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Cyclic Poly(α-peptoid)s and Their Block Copolymers from N-Heterocyclic Carbene-Mediated Ring-Opening Polymerizations of N-Substituted *N*-Carboxylanhydrides

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Poly(α-peptoid)s, which are structural mimics of poly(α-peptide)s, feature an N-substituted polyglycine backbone with proteinogenic or synthetic side chains on the nitrogen atom (Figure 1). They have attracted much attention for their potential as peptidomimetic therapeutic agents or drug delivery carriers due to their enhanced enzymatic and hydrolytic stability relative to poly(α-peptide)s.[1,2] In contrast to the poly(α-peptide)s, whose secondary structure (e.g., helix) is stabilized by hydrogen bonding, the conformation of poly(α-peptoid)s, which are free of hydrogen bonding interactions because of the N-substitution, is largely determined by the backbone rigidity and the steric and electrostatic characteristics of the side chains.[3] For example, oligomeric α-peptoids with aliphatic or aromatic chiral side chains have been shown to form a stable polyproline I helix.[4]

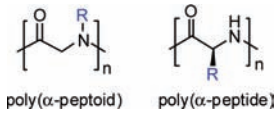


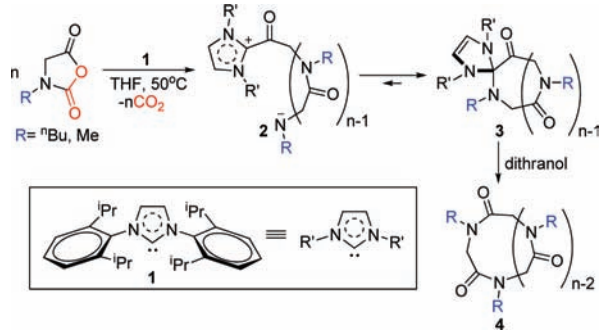
Figure 1. Molecular structures of poly(α-peptoid)s and poly(α-peptide)s (R = proteinogenic or synthetic side chain).

While linear poly(*N*-Me-glycine) (a.k.a., polysarcosin) can be synthesized from an amine-initiated ring-opening polymerization (ROP) of the corresponding N-substituted *N*-carboxylanhydride (^{N}R-NCA, R = Me),[5] the method is limited with respect to the scope of monomers. The reaction suffers from low efficiency and is heavily monomer-dependent,[5b] which makes it impractical for the general synthesis of poly(α-peptoid)s. Hence, the synthesis of poly(α-peptoid)s in a controlled manner remains a challenge.

A zwitterionic mechanism was proposed for the pyridine[5f]/tertiary amine[5i]/solvent[5j]-initiated or thermal ROP of ^{N}Me-NCA,[5k] but control over the polymer molecular weight (MW) and molecular weight distribution [as indicated by the polydispersity index (PDI)] is limited. N-Heterocyclic carbenes (NHCs) have been shown to mediate ROP of cyclic substrates (e.g., cyclic ester,[6] ethylene oxide)[6d] through a zwitterionic propagating species to yield polymers with controlled MW and PDI. Inspired by these studies, we reasoned that NHCs should mediate the ROP of ^{N}R-NCA in a controlled and efficient manner because of the enhanced nucleophilicity of both the NHC and the zwitterionic propagating species. Herein we report the first general and efficient synthetic route toward cyclic poly(α-peptoid)s from the controlled ROP of ^{N}R-NCA with an NHC initiator and demonstrate its utility in preparing cyclic block copoly(α-peptoid)s (Scheme 1).

^{N}Bu-NCA (**M$_1$**) and ^{N}Me-NCA (**M$_2$**) were synthesized from the corresponding N-substituted glycine precursors by the standard Fuchs method.[7] Polymerizations of ^{N}Bu-NCA in the presence of various loadings of bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**1**) were allowed to proceed for 16 h in tetrahydrofuran (THF) at 50 °C under a nitrogen atmosphere (Scheme 1). The polymers were isolated by precipitation with hexane and analyzed for their molecular structures and end groups by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and MALDI-TOF and electrospray ionization (ESI) mass spectrometry (MS). The polymer absolute molecular weight (M_n) and molecular weight distribution (PDI = M_w/M_n) were determined by size-exclusion chromatography (SEC) coupled with multiangle light scattering (MALS), viscometry (VISC), and differential refractive index (DRI) triple detection (SEC−MALS−VISC−DRI).

Scheme 1



The ^{1}H and ^{13}C{^{1}H} NMR spectra of the polymers are consistent with the proposed repeating unit structure formed from ROP of the corresponding substrates.[7] End-group analysis of a low-MW polymer sample by ^{1}H NMR spectroscopy and ESI MS revealed a major polymeric species (>95% by ^{1}H NMR integration) whose structure is consistent with an NHC−poly(*N*-Bu-glycine) spirocyclic adduct **3** (Scheme 1).[7] An analogous NHC−polyester spirocycle was reported previously in an NHC-mediated polymerization of *β*-lactone.[6b] Surprisingly, MALDI TOF MS analysis of the same sample revealed that the sample consists mainly of free cyclic poly(*N*-Bu-glycine) (**4**) (95% by mass) with spirocycle **3** notably absent.[7] To resolve the inconsistency in the ESI and MALDI TOF MS results, spirocycle **3** was treated with 2 equiv of dithranol, the matrix material used in the MALDI TOF MS experiment, in THF at room temperature. ^{1}H NMR analysis of the reaction product revealed the formation of a major polymeric species whose structure is consistent with **4**.[7]

To verify the cyclic architecture of **3** in the high-MW range, linear poly(*N*-Bu-glycine)s with different MWs were independently prepared by an amine-initiated polymerization of ^{N}Bu-NCA. SEC analysis revealed that poly(*N*-Bu-glycine)s (M_n = 10−30 kg mol^{-1}) obtained from NHC **1**-mediated polymerizations of ^{N}Bu-NCA exhibit lower intrinsic viscosities than the linear analogues having identical MWs (Figure 2). This indicates that the former polymers have physically more compact architectures. The $[\eta]_{cyclic}/[\eta]_{linear}$ ratio

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[0.83(2)] exceeds the theoretical prediction for cyclic polymers (0.662) based on the infinite freely jointed chain model.[8,9] It is consistent with samples being mostly cyclic polymers. While residual linear contaminants can cause the ratio to deviate, non-θ-condition, finite size, and real chain stiffness also contribute to the discrepancy.[10] Linear fits of the respective Mark−Houwink−Sakurada plots (log [η] vs log M_w) of the cyclic and linear poly(*N*-Bu-glycine)s (Figure 2a) yielded nearly identical Mark−Houwink exponents [α_{cyclic}= 0.65(1), α_{linear}= 0.66(2)]. They are consistent with self-avoiding walks or slightly extended conformations for both polymers,[11] hence eliminating conformational effects as being responsible for their intrinsic viscosity differences. The cyclic polymers also elute later than their linear analogues with identical MWs.[7] This is consistent with the former having a smaller hydrodynamic volume, assuming the absence of non-size-exclusion separation mechanisms.

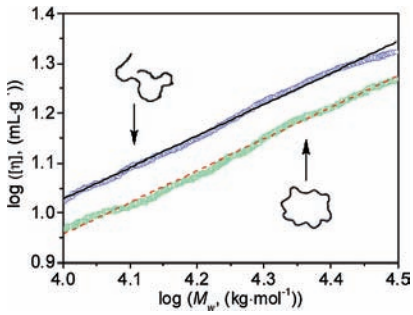

Figure 2. Mark−Houwink−Sakurada plot of cyclic (□) and linear (○) poly(*N*-Bu-glycine)s and their linearly fit curves (dashed line, cyclic; solid line, linear).

To assess the NHC control over the polymerization, reactions with different initial monomer to initiator ratios ($[\mathbf{M_1}]_0/[\mathbf{1}]_0$) were conducted. Pauci-disperse (PDI = 1.04−1.12) poly(*N*-Bu-glycine)s with predictable MWs ranging from ~3 to 30 kg mol^{-1} can be readily synthesized by controlling the $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ ratio and the reaction time (Table 1). The experimental polymer MWs generally concur with the theoretical values calculated from the conversion and $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ ratio for single-site initiation by NHC. Deviations of the experimental M_n from the theoretical values are more pronounced at the high-MW end (Table 1, entries 5 and 10), possibly as a result of the presence of impurities (e.g., H_2O) that can initiate the nucleophilic polymerization of $\mathbf{M_1}$.[5a−e] The good control over the cyclic polymer MW and PDI is maintained even at elevated initial monomer concentrations, in contrast to the case of conventional synthetic strategies for cyclic polymers, where high dilution conditions are required to inhibit linear polymer formation.

The reaction exhibits characteristics of a living polymerization with minimal inter- or intrachain transfer. For example, the polymer MW increases linearly with conversion while the PDI (1.04−1.17) remains low even at high conversions (up to ~97%) (Figure 3a). This suggests that the rate of cyclization of **2** to yield cyclic poly(*N*-Bu-glycine) **4** is much slower than that of propagation. Consistent with a living polymerization, preliminary kinetic studies ($[\mathbf{M_1}]$ = 0.4 M, $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 50:1, 50 °C, THF) revealed that the rate of polymerization has a first-order dependence on the monomer concentration ($d[\mathbf{M_1}]/dt = k_{obs}[\mathbf{M_1}]$, k_{obs}= 0.41(2) h^{-1}).

A chain-extension experiment with ^{N}Bu-NCA ($[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 50:1) was also conducted to verify the living nature of the polymerization. Upon complete conversion of the initial monomers, an additional 25 equiv of the identical monomers were added, and the reaction was allowed to continue to completion. SEC chromatograms of polymers obtained prior to and after the second monomer addition (Figure 3b) revealed an increase of polymer molecular weight M_n from 5.5 to 8.3 kg mol^{-1} and a change in PDI from 1.11 to 1.05. The latter values agree with those for polymers independently synthesized from a 75:1 $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ reaction (M_n = 8.7 kg mol^{-1}, PDI = 1.08). The MW distribution remains narrow after the chain extension, and no low-MW polymer was detected. Taken together, these results strongly indicate a living polymerization with minimal inter- or intrachain transfer. In contrast to other NHC-mediated ROPs of cyclic substrates, the activated functional group (i.e., the anhydride) of the ^{N}R-NCA monomer is different from those (i.e., amide) present in the polymer backbones. As the amide bonds are highly inert toward transamidation, inter- and intrachain transfer is significantly reduced.

Table 1. NHC **1**-Mediated ROP of ^{N}Bu-NCA ($\mathbf{M_1}$)[a]

				M_n (kg mol^{-1})		
entry	$[\mathbf{M_1}]_0/[\mathbf{1}]_0$	$[\mathbf{M_1}]_0$	conv. (%)[b]	calcd[c]	SEC[d]	PDI[d]
1	25:1	0.4	100	2.8	3.3	1.07
2	50:1	0.4	100	5.6	5.6	1.08
3	100:1	0.4	96	10.9	10.1	1.10
4	200:1	0.4	95	21.5	14.5	1.09
5	400:1	0.4	89	40.3	16.7	1.12
6	25:1	0.8	100	2.8	3.0	1.06
7	50:1	0.8	100	5.6	5.6	1.06
8	100:1	0.8	96	10.9	10.7	1.05
9	200:1	0.8	88	19.9	18.9	1.06
10	400:1	0.8	79	35.8	26.7	1.04

[a] All reactions were conducted at 50 °C in THF with $[\mathbf{M_1}]_0$ = 0.4 or 0.8 M and stopped after 16 h. [b] Conversion was calculated from the ^{1}H NMR spectrum of an aliquot of the reaction mixture. [c] Theoretical MW was calculated from the conversion and the $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ ratio. [d] Experimental MW and PDI were obtained from a tandem SEC−MALS−VISC−DRI system in 0.1 M LiBr/DMF solution at 50 °C using a measured d*n*/d*c* of 0.0714(13) mL g^{-1}.

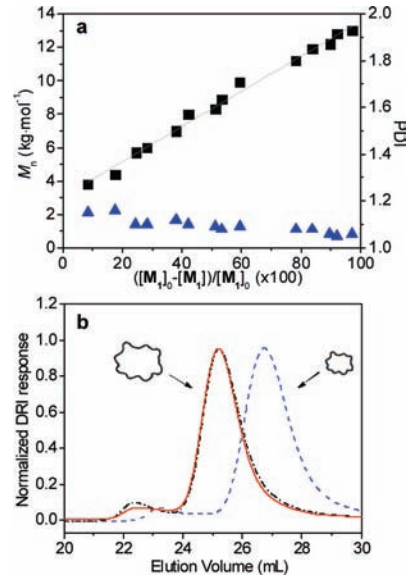

Figure 3. (a) Representative plots of experimental M_n (■) and PDI (▲) vs conversion ($[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 150:1, $[\mathbf{M_1}]_0$ = 0.4 M, 50 °C, THF). (b) SEC chromatograms of poly(*N*-Bu-glycine) prior to (dashed curve, $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 50:1) and after (solid curve, $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 25:1) the chain-extension experiment and of an independently synthesized poly(*N*-Bu-glycine) sample (dot-dashed curve, $[\mathbf{M_1}]_0/[\mathbf{1}]_0$ = 75:1).

It is evident that polymeric spirocycles **3** (Scheme 1) are the catalytic resting states during polymerization. By analogy to controlled radical polymerizations and the NHC-mediated zwitterionic polymerizations of β-lactones,[6b] the effective concentration

of active propagating species **2** is lowered via equilibrium with the dormant propagating species **3**, thereby reducing side reactions (e.g., step-growth polymerization, deprotonation) and enhancing control of polymer MW and PDI. In support of this hypothesis, when polymerizations were conducted in a solvent that can better stabilize the zwitterionic species [e.g., dimethyl formamide (DMF)],[12] control of the polymer MW was significantly compromised, and only low-MW polymers were obtained regardless of the initial monomer/initiator ratio.

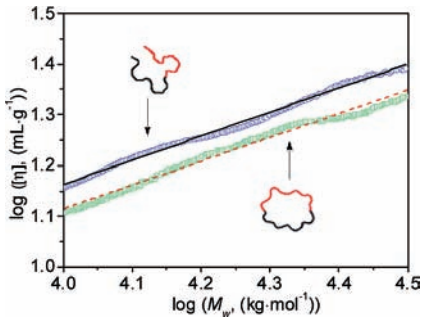

Figure 4. Mark−Houwink−Sakurada plot of cyclic (□) and linear (○) poly(*N*-Me-glycine)-*b*-poly(*N*-Bu-glycine) block copolymers with identical compositions and their linearly fit curves (dashed line, cyclic; solid line, linear).

The utility of this reaction for accessing cyclic block copoly(α-peptoid)s was demonstrated through the synthesis of a poly(*N*-Me-glycine)-*b*-poly(*N*-Bu-glycine) block copolymer by sequential addition of ^{N}Me-NCA ($[\mathbf{M_2}]_0/[\mathbf{1}]_0 = 50{:}1$) and ^{N}Bu-NCA ($[\mathbf{M_1}]_0/[\mathbf{1}]_0 = 25{:}1$). Both steps were allowed to reach completion. SEC analyses of polymers obtained prior to and after the second monomer addition revealed an increase of polymer MW from 4.4 kg mol^{-1} (PDI = 1.04) to 6.5 kg mol^{-1} (PDI = 1.03), in agreement with the theoretically predicted value (M_n = 6.4 kg mol^{-1}).[7] Extraction of the copolymer product with water did not yield any poly(*N*-Me-glycine) homopolymers, suggesting 100% living chains in the first polymerization step. ^{1}H and ^{13}C{^{1}H} NMR spectra of the purified polymers were consistent with the diblock copoly(α-peptoid) backbone structure.[7] SEC analysis of these block copolymer samples also revealed that the polymers exhibit lower intrinsic viscosities than their linear analogues (Figure 4).[7] The Mark−Houwink exponents for the cyclic and linear block copolymers are 0.51(4) and 0.57(9), implying self-avoiding-walk conformations for both polymers.[11] The $[\eta]_{cyclic}/[\eta]_{linear}$ ratio [0.84(5)] suggests that the former polymers are mostly cyclic, although the presence of residual linear contaminants cannot be completely ruled out. Furthermore, the cyclic polymers also eluted later than their linear analogues with identical MWs.[7] This implies a smaller hydrodynamic volume for the former, assuming the absence of non-size-exclusion separation mechanisms.

In summary, we have demonstrated that cyclic poly(α-peptoid)s can be synthesized with controlled polymer MWs and narrow MW distributions in high purity from an NHC-mediated ROP of N-substituted *N*-carboxylanhydride. The reaction exhibits characteristics of a living polymerization with minimal chain transfer and hence allows for the facile synthesis of cyclic diblock copoly(α-peptoid)s through sequential monomer addition. Elucidation of the reaction mechanism is currently in progress. Insights obtained from this study will guide the optimization of reaction conditions to ultimately produce high-MW cyclic poly(α-peptoid)s with 99+% purity.

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Supporting Information Available: ^{1}H NMR and ESI MS spectra of a low-MW spirocyclic NHC−poly(*N*-Bu-glycine) adduct; ^{1}H NMR and MALDI TOF MS spectra of a low-MW cyclic poly(*N*-Bu-glycine); MALDI TOF MS spectrum of a low-MW poly(*N*-Bu-glycine) sample obtained from NHC **1**-mediated polymerization of $\mathbf{M_1}$ in DMF; ^{1}H and ^{13}C{^{1}H} spectra of $\mathbf{M_1}$ and $\mathbf{M_2}$ monomers, high-MW cyclic poly(*N*-Bu-glycine), cyclic poly(*N*-Me-glycine), and cyclic poly(*N*-Me-glycine)-*b*-poly(*N*-Bu-glycine) block copolymer; SEC chromatograms of polymer samples prior to and after heterochain-extension experiments for cyclic block copoly(α-peptoid) synthesis; cyclic poly(*N*-Bu-glycine) MW and PDI data using calibration curves constructed with polystyrene standards; poly(*N*-Bu-glycine) MW and PDI data for polymerizations conducted in DMF; and Mark−Houwink−Sakurada plots for cyclic and linear poly(*N*-Bu-glycine) and poly(*N*-Me-glycine)-*b*-poly(*N*-Bu-glycine), with and without band-broadening corrections for MWs, and the corresponding logarithmic plots of MW versus elution volume. This material is available free of charge via the Internet at http://pubs.acs.org.

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