the anionic polymerization was purchased as a 98% grade and dried over sodium using benzophenone as an indicator. It was distilled freshly prior to every polymerization by cryo-transfer directly into the reaction flask.

SEC (gel permeation chromatography, GPC)
SEC measurements were performed with a PSS SECurity (Agilent Technologies 1260 Infinity) equipment including three SDV (PSS) columns (10^6, 10^4, 500 Å) and a PSS-WinGPC UniChrom (PSS) detector (RI, UV 254 nm) in THF at 30 °C and a flow rate of 1 mL min^{-1}. Calibration was carried out by using poly(methyl methacrylate) standards provided by Polymer Standards Service.
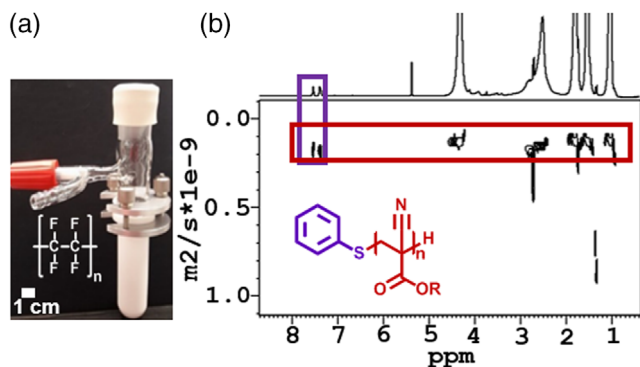
Figure 1. (a) PTFE reactor for the anionic polymerization of cyanoacrylates. (b) ^{1}H DOSY NMR spectra of PhSH-initiated poly(butyl cyano acrylate) (PBCA) proving successful attachment of the initiator to the polymer.

Nuclear magnetic resonance
The ^{1}H NMR measurements were performed with a 300, 500 and 700 MHz Bruker AMX system at 298.3 K. Diffusion ordered spectroscopy (^{1}H DOSY) was conducted with a Bruker 400 AMX NMR spectrometer under similar conditions as described above. The measured spectra were referenced to the residual proton signal of the deuterated solvent (CDCl$_3$ (^{1}H) = 7.26 ppm; methylene chloride-d_2 (^{1}H) = 5.32 ppm; THF-d_8 (^{1}H) = 3.58 ppm) and evaluated with TopSpin 3.5 (Bruker) and MestReNova 12.0.1 software (Mestrelab Research SL).

Syntheses: Anionic Polymerization of ACAs
All glassware was treated with concentrated nitric acid, washed thoroughly with deionized water, and finally Milli-Q® water to inactivate the glass surface. The Teflon reactors were used without acid treatment. After cleaning, the reaction vessels (glass or Teflon) were dried overnight in an oven at 100 °C and attached to a Schlenk apparatus for drying at reduced pressure. In the case of the Teflon reactors, dried benzene (2 mL) was added and the apparatus was dried *in vacuo* overnight to remove any remaining water. The procedure for solution polymerization of ACA was as follows: 1 mL of ACA was dissolved in 15 mL of freshly cryo-distilled THF under argon. To this solution, the initiator and catalyst (according to Table 1) dissolved in dry THF were added quickly with constant stirring. After the polymerization process was finished (NMR control), the polymerization was terminated with HCl-acidified methanol. The reaction solution was precipitated in a cooled mixture of acidified methanol and water (1:1). The precipitate was collected by centrifugation at 4000 rpm and the wet solid was freeze-dried overnight to afford a colorless powdery polymer. The yields of the produced polymer were typically 80% quantitative (see Table 1 for details; Figs S1–S3 show the ^{1}H NMR spectra, Figures S6–S8 the ^{1}H DOSY NMR spectra).

RESULTS AND DISCUSSION
Since ACAs can be initiated by most nucleophiles, even small amounts of impurities in the reaction setup reduce the control over the polymerization.[37–39] Competing nucleophiles may lead to a broadening of the molar mass dispersity due to additional initiations, e.g. from the glass surface. The undesired initiation of ACAs by the glass was previously prevented by inactivating the glass surface with nitric acid.[5] However, the treatment with the acid and rinsing of the glass flask is an additional step and more importantly not controllable. We designed a new reactor made of inert PTFE, which was equipped with a connector to a vacuum line and a septum (Fig. 1(a)). We demonstrated the selective initiation of BCA by the chosen initiating/catalyst species (PhSH, PhSLi, or PhSH plus organocatalysts) in our PTFE reactor (Fig. 1(b)). In contrast to a reaction in a glass flask, the PTFE reactor provided reproducibly a monomodal molar mass distribution of resulting poly(butyl cyanoacrylate) (PBCA), while glass reactors sometimes produced multimodal molar mass distributions (Fig. S4).

The control of the initiating step is important to ensure control of the molar mass (M_n) and Đ of the synthesized polymers. In addition, the selective initiation of monomers enables possibilities to introduce chemical functionalities and tailor the polymer properties. Here, we used PhSH as a UV-active nucleophile to demonstrate selective initiation in the AP of BCA (Scheme 1). The attachment of the initiator to the polymer chain was evidenced by the ^{1}H DOSY NMR spectra (Fig. 1(b)). The aromatic resonances of thiophenol at 7.56 ppm were detected at the same diffusion

Table 1. Characterization data for the poly(alkyl cyano acrylate)s: BCA (entries 1–8 and 11–15), ECA (entry 9), and HCA (entry 10) using thiophenol and superbases as catalyst

Entry	Base	[M]:[I]:[B]	M_n (NMR) (kg mol^{-1})[a]	M_n (SEC) (kg mol^{-1})[b]	Đ[b]	Conversion (%)[a]	Yield (%)[c]
1	None	100:1:0	29	4	4.53	88	53
2	P$_4$-tBu	100:1:1	16	7	1.70	98	88
3	P$_4$-tBu	300:1:0.01	38	11	1.68	98	93
4	P$_4$-tBu	300:1:0.1	45	10	1.68	99	86
5	P$_4$-tBu	300:1:0.5	56	11	1.59	99	89
6	P$_4$-tBu	300:1:1	45	11	1.47	98	87
7	P$_4$-tBu	600:1:1	99	15	1.29	94	70
8	P$_4$-tBu	900:1:1	n.d.[d]	22	1.39	>99	86
9[e]	P$_4$-tBu	300:1:1	33	13	1.23	98	87
10[f]	P$_4$-tBu	300:1:1	47	6	1.80	98	66
11	DBU	100:1:1	7	7	1.54	>99	89
12	DBU	300:1:0.01	49	10	1.36	97	>99
13	DBU	300:1:0.1	46	10	1.38	99	98
14	DBU	300:1:0.5	44	9	1.42	97	>99
15	DBU	300:1:1	44	9	1.49	98	98

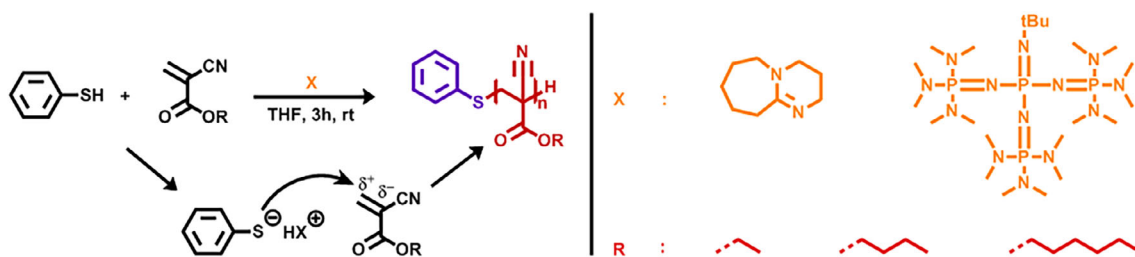[a] Determined via ^{1}H NMR of PACA in methylene chloride-d_2.
[b] Determined via SEC of PACA in THF after precipitation (*vs* poly(methyl methacrylate) standard).
[c] Determined after precipitation.
[d] Not determined.
[e] ECA monomer.
[f] HCA monomer.

Scheme 1. Scheme of the anionic polymerization of the alkyl(cyano acrylate)s (ACAs) using thiophenol as the initiator mediated by superbases.

coefficient as the polymer backbone at 4.28 ppm. Furthermore, the polymer trace in SEC shows a matching UV signal from the thiophenol initiator, indicating a successful selective initiation of BCA with PhSH (Fig. S5). The thiol of PhSH is a stronger nucleophile than alkoxides or water. However, the AP of BCA with PhSH alone resulted in a broad and multimodal molecular weight distribution (Fig. 2(a), purple trace). The initiator's acidity was probably not sufficient to completely deprotonate PhSH under these conditions in THF. Thus, PhSH alone did not provide a sufficiently fast initiation for optimal simultaneous chain propagation. Strong bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; pK$_a$ *ca* 21 in THF[40]) and phosphazene base (P$_4$-tBu; pK$_a$ *ca* 29[40]) have been widely used in AP as activating additives to achieve higher initiation rates and control over polymerization.[33–36] The PhSH/base combination (1:1 ratio) with P$_4$-tBu (Fig. 2(a), blue curve) and DBU (Fig. 2(a), green curve) exhibited high catalytic performance with the incorporation of PhSH into PACA. The attachment of the initiator was confirmed by ^{1}H DOSY NMR (Figs S6–S8). As a result, monomodal-distributed PBCA was obtained for both bases P$_4$-tBu and DBU (note: in P$_4$-tBu-catalyzed reactions, the phosphazene base needs to be removed prior to GPC analyses (Fig. S9)). The activation of PhSH with equivalent amounts of superbases

improved the molar mass dispersities. For P$_4$-tBu, Đ = 1.70 was obtained (Table 1, entry 2), whereas DBU-catalyzed polymerizations produced distributions with Đ = 1.54 (Table 1, entry 11).

The possibility of base initiation through a zwitterionic mechanism increases with increasing amount of base.[30, 41] Excess of the base may also activate/deprotonate competing nucleophiles in the reaction solution, which leads to increasing amounts of oligomers and a shifting of the maximum of the SEC trace (M_P) to lower molecular weights. We decreased the amount of base to determine if they still offer high proton exchange rates and maintain sufficient initiation rates. The AP of BCA with PhSH and different molar ratios of P$_4$-tBu shows a high activity of the initiator even as low as 0.01 eq. of base (Fig. 2(b)). The resulting polymers had in all cases monomodal distributions with moderate molar mass dispersities and full incorporation of the initiator (Table 1, entries 3–6). For DBU, high catalytic efficiency, and selective initiation were maintained with down to 1% DBU with respect to PhSH (Fig. 2(c)). Moreover, similar M_P is observed for all PhSH/DBU ratios indicating high initiation rates and efficient propagation. Decreasing the amount of base and maintaining high control over the AP of BCA highlight the catalytic efficiency of both superbases.
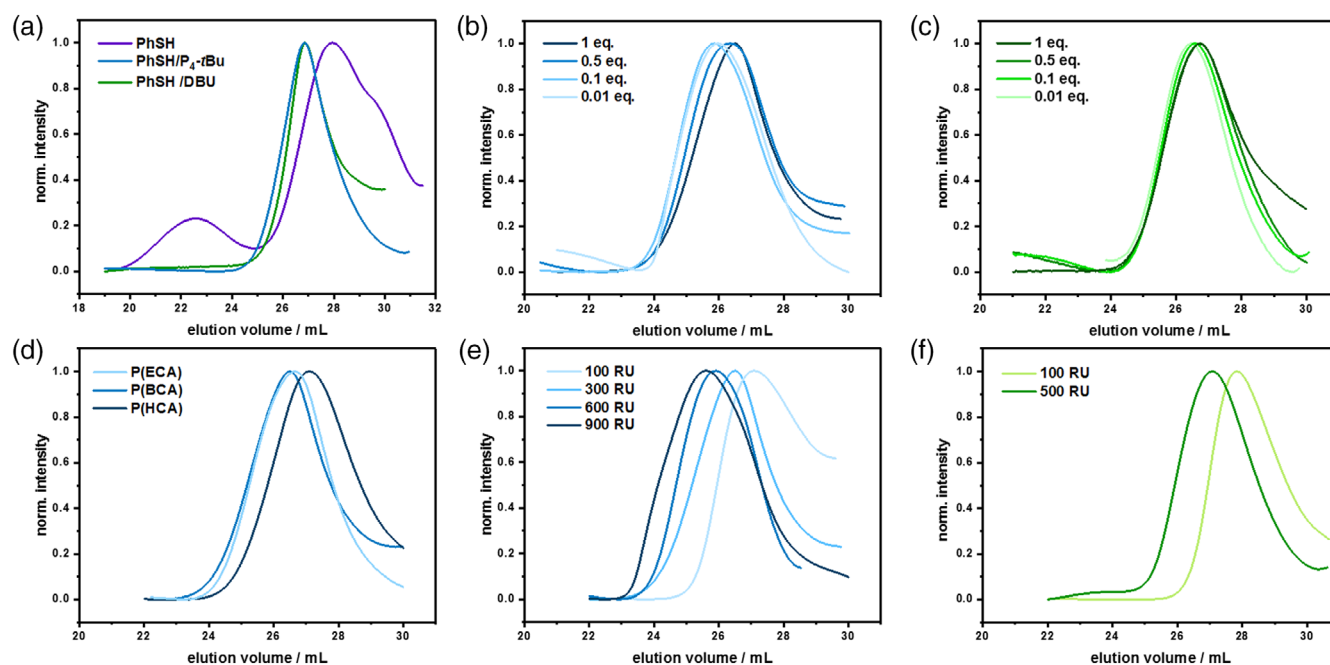
Figure 2. (a) SEC traces of PBCA initiated with PhSH, PhSH/P$_4$-tBu and PhSH/DBU. SEC traces of PhSH-initiated PBCA with different equivalents of (b) P$_4$-tBu and (c) DBU. (d) PhSH/P$_4$-tBu-initiated ACAs with ethyl, butyl and hexyl side chains. (e) PhSH/P$_4$-tBu-initiated PBCA with backbones of different repeat units. (f) PhSH/DBU-initiated chain extension experiment of PBCA (100 RU) with HCA (500 RU).

Controlled molar masses are important for medical applications, as shorter PACAs have been reported to be toxic.[14, 22, 42] Thus, a narrow distribution has to be maintained to decrease the amount of oligomers. M_n of synthesized PBCA could be adjusted with the monomer-to-initiator ratio. With P$_4$-tBu as a catalyst, PBCAs with M_n up to 22 kg mol^{-1} and Đ < 1.5 were obtained in high yields within 3 h (Fig. 2(e)). To demonstrate the excellent initiating abilities of the PhSH/base combination, ECA and HCA were polymerized under the same conditions (Fig. 2(d)). Both ACA derivatives also produced PACAs with high control over M_n and Đ. Moreover, the commercial mixture (containing ECA from UHU®) was polymerized with the PhSH/P$_4$-tBu mixture and produced polymers with moderate dispersity.

In living polymerization, the carbanion at the chain end remains active, if no terminating species are present. Therefore, the propagation of the active chain can be continued with further monomer addition. Here, the living character of the polymerization was investigated by chain extension experiments (Fig. 2(f)). The AP of BCA with PhSH/DBU gave a monomodal-distributed polymer (M_n = 3 kg mol^{-1}, Đ = 1.67). With the addition of a second ACA, here HCA, an increase of molecular weight to 6 kg mol^{-1} was observed proving the formation of block copolymer PBCA-b-PHCA. Moreover, the molecular weight distribution did not change significantly (Đ = 1.62), indicating the propagation and high chain-end fidelity under these conditions. The chain extension demonstrates not only stable and active carbanions at the polymer chain end but also the possibility of synthesizing PACA block copolymers.

CONCLUSION

We report the AP of ACA using superbases and thiol initiators. The enhanced initiation rates enabled high control over both the molar mass and distribution of the polymers. Further, employing a custom-designed PTFE reactor for the polymerization yielded improved reproducibility and selectivity compared to conventional glass flasks. Our results help in expanding the possibilities for preparing tailored PACAs with desired properties, including biocompatibility, degradability, and functionality, specifically for biomedical applications.

AUTHOR CONTRIBUTIONS

The paper was written through the contributions of all authors. All authors gave approval to the final version of the manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

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1083