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Ring-Opening Polymerization of Imidazole Epoxides for the Synthesis of Imidazole-Substituted Poly(ethylene oxides)

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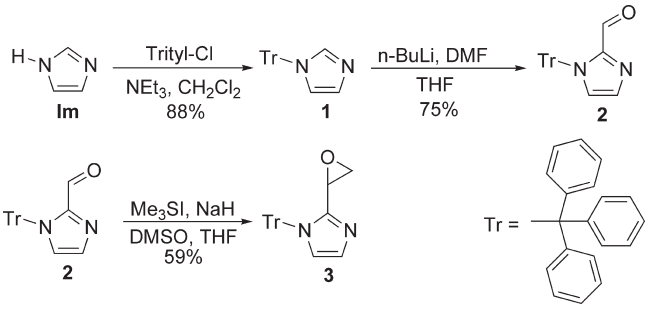
Introduction. The ability to tune molecular weight, topology, architecture, and functionality has catalyzed the discovery of biocompatible polymers for emerging biomedical technologies.[1] The attachment of poly(ethylene glycol) (PEG) to polymers, peptides, nucleic acids, and nanoparticles, often termed PEGylation, is a simple strategy to shield biomaterials from their biological environment due to hydrophilicity, low toxicity, reduced immunogenicity, and low protein binding affinity.[2−6] Many synthetic strategies exist for the design of PEG-containing macromolecules, including the synthesis or subsequent functionalization of poly(glycidols)[7−9] and the well-established anionic ring-opening polymerization (ROP) of epoxides.[10] This latter strategy enables complex polymeric architectures with tailored biofunctionality as pendant sites on the PEG main chain. However, the introduction of imidazole, which is a key functionality in histidine, has remained elusive as a substituent in anionic ROP. Imidazole and imidazole-containing polymers offer a vast array of applications including catalysis,[11] proton transfer,[12] RNA cleavage,[13] nonviral gene transfection,[14,15] metal coordination,[16] and ionic liquids.[17] Other related heterocyclic vinyl monomers, such as vinyl triazoles, have received recent attention as modular monomers for the introduction of nitrogen-containing heterocyclic rings on a hydrocarbon backbone.[18] Herein, we report the synthesis and polymerization of imidazole-substituted epoxides, a novel family of monomers and polymers, for potential incorporation into polymeric therapeutics, ion-transport membranes, and catalysis/metal coordination. An important distinction relative to vinyl monomers is the introduction of the imidazole ring on a poly(alkylene oxide) backbone, which imparts additional backbone flexibility and potential biological compatibility.

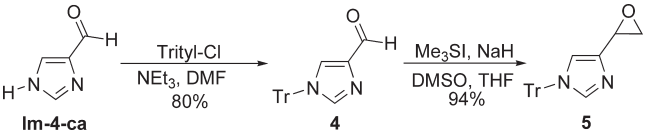
Results and Discussion. Imidazole-substituted epoxide monomers, 1-tritylimidazole-2-ethylene oxide (TIm-2-EO) (**3**) and 1-tritylimidazole-4-ethylene oxide (TIm-4-EO) (**5**), were prepared using a three-step and two-step synthetic approach starting from imidazole (Im) or imidazole-4-carboxaldehyde (Im-4-ca), respectively (Scheme 2). First, Im was protected with triphenylmethyl (trityl) chloride to produce 1-tritylimidazole (**1**). Reaction of **1** with *n*-BuLi/DMF produced 1-tritylimidazole-2-carboxaldehyde (**2**). Compound **2** was subsequently converted to the 1-tritylimidazole ethylene oxide (**3**) in 39% overall yield using the Corey−Chaykovsky epoxidation strategy.[19] In a similar fashion, TIm-4-EO (**5**) was synthesized from commercially available Im-4-carboxaldehyde (Scheme 2). The protection of the 1-H-imidazole was required for the synthesis of the 4-ethylene oxide isomer **5**. Protection of imidazole-4-carboxaldehyde with a benzyl or dimethylaminosulfonyl group yielded a mixture of 4- and 5-substituted regioisomers, products that were often oils and very difficult to separate. Isomerization did not occur during trityl protection, and 1-tritylimidazole-4-carboxaldehyde (**4**) was obtained in high overall yield (80%) as a solid that was amenable to recrystallization. Furthermore, the trityl group was stable under basic epoxidation conditions and was easily and quantitatively cleaved under acidic conditions.

Remarkably, these sterically hindered epoxides, **3** and **5**, were both readily polymerized using potassium *tert*-butoxide initiator to yield poly(1-tritylimidazole-2-ethylene oxide) (**6**) and poly(1-tritylimidazole-4-ethylene oxide) (**8**) (Scheme 3). Typically, hindered epoxides, such as styrene oxide, are often difficult to polymerize under anionic ROP conditions, and only oligomers are obtained. For example, Yang et al. polymerized trityl-substituted epoxides via ROP; however, the investigators achieved 10 000 g/mol oligomers maximum.[20] Polymerization of **3** yielded higher molecular weight polymers with degrees of polymerization (DP) ranging from 17 to 90 and number-average molecular weights (M_n) ranging from 10 000 to 30 000 g/mol (Table 1). The polymerization of **5** also yielded polymers with DPs of 17−77 and M_n = 5900−27 000 g/mol, which scaled with initiator concentration. The initiator efficiencies (*f*) were typically between

Scheme 1. Synthesis of 2-Substituted Im-Epoxide Monomer



Scheme 2. Synthesis of 4-Substituted Im-Epoxide Monomer



Scheme 3. Anionic ROP of Imidazole-Substituted Epoxides

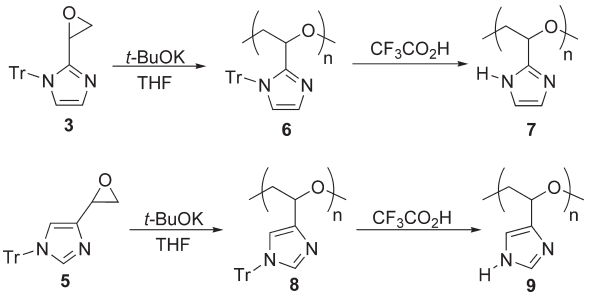


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Table 1. Initiation Efficiency and Final Molecular Weights

	M (mmol)	I (mmol)	% conv[a]	DP	*f*	M_n (g/mol)[b]
6a	2.82	0.10	75	90	0.23	31 700
6b	2.82	0.20	82	45	0.27	15 900
6c	2.82	0.30	78	30	0.23	10 600
8a	2.82	0.10	68	77	0.26	27 100
8b	2.82	0.20	94	23	0.56	8 100
8c	2.82	0.30	94	17	0.47	5 900

[a] Conversion determined gravimetrically. [b] Number-average molecular weights determined using ^{1}H NMR spectroscopy.

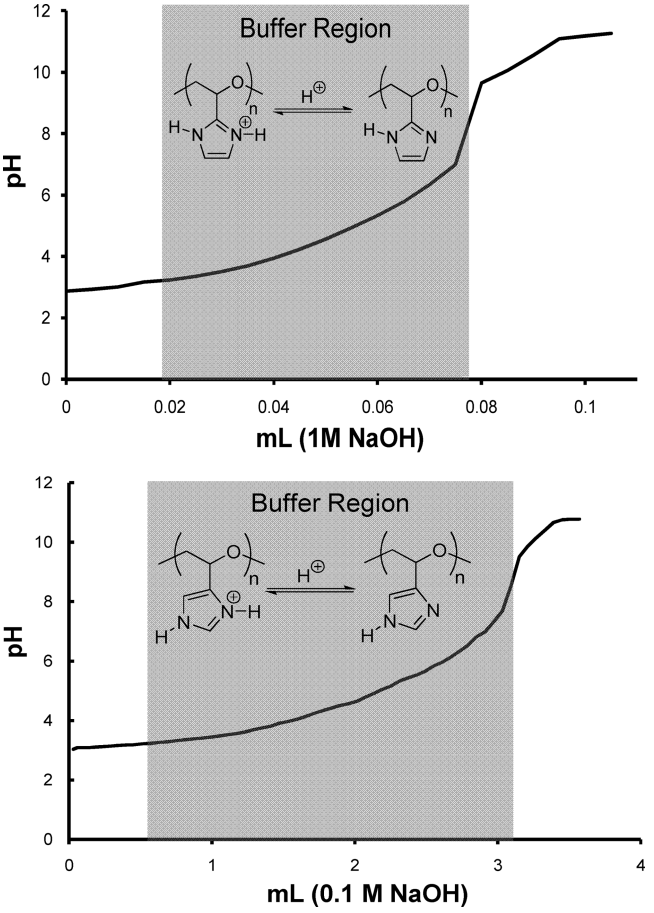

Figure 1. Potentiometric titration of **7** (top) and **9** (bottom). Gray area highlights buffering region of polymer.

0.23 and 0.56, which was attributed to the steric hindrance of the trityl-protecting group and low monomer solubility in the reaction solvent at 20−30% w/v. It was presumed that the relatively higher initiator efficiency for polymerization of **5** was largely due to the accessibility of the epoxide to nucleophilic attack.

The polymerization reactions were initially yellow, heterogeneous solutions that became homogeneous as polymerization progressed. The resulting polymers were readily soluble in organic solvents such as THF, DMF, and $CHCl_3$. Despite possessing a PEG backbone, these polymers were insoluble in water and alcohols due to the hydrophobicity of the trityl group. ^{1}H NMR spectroscopy confirmed polymerization of **3** based on disappearance of the epoxide signals (2.50, 3.08, and 3.13 ppm) and broadening PEG signals (2.12 and 3.50 ppm); the trityl resonance also broadened suggesting formation of polymer. The methyls of the *tert*-butyl initiator fragment were assigned between 0.9 and 1.15 ppm and used to calculate number-average molecular

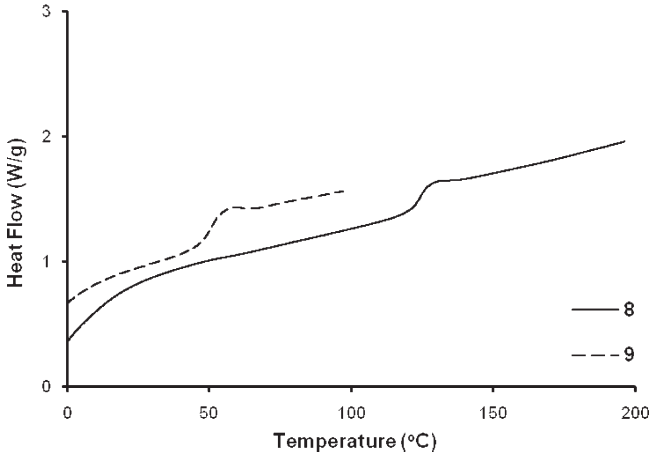

Figure 2. DSC spectra of **8** and **9**. Samples ran at a ramp rate of 10 °C/min under N_2 and the second heat cycle shown.

weight. The ^{1}H NMR spectrum of **6** displayed broad resonances associated with the PEG backbone (3.51 and 4.25 ppm) and the Im and trityl group (6.50−7.50 ppm).

The pH sensitivity of biopolymers in aqueous environments is an important metric for efficient drug and gene delivery. Trityl protecting groups were quantitatively removed with trifluoroacetic acid (TFA) to yield aqueous soluble poly(Im-2-EO) (**7**) and poly(Im-4-EO) (**9**) (Scheme 2). Quantitative removal of the trityl protecting groups was confirmed with ^{1}H NMR spectroscopy. The buffering capacity of the pendant imidazole sites was determined with acidic titration. Imidazole is amphoteric with a $pK_a \sim 7.1$ for its conjugate acid form.[21] Conjugate acids of **7** and **9** were titrated with an aqueous solution of NaOH. The buffering range for **7** and **9** occurred within a pH ranges of 3.0−6.5 (Figure 1). These curves confirmed pH sensitivity, and current studies involve nucleic acid binding for nonviral gene delivery.

Thermogravimetric analysis revealed an onset of decomposition (T_d) of 268 and 161 °C for **8** and **9**, respectively. Glass transition temperatures (T_g) for **8**, **9**, and **7** were 127, 51, and 60 °C, respectively. The large decrease in T_g was assigned to the removal of the bulky trityl groups, presumably allowing more facile segmental motion of the polymeric main chain. The low T_g values for **9** and **7** were attributed to increased chain mobility of the poly(ethylene oxide) backbone (Figure 2).

Conclusion. Novel imidazole-substituted epoxide monomers were successfully synthesized and polymerized using anionic ROP. The resulting polymers were synthesized in high yields (64−94%), and ^{1}H NMR spectroscopy revealed that the PEG-based polymers had relatively high number-average molecular weights (~30 000 g/mol). Poly(TIm-2-EO) and poly(TIm-4-EO) were readily deprotected to yield poly(Im-2-EO) and poly(Im-4-EO), which are both water-soluble pH-sensitive polymers. We are currently exploring different derivatives of imidazole epoxides monomers and evaluating subsequent PEG-based polymers for applications in electroactive devices and biological complexation such as nucleic acid binding.

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Supporting Information Available: Experimental details for the synthesis of compounds **1**−**9**, potentiometric titrations, NMR spectra, and DSC of polymers **8** and **9**. This material is available free of charge via the Internet http://pubs.acs.org.

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