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N-Heterocyclic Carbene-Mediated Zwitterionic Polymerization of N-Substituted *N*-Carboxyanhydrides toward Poly(α-peptoid)s: Kinetic, Mechanism, and Architectural Control

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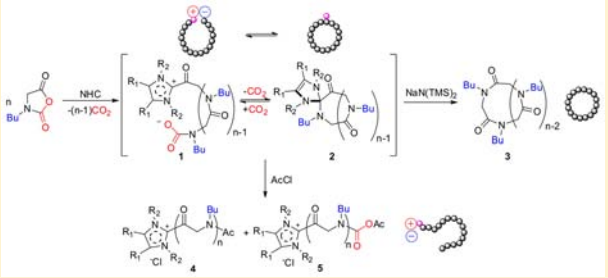
Supporting Information

ABSTRACT: *N*-Heterocyclic carbene (NHC)-mediated polymerizations of *N*-butyl *N*-carboxyanhydride (Bu-NCA) to produce cyclic poly(*N*-butyl glycine)s (c-NHC-PNBGs) have been investigated in various solvents with NHCs having differing steric and electronic properties. Control over the polymer molecular weight (MW) and polymerization rate is strongly dependent on the solvent and the NHC structure. Kinetic studies reveal that the propagating intermediates for the polymerization in low dielectric solvents (e.g., THF or toluene) maintain cyclic architectures with two chain ends in close contact through Coulombic interaction. The NHCs not only initiate the polymerization, but also mediate the chain propagation as intramolecular counterions. Side reactions are significantly suppressed in low dielectric solvents due to the reduced basicity and nucleophilicity of the negatively charged chain ends of the zwitterions, resulting in quasi-living polymerization behavior. By contrast, the two charged chain ends of the zwitterionic species are fully dissociated in high dielectric solvents. The chain propagation proceeds as in conventional anionic polymerizations, wherein side reactions (e.g., transamidation) compete with chain propagation, resulting in significantly diminished control over polymer MW. The cyclic zwitterionic propagating species can be converted into their linear polymeric analogues (l-NHC-PNBGs) by end-capping with electrophiles (e.g., acetyl chloride) or the NHC-free cyclic analogues (c-PNBGs) by treatment with $NaN(TMS)_2$, as evidenced by MALDI-TOF MS, NMR, and SEC analysis.



INTRODUCTION

Poly(N-substituted glycine)s, a.k.a. poly(α-peptoid)s, are a class of pseudopeptidic polymers having structures analogous to polypeptides, poly(2-oxazoline) or poly(*N*-substituted arylamide). Although they lack the hydrogen bonding and backbone chirality that is crucial for forming secondary structures in poly(α-peptide)s, poly(α-peptoid)s can still fold into stable secondary structures (e.g., PPI helix) as governed by the backbone rigidity, steric and electrostatic characteristics of the side chains.[1−4] Studies of oligomeric α-peptoids reveal their enhanced proteolytic stability[5,6] and membrane permeability[7] relative to poly(α-peptide)s as well as their amenability to thermal processing.[8,9] The combination of these attributes make poly(α-peptoid)s potentially useful for various biomedical applications (e.g., drug delivery carriers,[10,11] antimicrobial agents,[12] and lung surfactants).[13]

N-substituted *N*-carboxyanhydrides (R-NCA) have been shown to undergo ring-opening polymerization using nucleophilic initiators such as primary amines to yield poly(α-peptoid)s[14] in analogy to the polymerization of NCA monomers to produce poly(α-peptide)s. The propagating species bears a neutral secondary amino chain end in the case of R-NCA polymerization. The nitrogen (and in some cases α-carbon) substituent sterics strongly influence the reaction,[15,16] resulting in polymerization rates that span several orders of magnitude.[17] This significantly limits the scope of the monomers amenable to polymerization. Sarcosine-derived Me-NCA is the most well-studied monomer, and the polymerization of R-NCA with bulky side chains remain challenging.[18,19] Recently, Luxenhofer and co-workers have extended the methodology to a series of R-NCAs having up to four carbon alkyl side chains and synthesized well-defined amphiphilic block copoly(α-peptoid)s by sequential monomer addition.[11] The copolymers efficiently encapsulate hydrophobic molecules in aqueous solution, rendering them potentially useful for drug delivery applications. We have reported the primary amine-initiated polymerization of R-NCA bearing bulky chiral side chains (i.e., R = 2-ethylphenyl) to yield poly(α-peptoid)s of modest polymer MW, a consequence of extensive intramolecular transamidation.[4]

Cyclic α-peptoid oligomers with discrete ring sizes have been prepared recently by head-to-tail cyclization of linear precursors through stepwise solid-state synthesis methods.[20,21] The conformational homogeneity of these cyclic α-peptoids is greater than their linear analogues.[20,21] Cyclic poly(*N*-methyl

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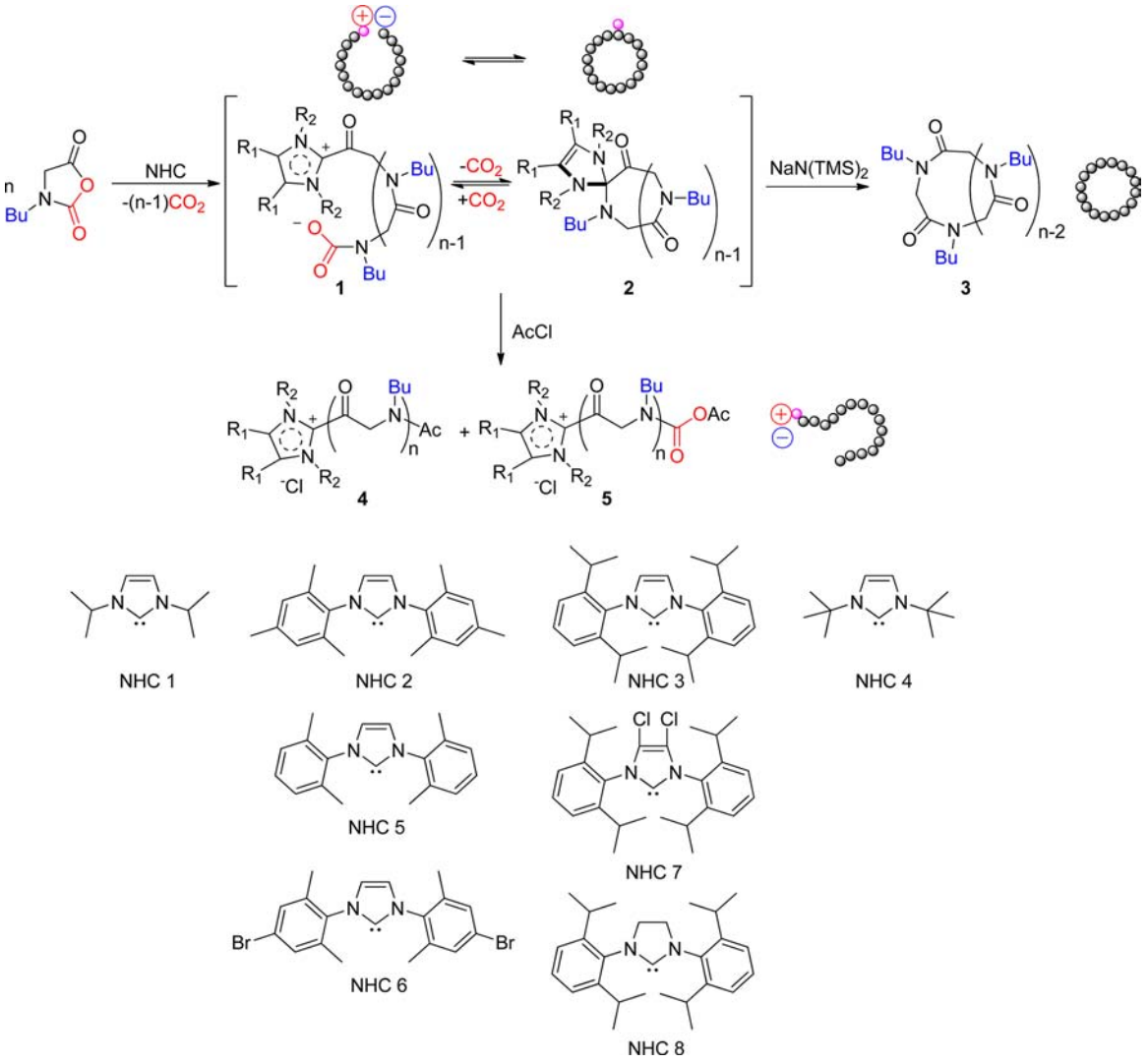
Scheme 1



glycine)s (a.k.a. polysarcosines) have also been synthesized from solvent/thermal-induced polymerization of Me-NCAs.[22,23] However, the polymer molecular weight or the average ring size is limited. We have recently reported that *N*-heterocyclic carbene (NHC) can mediate the ROP of R-NCA (R = Bu, Me) to yield the respective cyclic poly(α-peptoid)s with controlled polymer molecular weight (MW) and narrow molecular weight distribution (PDI).[24] The reaction proceeds in a quasi-living manner, enabling the synthesis of well-defined cyclic block copoly(α-peptoid)s by sequential monomer addition.[9,24,25] Waymouth, Hedrick, and co-workers have previously reported NHC-mediated ROP of cyclic esters (e.g., DL-lactide,[26,27] γ-caprolactone,[28] β-lactone,[29] or δ-valerolactone/γ-caprolactone)[30] to yield the respective cyclic homo or copolyesters. In their studies, termination by cyclization accompanied by the simultaneous release of the NHC appears to be competitive with propagation.[26,27] The only high MW cyclic polyesters were obtained for caprolactone polymerizations due to the extremely slow initiation relative to propagation.[28] By contrast, NHC-mediated ROP of ethylene oxide affords exclusively linear poly(ethylene oxide) (PEO) which can be end-functionalized to form telechelic PEO as recently reported by Taton, Gnanou, and co-workers.[31,32] All reactions were proposed to occur through a zwitterionic polymerization mechanism.

We now report a mechanistic investigation of the NHC-mediated polymerization of R-NCA. Kinetic studies combined with NMR and FT-IR spectroscopic analysis reveal that the polymerization occurs through zwitterionic propagating intermediates, where the solvent and the NHC significantly influence the polymerization rate and the polymer MW control. The NHC appears to initiate the polymerization in two distinct pathways, both resulting in the formation of zwitterionic initiating species. Synthetic strategies that convert the zwitterionic propagating intermediates into the linear or NHC-free cyclic polymeric analogues have also been developed. The polymerization method is applicable to a variety of R-NCAs, enabling the synthesis of poly(α-peptoid)s with diverse side chain structures.

RESULTS AND DISCUSSION

We have previously reported that 2,6-diisopropylphenylimidazol-2-ylidene (NHC3) -mediated polymerizations of Bu-NCA in THF produce poly(*N*-butyl glycine)s (PNBGs) with controlled polymer MW and narrow molecular distribution (PDI) (Scheme 1). ^{1}H NMR and ESI MS analysis reveals that

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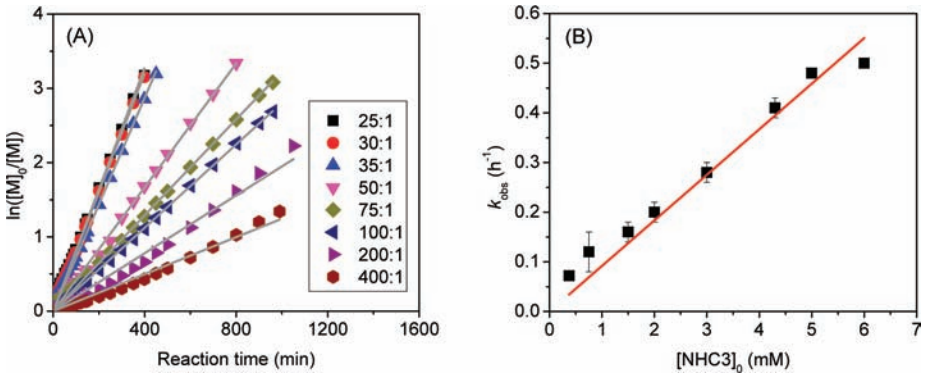

Figure 1. (A) Plots of $\ln([M]_0/[M])$ versus time for NHC3-mediated polymerization of Bu-NCA in toluene-d_8 at 50 °C with $[M]_0$ = 0.15 M and different $[M]_0$:$[NHC3]_0$ ratio; (B) plot of observed polymerization rate constant (k_{obs}) versus the initial NHC3 concentration.

the polymer has the desired poly(*N*-butyl glycine) backbone with one NHC affixed to the chain end, consistent with the proposed polymeric spirocycle **2** (Scheme 1).[24] Intrinsic viscosity studies conducted in DMF/LiBr (0.1M) suggest that the polymers have a cyclic architecture. We have also shown that **2** is photolabile and can be converted into NHC-free cyclic PNBGs **3** under MALDI-TOF MS conditions in selected matrices (Scheme 1).[33] Preliminary studies have also revealed the solvent dependence of the polymerization behavior, that is, polymerization in DMSO produces only low MW PNBGs irrespective of the initial monomer to NHC ratio, suggesting the prevalence of side reactions in this solvent.

In this contribution, we investigated the polymerization of Bu-NCA with NHCs having differing steric and electronic properties in solvents of differing dielectric strength. The effects of NHC, solvent, CO_2 pressure, and monomer structure on the polymerization rate have also been studied to gain insight to the reaction mechanism. Initiation events have been investigated by NMR and FT-IR spectroscopy. Furthermore, we reported synthetic strategies that enable the architectural conversion of the cyclic propagating species into their linear (**4**/**5**) and NHC-free cyclic analogues (**3**).

NHC and Solvent Effect on Polymer MW Control. Polymerization of Bu-NCA has been investigated with several NHCs at various initial monomer to NHC ratios ($[M]_0/[NHC1-4]_0$). All reactions were allowed to proceed in THF at 50 °C under a nitrogen atmosphere before the polymer was isolated by precipitation with excess hexane. The polymerization conversion was determined by ^{1}H NMR analysis of the reaction aliquots. The polymer MW and PDI were measured by SEC coupled with multiangle light scattering and a differential refractive index detector (SEC-MALS-DRI). ^{1}H NMR and MS analysis confirms the desired PNBG backbone structure.[24] The experimental polymer MWs agree reasonably well with the theoretical MWs based on the single-site initiation by the NHCs (Supporting Information Table S1). Polymer MW distribution (PDI) also remains narrow for all samples (PDI < 1.2). The SEC chromatogram of the PNBGs sometimes exhibits a high MW shoulder, which we attribute to the polymer aggregation (Supporting Information Figure S1). This is supported by the monomodal distribution of polymeric mass ions in the MALDI-TOF MS spectra. In addition, prolonged reaction time beyond that required for 100% conversion did not result in the increase of polymer MW, suggesting the absence or limited extent of interchain coupling reaction, which may otherwise result in higher MW polymers.

When polymerization was conducted in reduced initial monomer concentration, deviation of the polymer MW from the theoretical values became more pronounced at the high MW end (M_n > ~15 kg·mol^{-1}) (entries 1−6, Supporting Information Table S2). This suggests the possible presence of nucleophilic impurities that may initiate the chain growth, or the occurrence of chain transfer/termination events. For instance, intramolecular cyclization of **1**/**2** would yield cyclic PNBGs **3** by liberating NHCs which can initiate another chain growth, resulting in lower polymer MWs than the theoretical values.[26] In general, NHC1−4 provides comparable control over polymer MW and PDI in the polymerization of Bu-NCA in THF. This is in contrast to the NHC-mediated polymerization of cyclic esters where the polymer MW control is strongly dependent on the NHC structure.[27−30]

Polymerization of Bu-NCA with NHC3 has also been investigated in several solvents with a range of dielectric constants (ε) including toluene (ε = 2.4), THF (ε = 7.5), nitrobenzene (NB, ε = 34.8), DMF (ε = 36.7), and DMSO (ε = 46.7) at 50 °C.[34] Polymerization in solvents with low dielectric constant (e.g., toluene and THF) produces polymers with controlled MW and low PDI (entries 1−6, Supporting Information Tables S1 and S2). For polymerizations conducted in nitrobenzene, polymer MW control is reasonable at the low MW range, whereas deviation of the polymer MW becomes more notable at the high MW range (entries 7−10, Supporting Information Table S2). By contrast, when solvents of high dielectric constant such as DMSO or DMF are used, polymer MW control is substantially diminished, resulting in low MW polymers regardless of the initial monomer to NHC ratio ($[M]_0/[NHC3]_0$) (entries 11−13, Supporting Information Table S2).[24] In addition, MALDI-TOF MS analysis of the polymer product reveals that the major species are the NHC-free cyclic PNBGs (Supporting Information Figure S2a,b). The cyclic PNBGs with one NHC moiety affixed to the chain (Supporting Information Figure S2d) are only present in small amounts, in contrast to the polymerization in THF or toluene where **2** (Scheme 1) is the major product (Supporting Information Figure S14A). We have found that heating the purified PNBG polymer **2** (Scheme 1) in 50 °C DMSO over a period of 24 h results in a significant reduction of the polymer MW, consistent with intramolecular transamidation taking place in this solvent. These results strongly suggest the prevalence of side reactions in DMSO that compete with chain propagation, yielding low MW polymers. As a control experiment, freshly distilled DMSO, DMF, and NB solutions of Bu-NCAs in the absence of NHCs were heated at 50 °C for 16

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h. The monomer remains intact, in contrast to an early report on the spontaneous polymerization of Me-NCAs to form polysarcosine oligomers in selected solvents [e.g., DMF, DMSO, and *N*-methyl pyrrolidone (NMP)].[22] The reported polymerization is presumably initiated by nucleophilic impurities present in the solvent.

Kinetic Rate Law in Low Dielectric Solvents. Polymerization of Bu-NCA ($[M]_0$ = 0.15M) in the presence of variable amounts of NHC3 ($[M]_0/[NHC3]_0$= 400:1, 200:1, 100:1, 75:1, 50:1, 35:1, 30:1, 25:1) have been conducted at 50 °C in toluene-d_8 in resealable NMR tubes. Progression of the polymerization reaction was monitored by ^{1}H NMR spectroscopy at fixed time intervals for a minimum of four half-lives. Approximately 0.5−15% monomer had been converted into polymer by the time the first spectrum was collected. The polymerization exhibits a first-order dependence on the monomer concentration and on the NHC3 concentration (i.e., $-d[M]/dt = k_p[M]_0[NHC3]_0$) with a propagating rate constant k_p = 92 (6) M^{-1} h^{-1} in toluene (Figure 1, Supporting Information Table S3) that is larger than that in THF [k_p = 51 (3) M^{-1} h^{-1}] by a factor of 1.7.[24] The polymerization follows the same kinetic rate law for all monomer concentrations (i.e., $[M]_0$ = 0.08−0.3 M, Supporting Information Figure S3). While the rate of polymerization at the early stage of the reaction (0.5−15% monomer conversion) was not captured, the plot of $\ln([M]_0/[M])$ versus time exhibits excellent linearity over the remaining course of polymerization. This suggests that initiation must be fast or comparable to chain propagation under the experimental conditions.[35] A slow initiation relative to propagation would have resulted in curved plot of $\ln([M]_0/[M])$ versus time with gradually increasing slopes.[38] The slope at the early stage of the reaction would correspond to the initiation rate constant (k_i), whereas the slope toward the end of the reaction would reflect the propagation rate constant (k_p). Additionally, an increase in the temperature leads to an increase in the polymerization rate. Fitting the plot of k_p versus the reaction temperature to the Eyring and Arrhenius equations (Supporting Information Figure S4) affords the activation enthalpy [$\Delta H^{\ddagger}$ = 31 (4) kJ·mol^{-1}] and the activation entropy of the polymerization [$\Delta S^{\ddagger}$ = −235(12) J·mol^{-1}·K^{-1}] as well as the activation energy [E_a = 34 (4) kJ·mol^{-1}].

The Monomer Effect on the Polymerization Rate. Polymerization of R-NCAs with differing N-substitution [R = Me, Et, Pr, Allyl, Bu, and ^{i}Bu] has also been investigated using NHC3 as the initiator in toluene-d_8 (50 °C, $[M]_0/[NHC3]_0$ = 50:1, $[M]_0$ = 0.15M). The reaction became heterogeneous for the polymerizations of Me-NCA and ^{i}Bu-NCA due to the limited solubility of the forming polymers in the solvent (i.e., toluene), resulting in aberrant polymerization kinetics. By contrast, polymerizations of Et-NCA, Pr-NCA, Allyl-NCA, and Bu-NCA are homogeneous throughout the reaction course and exhibit first-order dependence on the respective monomer concentration (Supporting Information Figure S5). While the polymerization rate is dependent on the monomer structure, the relative values differ by less than a factor of 3 (Supporting Information Table S4). Pr-NCA [k_{obs} = 0.27(4) h^{-1}] and Bu-NCA [k_{obs} = 0.28(2) h^{-1}] have nearly identical polymerization rates, both of which are lower than those of the Et-NCA [k_{obs} = 0.41(1) h^{-1}] by approximately 1.5-fold (Supporting Information Table S4). The polymerization of Allyl-NCA [k_{obs} = 0.15(1) h^{-1}] is the slowest of this monomer series in spite of its steric bulk being comparable to that of the Pr-NCA. This clearly indicates that both the steric and electronic properties of the N-substituents play a role in the polymerization rate of the respective R-NCA monomers.

NHC and Solvent Effect on the Polymerization Rate. We have proposed that the NHC-mediated polymerization of Bu-NCA occurs through a zwitterionic propagating species **1** (Scheme 1),[24] where the two charged chain ends are in close contact due to Coulombic interaction. The NHC structure would be expected to influence the monomer addition and hence the chain propagation rate. To test this hypothesis, we investigated the polymerization of Bu-NCA with NHCs having differing steric and electronic properties (Scheme 1). NHC1−4 vary systematically in the steric congestion around the carbene carbon, with NHC1 being the least congested and NHC4 being the most congested.[36−38] The relative steric congestion, which was quantified by the percentage buried volume (V_{Bur}, Table 1), has been validated experimentally and computationally.[36−38] Two series of NHCs (2, 5, 6; or 3, 7, 8, Scheme 1) vary in their relative electron-with drawing ability.

Table 1. Observed Rate Constant (k_{obs}) of NHC-Mediated Polymerization of Bu-NCA Using NHCs of Differing Steric Congestion (V_{Bur})[36−38] in Toluene-d_8 and DMSO-d_6, Respectively[a]

NHC	V_{Bur} (%)	k_{obs} (h^{-1}) toluene-d_8	k_{obs} (h^{-1}) DMSO-d_6	k_{obs} (toluene-d_8)/k_{obs}(DMSO-d_6)
NHC1	23	0.75(1)	0.076 (11)	9.8
NHC2	26	0.30(2)	0.094(2)	3.2
NHC3	29	0.28(2)	0.084(3)	3.4
NHC4	37	0.048(2)	0.074(6)	0.6

[a]Reaction conditions: 50 °C with $[M]_0$ = 0.15 M and $[M]_0/[NHC1-4]_0$ = 50:1.

All polymerizations of Bu-NCA with different NHC1−4 exhibit first-order dependence on the monomer concentration under the standard conditions (i.e., $[M]_0$ = 0.15 M, $[M]_0/[NHC1-4]_0$ = 50:1, 50 °C, toluene-d_8) (Figure 2A). The polymerization rate exhibits a notable dependence on the NHC structure, strongly suggesting that the NHC not only initiates the polymerization, but also mediates the monomer addition and the chain propagation through a unique intramolecular counterion effect. This is consistent with the proposed zwitterionic propagating species where the cationic NHC moiety at one chain end is closely associated with the other anionic chain end by Coulombic interaction (Figure 2A).

There is an approximately 15-fold difference in the observed rate constants (k_{obs}) of the fastest and slowest NHC-mediated polymerization of Bu-NCA (Table 1). The magnitude of this intramolecular counterion effect on the polymerization rate is comparable to that of the anionic polymerization of methacrylate in dioxane, where a 20-fold increase in the polymerization rate occurred when the countercation was changed from lithium to cesium.[39,40] Furthermore, k_{obs} exhibits an inverse relationship with the steric effects of the NHC: polymerization is fastest with the least sterically congested NHC [k_{obs} (NHC1) > k_{obs} (NHC2) > k_{obs} (NHC3) > k_{obs} (NHC4)] (Figure 2A, Supporting Information Figure S6, and Table 1). This suggests that the interaction between the NHC and the monomer is sterically controlled: the less sterically bulky NHC promotes the addition of the monomer to the anionic chain end and hence the chain propagation. When NHCs (i.e., 2, 5, 6; and 3, 7, 8) having comparable sterics but

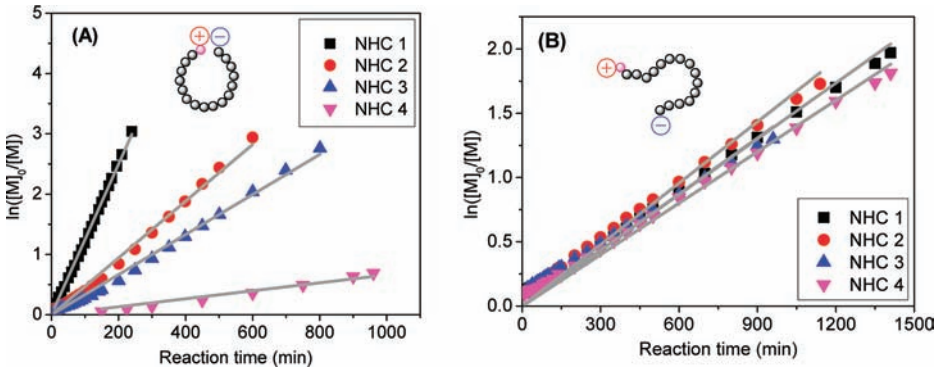

Figure 2. Plots of $\ln([M]_0/[M])$ versus time for the NHC-mediated polymerization of Bu-NCA using NHCs of differing steric effect around the carbene carbon in toluene-d_8 (A) or in DMSO-d_6 (B) (50 °C, $[M]_0$ = 0.15 M, $[M]_0/[NHC1-4]_0$ = 50:1), respectively.

differing electronic properties are used (Scheme 1), the observed polymerization rate constant also differs by a factor of 1.4 for the NHC 2, 5, and 6 series (entries 5−7, Supporting Information Table S5) or 2.3 for the NHC 3, 7, and 8 series (entries 8−10, Supporting Information Table S5), respectively: the NHC which bears the most electron withdrawing group (or has the least stabilizing effect on the positively charged imidazolylidenium intermediate) gives rise to the fastest polymerization (Supporting Information Figure S7).

If the chain propagation occurs through the proposed zwitterionic intermediate **1** (Scheme 1), the Coulombic interaction between the two oppositely charged chain ends in the zwitterion would be weakened in solvents with high dielectric constants, resulting in a diminished dependence of the polymerization rate on the NHC structure. To test this hypothesis, kinetic studies have been conducted for the polymerization of Bu-NCA with NHC1−4 in DMSO-d_6 at 50 °C similarly to those in toluene-d_8.

All polymerizations of Bu-NCA in DMSO-d_6 maintain the first-order dependence on the monomer concentration irrespective of the NHC structure (Figure 2B). The polymerization rates are nearly identical regardless of the NHC being used (Figure 2B and Table 1), consistent with the proposed zwitterionic propagating species **1** whose chain ends are completely dissociated. The Coulombic interaction between the two chain ends of **1** is shielded by the polar solvent molecules, resulting in propagating species whose structures are analogous to those observed in the anionic polymerization of Bu-NCA using NaOPh initiator and hence having comparable polymerization rate constants [k_{obs} = 0.089(5) h^{-1}, Supporting Information Figure S8].

In polar solvents such as DMSO, many side reactions (e.g., transamidation) compete with chain propagation due to the enhanced nucleophilicity and basicity of the naked propagating anions. This results in intra- or interchain transfer or termination, and thereby diminishes polymer MW control.

CO_2 Pressure Effect on the Polymerization Rate. To ensure efficient gas transport, we conducted kinetic experiments of NHC3-mediated polymerization of Bu-NCA ($[M]_0$ = 0.15 M, $[M]_0/[NHC3]_0$ =100:1, 50 °C) under varying initial CO_2 pressure in a pressurized *in situ* reactive FT-IR reactor with stirring. All the polymerizations in toluene and DMSO exhibit first-order dependence on the monomer concentration. As the initial CO_2 pressure is increased from 0 to 60 and 120 psi, the polymerization rate remains invariant in both solvents (Supporting Information Table S6), implying that the CO_2 elimination is not the rate-determining step (RDS) in chain propagation.

Investigation of the Initiation Event. To gain insight into the initiation reactions, NHC1 (Scheme 1) was allowed to react with Bu-NCA in 1:1 ratio in room temperature THF ([M] = 0.15M). The reaction solution turned from colorless to yellow instantaneously. ^{1}H NMR analysis of the reaction mixture reveals the disappearance of the starting materials and the appearance of two distinct sets of proton resonances due to the NHC1 moieties in 1:2 ratio and broad proton resonances due to low MW PNBGs, suggesting initiation is comparable relative to chain propagation. The major NHC1 moiety is consistent with a bis(isopropyl)imidazole-2-ylidenium species, as evidenced by the characteristic singlet at 10.8 ppm in the ^{1}H NMR spectrum (Supporting Information Figure S9) and the HSQC analysis (Supporting Information Figure S10). It is presumably formed from protonation of the NHC1 by Bu-NCA owing to their comparable pK_a values.[41,42] ^{1}H NMR analysis of the product from the reaction between NHC1 and Bu-NCA in 1:2 ratio reveals that the ratio of the two NHC moieties decreases to 1:12 with a majority of NHC1 present as the bis(isopropyl)imidazole-2-ylidenium species (Supporting Information Figure S9). These results strongly suggest the presence of two initiating pathways.

FT-IR analysis of the 1:1 NHC1 and BuNCA reaction mixture revealed five carbonyl stretching bands in the 1500−1900 cm^{-1} range (Supporting Information Figure S11). Three bands at 1569, 1652, and 1757 cm^{-1} are assigned to the carbamate end-group, amide of the backbone and carbonyl adjacent to the imidazole-2-ylidenium end-group, consistent with the proposed zwitterionic propagating species bearing one NHC moiety at one chain end and carbamate at the other (**1**, Scheme 1). The origin of the other two carbonyl stretching bands (ν_{CO} = 1682 and 1717 cm^{-1}) remains unknown. They are presumably due to end-group structures formed from alternative initiating pathways and will be discussed shortly.

A series of low MW PNBG polymers have been synthesized under identical condition (i.e., $[M]_0$ = 0.4 M, $[M]_0$:$[NHC]_0$ = 25:1, 50 °C, THF) using different NHCs (i.e., NHC1−4) and analyzed by ^{1}H NMR spectroscopy (Supporting Information Figure S12A). ^{1}H NMR analysis of the polymer product from the NHC2 or NHC3-mediated polymerization in selected solvent (i.e., THF-d_8 or CD_2Cl_2) also revealed two sets of proton resonances due to the NHC moieties in 1:1.5 and 1:3.6 ratios, respectively (Supporting Information Figure S12B). The minor component appears to be the imidazole-2-ylidenium species formed from protonation of the NHCs. In contrast,

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only one set of NHC proton resonances due to the protonated NHCs was observed, when NHC1 and NHC4 were used as initiator (Supporting Information Figure S12B). Importantly, these ratios remain invariant upon change of temperature, solvent, and CO_2 pressure, strongly suggesting the two NHC chain-end structures are not in equilibrium. This is consistent with the presence of alternative initiating pathway that results in different end-group structures.

Conversion of Cyclic Zwitterions into the Linear Polymeric Analogues. Since the polymers prepared from NHC-mediated polymerization of Bu-NCA present as the reactive forms **1**/**2**, we hypothesized that they could be converted into the linear analogue by reaction with electrophiles (Scheme 1). Indeed, treatment of the PNBG polymer prepared from NHC3-mediated polymerization with acetyl chloride (AcCl) in room temperature THF results in an instantaneous disappearance of the pale yellow color. ^{1}H NMR and MALDI-TOF MS analysis of the resulting product reveals that the major polymeric species are linear poly(*N*-butyl glycine), where chain ends bear one NHC and one acetyl or acetoxycarbonyl moiety (Supporting Information Figures S14B and S15B). FT-IR analysis also reveals the formation of acetoxycarbonyl end-groups, as evidenced by the disappearance of the carbamate band at 1572 cm^{-1} and the appearance of the characteristic anhydride bands at 1779 and 1838 cm^{-1} (Supporting Information Figure S13).[43−45] The amide stretching band at 1654 cm^{-1} due to the PNBG backbone remains unchanged. The band assigned to the carbonyl adjacent to the imidazole-2-ylidenium end-group is slightly red-shifted to 1753 cm^{-1}. There results are consistent with the proposed zwitterionic carbamate propagating intermediate **1** (Scheme 1). Furthermore, SEC analysis of the resulting polymers reveals that the sample elutes earlier than the **1**/**2** precursor (Figure 3), suggesting that the former has an

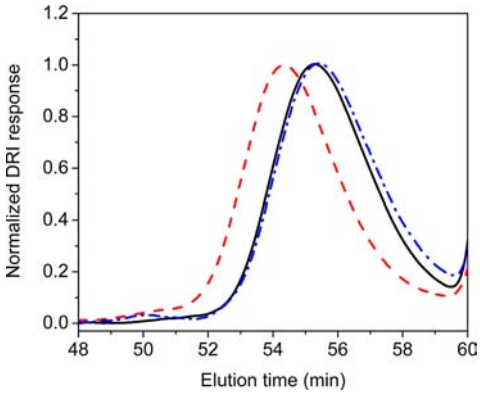


Figure 3. SEC chromatograms [LiBr(0.1M)/DMF, 50 °C] of NHC3-poly(*N*-butyl glycine) adduct **1**/**2** (Scheme 1) (—), the linear analogue **4**/**5** (---), and the NHC-free cyclic analogue **3** (-•-) obtained by treatment of **1**/**2** with AcCl and NaN(TMS)$_2$, respectively.

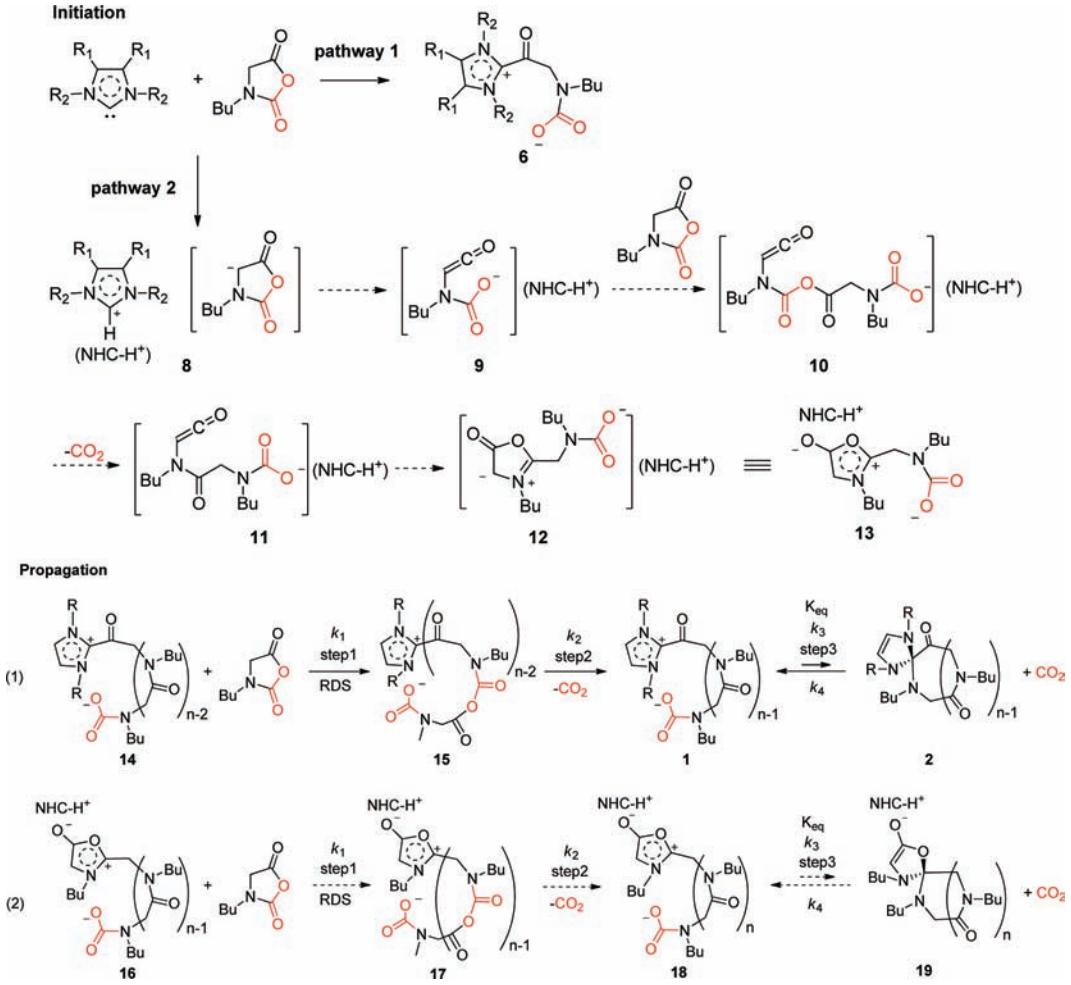
increased hydrodynamic volume indicating the successful conversion of the cyclic propagating species (**1**/**2**, Scheme 1) into their linear analogues (**4** and **5**, Scheme 1). The architectural transformation has been verified for PNBG polymers prepared with various NHC initiators (i.e., NHC1−4).

We have previously demonstrated that the NHC moieties on the cyclic zwitterions and spirocycles (**1**/**2**) are photolabile and can be eliminated from the polymers in the solid state upon laser irradiation.[33] The mixing of **1**/**2** with appropriate matrix materials such as dithranol facilitates its elimination presumably due to enhanced laser energy absorption and transfer. As a result, "soft" matrix materials such as α-cyano-4-hydroxycinnamic acid (CHCA) or 3-hydroxypicolinic acid (3-HPA) should be used in the MALDI-TOF MS analysis of this class of polymers to ensure that the original polymer (end-group) structures remain intact. Treatment of **1**/**2** with dithranol also results in the formation of NHC-free cyclic PNBGs **3** (Scheme 1), as verified by ^{1}H NMR and the MS analysis. However, the fate of NHC and the reaction mechanism remain unknown. This method gives low yields of polymer due to inefficient chromatographic separation and is therefore not amenable to the large-scale synthesis of NHC-free cyclic PNBGs. We have found that treatment of **1**/**2** with 5 equiv of NaN(TMS)$_2$ in THF at 50 °C results in the formation of cyclic PNBGs **3** as the main product (Scheme 1), as verified by MALDI-TOF MS (Supporting Information Figure S14C) and ^{1}H NMR spectroscopy (Supporting Information Figure S15C). [Note: it is important to control the stoichiometry of NaN(TMS)$_2$, as we have found that NaN(TMS)$_2$ in much greater excess can cause partial degradation of the polymer backbone.] The eliminated NHCs can be recovered from the hexane extract. While the reaction mechanism remains to be investigated, this method is scalable and produces NHC-free cyclic PNDGs **3** in high yields. SEC analysis reveals that the cyclic PNBGs **3** elute at approximately the same time as the zwitterionic/spirocyclic precursors **1**/**2**, suggesting a nearly identical hydrodynamic size and thus confirming the cyclic architecture of the former (Figure 3).

Modified Reaction Mechanisms and Discussion. We have shown that various NHC-mediated polymerization of Bu-NCA produced PNBG polymers that have cyclic architectures and can be converted into their respective linear analogues by acylation reaction. This is consistent with the proposed cyclic zwitterionic propagating species (Scheme 1). While MS analysis of the polymer products suggests that the each polymer chain has one NHC moiety affixed to it, NMR analysis reveals that the NHC moieties present in two different forms: one is consistent with the proposed acyl-imidazole-2-ylidenium species **1** (Scheme 2); the other appears to be imidazole-2-ylidenium species **8** presumably formed from protonation of the NHCs by Bu-NCA (Scheme 2). These results suggest the presence of two initiating pathways.

While the subsequent formation of a cyclic zwitterionic propagating species seems reasonable by the initiation pathway 1 (Scheme 2) which entails regioselective insertion of the NHC into the 5-carbonyl of Bu-NCA to form the zwitterionic initiating species **6**, it is not entirely clear how deprotonation of Bu-NCA by the NHCs (pathway 2, Scheme 2) may lead to a cyclic propagating intermediate. We propose the possible formation of a Münchnone initiating species **13** from an *N*-acyl ketene intermediate **11**, which forms from the reaction of the deprotonated Bu-NCA with another Bu-NCA (pathway 2, Scheme 2).[46−48] Münchnone **13** bears an exocyclic carbamate group from which subsequent monomer addition may occur in a similar manner as the zwitterionic carbamate species **6**. While the Münchnone species **13** has not been unambiguously characterized, the two unknown carbonyl stretching bands at 1682 and 1717 cm^{-1} observed in the FT-IR spectra of the 1:1 reaction product of NHC1 and Bu-NCA are consistent with its formation.[48]

Scheme 2



The propagation occurs by monomer addition to the cyclic zwitterionic propagating species **14**/**16** at the carbamate chain end to form zwitterionic mixed anhydride propagating species **15**/**17**, which undergoes intramolecular rearrangement and liberate CO_2 irreversibly to regenerate the zwitterionic propagating intermediate **1**/**18** for further enchainment (Scheme 2). Mixed anhydride model compounds are unstable and have been shown to rapidly undergo skeletal rearrangement to lose CO_2 and form amide linkages.[44,49] The Münchnone propagating intermediate **18** maintains the cyclic architecture by Coulombic interaction similarly to the zwitterionic propagating species **1**.

The zwitterionic propagating species **1**/**18** establish equilibria with the spirocyclic propagating species **2**/**19** rapidly through reversible decarboxylation prior to monomer addition, which is the rate-determining step (RDS) (k_2, k_3, $k_4 > k_1$). We have shown that the polymerization maintains the first-order dependence on the monomer concentration and the polymerization rate remains invariant under varying CO_2 pressure. Two possible scenarios regarding the relative rate of monomer addition toward **1**/**2** (and **18**/**19**) may account for the observed polymerization kinetic. (Derivation of the kinetic rate law can be found in the Supporting Information). In the first scenario, the rates of monomer addition to **1**/**18** and **2**/**19** are very similar. We consider this situation to be unlikely due to the structural difference between the zwitterionic (**1**/**18**) and spirocyclic species (**2**/**19**). In addition, how the spirocyclic species **2**/**19** may react with an electrophilic monomer is not entirely clear and warrants further study. An analogous NHC-ester spirocycle has previously been shown to initiate the polymerization of β-lactone.[29] Crystal structure analysis of the NHC-ester spirocyclic compound revealed an elongated C(bridged)−O bond,[30] suggesting the bond is weakened and potentially enhancing reactivity toward electrophilic substrates. Alternatively, it is conceivable that the spirocycle **2**/**19** may undergo ring-opening to form its zwitterionic analogue with the anionic amido chain end, which proceeds to react with the monomer. However, this species would be highly basic, its presence in a large concentration would have caused side reactions such as deprotonation or transamidation, resulting in nonliving polymerization behavior.

In the second scenario, the spirocyclic species **2**/**19** has significantly reduced reactivity relative to the zwitterionic species **1**/**18** toward monomer addition, and the equilibrium between **1** and **2** (or **18** and **19**) is substantially biased toward the **1**/**18**. This will also result in the observed polymerization kinetic, that is, polymerization rate being independent of the CO_2 pressure. We consider this to be the likely case in view of the reported stability of carbamate against decarboxylation.[50]

The polymerization rate is inversely related to the solvent polarity with the reaction being the fastest in toluene and slowest in DMSO. This can be attributed to enhanced nucleophilicity of the zwitterionic carbamate propagating species **2**/**18** due to reduced solvation in the former solvent.

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Both the steric and electronic properties of NHC and the monomers have been shown to affect the polymerization rate. As the NHC becomes more sterically congested around the Münchnone carbon or the N-substituents on the monomer increase in size, the polymerization rate decreases accordingly, in agreement with the proposed RDS in the chain propagation. NHCs or the monomers bearing more electron withdrawing groups also give rise to faster polymerization, but the effect is much more moderate.

The unique cyclic topology of the propagating species maintained by the NHC moieties is critical for the quasi-living polymerization behavior observed in THF and toluene. In addition to initiating the chain growth, the NHC moieties also facilitate the chain propagation by mediating monomer addition through an intramolecualr counterion effect and managing potential side reactions by modulating the basicity and nucleophilicity of the zwitterionic propagating intermediates **1**/**18**. In the zwitterionic propagating species, where two oppositely charged chain ends are in close contact, the effective basicity of the anionic chain end is reduced due to the Coulombic interaction, thereby suppressing possible side reactions such as transamidation.

In contrast to polymerization in toluene, NHC3-mediated polymerization of Bu-NCA in DMSO produces only low molecular weight PNBGs irrespective of the initial monomer to NHC ratio, attesting to the prevalence of side reactions (e.g., intramolecular transamidation) in DMSO. ^{1}H NMR analysis of the polymer product in DMSO revealed the exclusive formation of bis(2,6-diisopropylphenyl)imidazole-2-ylidenium species due to protonation of NHC3 (Supporting Information Figure S16), suggesting that the polymerization is likely to be initiated through the Münchnone initiating species **13** and undergo propagation through **18** (Scheme 2). While the propagating intermediate is zwitterionic, the Coulombic interaction between the oppositely charged chain ends is significantly weakened in high dielectric solvent such as DMSO. This results in a carbamate propagating species that are identical to those formed from the anionic polymerization of Bu-NCA using alkaline metal alkoxide or phenoxide initiators (e.g., NaOPh, NaOMe) in DMSO, as evidenced by their nearly identical polymerization rate (Figure 2B and Supporting Information Figure S8). The two oppositely charged chain ends of the zwitterionic propagating species (**1**/**18**, Scheme 2) are fully dissociated, and the NHC chain end has no effect on the monomer addition to the anionic chain end. The naked anion, without any positive charge to modulate its reactivity as in the zwitterionic polymerization in toluene, is prone to side reactions such as transamidation, resulting in diminished control over polymer molecular weight.

CONCLUSIONS

Kinetic studies of NHC-mediated polymerization of Bu-NCA suggest that the polymerization proceeds by zwitterionic propagating intermediates that retain a cyclic topology in low dielectric solvents. The NHC appears to initiate the chain growth by two different pathways, both of which result in the formation of zwitterionic species from which enchainment ensues. In addition to initiating the chain growth, the NHC also mediates the chain propagation through an intermolecular counterion effect. The positively charged NHC chain ends in the propagating zwitterions reduce the basicity and nucleophilicity of the anionic carbamate chain end via Coulombic interactions, thereby minimizing side reactions (e.g., transamidation). The zwitterionic/spirocyclic propagating intermediates can be readily converted into their linear analogues by end-capping with electrophiles (e.g., AcCl) or to NHC-free cyclic polypeptoid analogues by treatment with NaN(TMS)$_2$, providing a convenient method for preparing poly(α-peptoid)s having identical molecular weights but differing architectures. In contrast to reactions in low dielectric solvents, polymerization in polar solvents (e.g., DMSO, DMF) gives only low MW polymers regardless of the initial monomer to initiator ratio. This has been attributed to the enhanced nucleophilicity and basicity of the naked propagating anion, resulting in extensive side reactions that compete with chain propagation. The study has provided mechanistic insight to the NHC-mediated quasi-living polymerization of N-substituted *N*-carboxyanhydrides in selected solvents which will guide rational design of new initiators and optimization of experimental conditions for the synthesis of cyclic or linear poly(α-peptoid)s with diverse structures, controlled molecular weights, and architectural purity.

ASSOCIATED CONTENT

Supporting Information

Tables that summarize the polymer molecular weight and molecular weight distribution from NHC-mediated polymerization of Bu-NCA in various solvents, tables that summarize the kinetic results of NHC-mediated or NaOPh-initiated polymerization of various R-NCAs in various solvents at differing temperature and initial pressure, Eyring and Arrhenius plots for the NHC3-mediated polymerization of Bu-NCA, ^{1}H NMR and HSQC spectra of 1:1 and 1:2 NHC1 and Bu-NCA reaction product, ^{1}H NMR and MALDI-TOF MS spectra of low MW poly(*N*-butyl glycine) obtained from NHC-mediated polymerization of Bu-NCA in DMSO at 50 °C, MALDI-TOF MS, FT-IR and ^{1}H NMR spectra of low MW NHC-poly(*N*-butyl glycine) adduct **1**/**2** and the polymer product obtained after treatment of **1**/**2** with AcCl and NaN(TMS)$_2$, derivation of the kinetic rate law. 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.

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