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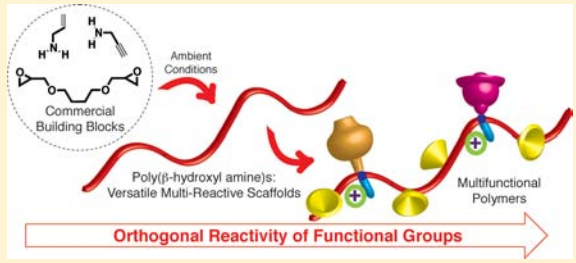
Facile and General Preparation of Multifunctional Main-Chain Cationic Polymers through Application of Robust, Efficient, and Orthogonal Click Chemistries

Animesh Saha,[†] Swati De,[†] Mihaiela C. Stuparu,[‡] and Anzar Khan*[,†]

[†]Department of Materials, ETH-Zürich, CH-8093 Zürich, Switzerland
[‡]Institute of Organic Chemistry, University of Zürich, CH-8057 Zürich, Switzerland

Supporting Information

ABSTRACT: Poly(ß-hydroxyl amine)s are prepared from readily available small molecular building blocks at ambient conditions. These macromolecules can be transformed into main-chain cationic polymers upon quaternization of the backbone amine units. The modular and mild nature of the synthesis allows for incorporation of multiple (2−4) chemically distinct reactive sites in the polymer chain. Modifications of the reactive sites afford multifunctional polymers with tunable properties. The orthogonal nature of the involved chemistries sets the synthetic pathway free from any functional group protection/deprotection requirements. This feature also allows for alteration of the modification sequence.



INTRODUCTION

Efficient and ambient synthesis of functional macromolecules from readily available starting materials has been a significant goal of polymer chemistry.[1,2] To meet this challenge, the concept of utilizing robust, efficient, and orthogonal (REO) chemical reactions is particularly attractive.[2,3] In this approach, high yielding chemical reactions that can be carried out under ambient conditions and proceed with high regioselectivity, functional group tolerance, and atom economy are employed.[4,5] The tolerance and compatibility of these reactions with a variety of functional groups and reaction conditions are an important aspect of the REO concept. This feature can be exploited for facile preparation of multifunctional structures by avoiding the typical functional group protection/deprotection strategies. Furthermore, the efficiency and regioselectivity of the REO processes allow for high-fidelity construction of well-defined macromolecules with precise control over the placement of the functional groups. Finally, the robust nature of REO processes entails a simple synthetic protocol. Recently, Hawker and co-workers elegantly illustrated these concepts in the preparation of triply functionalized cross-linked polymer thin films.[6] In the synthesis of chemically well-defined linear polymers, however, the REO approach is limited to the preparation of singly[7,8] and doubly functional structures.[3b,9,10] Since multifunctionalization (3−4 functional groups) is expected to increase the range of possible applications as well as performance of the functionalized structures,[11,12] our efforts are focused on developing robust and modular strategies that can give facile access to polymers with more than two orthogonal reactive sites from readily available and inexpensive small molecular building blocks at ambient conditions. Here, we elaborate on such a versatile scheme with the help of main-chain cationic polymers. In our scheme, the amine−epoxy "click" reaction between an alkyl amine and a diglycidyl ether is employed as the polymerization reaction (Figure 1).[13] This process offers many advantages: (i) the polymerization reaction proceeds at room temperature under solvent-less conditions and in the presence of moisture and air; (ii) the process does not require any catalyst/reagent, and hence, simple mixing of the two monomers is needed; (iii) the coupling reaction unmasks a reactive hydroxyl group that is available for further functionalization; (iv) another reactive site is created upon polymerization in the form of tertiary amines that can be transformed into positively charged quaternary structures by protonation/alkylation; (v) a number of amines and epoxides are commercially available, inexpensive, and often in the list of common laboratory chemicals; and (vi) the amine−epoxy coupling process is tolerant to various reactive groups and functionalities such as alkynes and nonconjugated olefins. This functional group tolerance allows for utilization of amine monomers carrying free acetylene and alkene groups. Hence, by using the amine−epoxy reaction between appropriate monomers, a reactive polymer scaffold with 2−4 chemically distinct reactive sites can be generated at ambient conditions in one simple step (Figure 1). These polymers represent a novel family of main-chain cationic polymers and are named as poly(ß-hydroxyl amine)s. Direct functional group manipulations on the prepared poly(ß-hydroxyl amine)s give rise to desired multifunctional (2−4 functional sites) structures.

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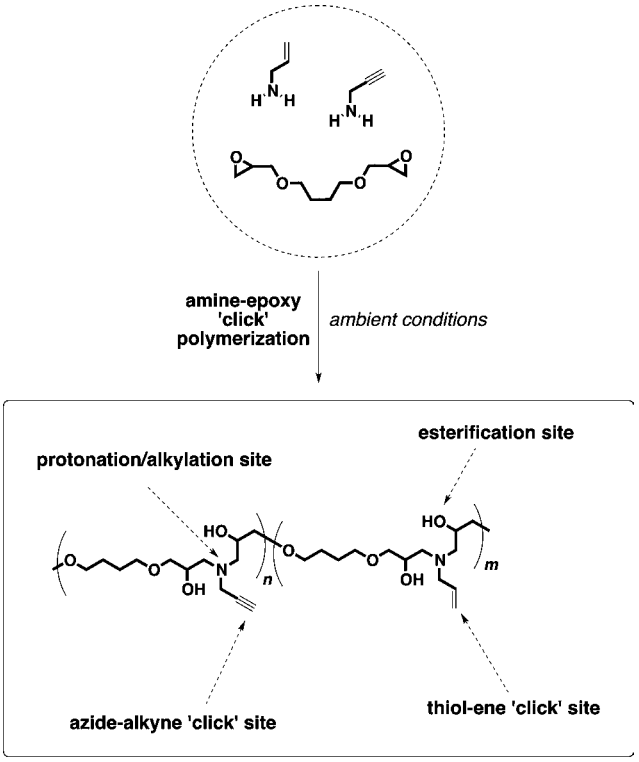
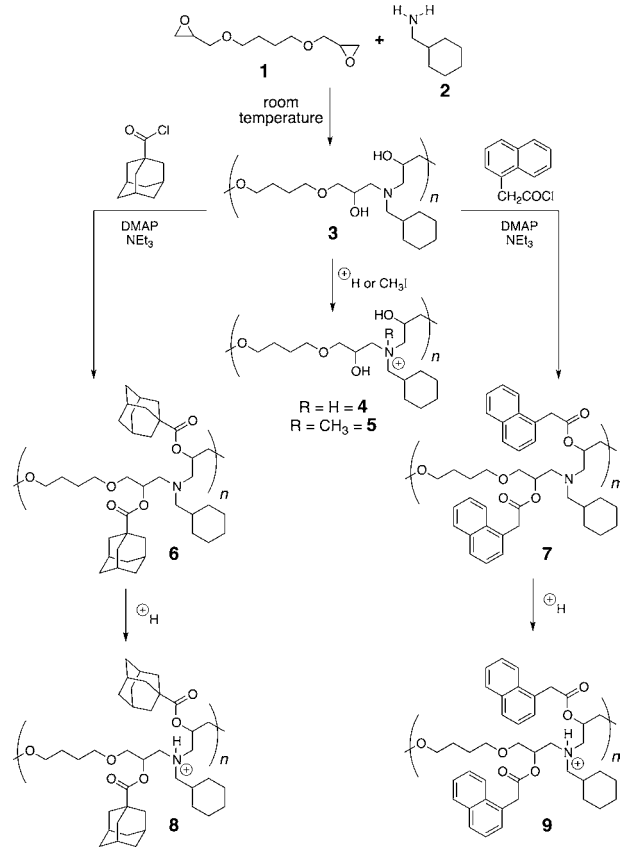


Figure 1. One-step preparation of a novel family of multireactive polymers, poly(ß-hydroxyl amine)s, at ambient conditions and from readily available and inexpensive small molecular building blocks.

RESULTS AND DISCUSSION

Cationic polymers are of immense utility in a myriad of applications. Some prominent examples include gene delivery,[14] DNA sensing,[15] and antimicrobial applications.[16] Based upon earlier work,[17−20] we envisaged that the reaction of amines with diglycidyl-terminated small molecules might present a simple synthetic pathway for the preparation of main-chain ammonium-based cationic structures.[18−20] To examine this possibility, initially 1,4-butanediol diglycidyl ether, **1**, and cyclohexanemethylamine, **2**, were employed as the monomers (Scheme 1). The epoxide groups in **1** represent an AA-type of bifunctional monomer while the primary amine group in **2** represents a BB-type of bifunctional monomer. Typically, the polymerizations were carried out at room temperature, in open systems (to air and moisture), and under solvent-less conditions. Mechanical stirring of the reactions was deemed necessary due to high viscosity of the polymerization mixture. In this way, a polyaddition reaction between **1** and **2** afforded polymer **3** (Scheme 1).[21−23] The polymer yield ranged from 75% to 80% with some material loss that was inevitable due to the highly viscous nature of the materials and strong adherence of the polymers to the glass surfaces. In addition, some fractionation may also be the reason for low polymer yields. Figure 2 shows the ^{1}H NMR spectra of monomer **1**, monomer **2**, and polymer **3**. Monomer **1** showed the typical epoxy proton resonances at 2.6, 2.8, and 3.1 ppm, which disappeared upon polymerization with monomer **2** (Figure 2). Other expected shifts in the proton resonances from the methylene groups were also observed. The molecular weights of the polymers were determined against polystyrene standards and ranged between 13 and 30 kDa with polydispersity indices (M_w/M_n) ranging from 2 to 3 (Figure 3). Monomer stoichiometry plays a

Scheme 1



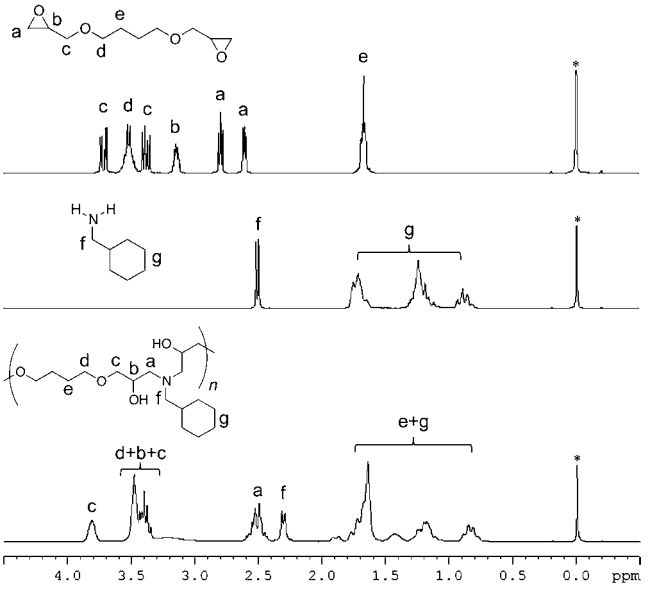


Figure 2. ^{1}H NMR spectra of monomer **1** (top), monomer **2** (middle), and polymer **3** (bottom) in $CDCl_3$. Tetramethylsilane signals are shown with an asterisk.

central role in defining the molecular weights of the polymers in AA-BB-type of step-growth polymerization. Hence, a stoichiometric imbalance of the reactive functional groups in the polymerization media is a likely reason for the low molecular weights of the present polymers.

Polymer **3** was found to be soluble in a range of typical organic solvents but insoluble in water (Supporting Informa-

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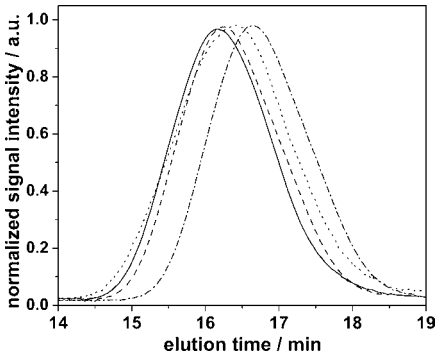


Figure 3. Size-exclusion chromatograms of the precursor polymers **3** (solid), **18** (dash-dot), **23** (dot), and **27** (dash) in DMF.

tion, Table S1). However, upon protonation, polymer **3** transformed into ionic polymer **4** and became completely water-soluble. Figure S1 of the Supporting Information shows the ^{1}H NMR spectrum of polymer **4** in D_2O. As expected, the proton resonances of the methylene groups located adjacent to the nitrogen atom (designated "a" and "f" in Figure S1 of the Supporting Information) shifted downfield upon protonation, in agreement with the previously reported examples.[24] Since the precursor polymer **3** was soluble in methanol, proton spectra of polymer **3** and its cationic form, **4**, were recorded in deuterated methanol for a direct comparison (Supporting Information, Figure S2). Similar shifts were observed as in the case of D_2O and indicated that the changes in the NMR spectrum were due to a change in the chemical structure of the polymer and not due to the change in the chemical nature of the NMR solvent. Alternatively, permanent backbone quaternization could be carried out using methyl iodide as a methylation reagent to afford polymer **5** (Scheme 1 and Supporting Information, Figure S3). However, this polymer was found to be insoluble in water as well as chloroform but highly soluble in methanol.

To investigate the availability of the other reactive site on the polymer chain, the hydroxyl units of polymer **3** were subjected to a postpolymerization modification reaction using adamantanecarbonyl chloride and naphthaleneacetyl chloride to furnish polymers **6** and **7**, respectively (Scheme 1). Conversion of the hydroxyl groups into an ester moiety was evidenced by a shift of the hydroxy-substituted-CH proton signal (labeled "b" in Figure 4) from 3.4 to 5 ppm. Moreover, proton signals from the adamantane moiety could be observed in the range 1.6–2 ppm (designated "i", "j", and "k" in Figure 4). The functionalized polymers **6** and **7** were protonated to give cationic structures **8** and **9**, respectively. In contrast to cationic polymer **4**, polymers **8** and **9** were found to be insoluble in water (Supporting Information, Table S1).

To vary the nature of the amine monomer, diethylenediamine **10** was used as an AA-type of bifunctional monomer (Scheme 2). The resulting polymer, **11**, was found to be soluble in water. This water-soluble neutral polymer was converted into its ionic structure, **12**. Due to the water solubility of polymers **11** and **12**, proton NMR spectra of the polymer before and after ionization could be directly compared in deuterated water. Once again, similar shifts in the proton resonances were observed upon ionization as seen in the previous examples (Figure 5). The use of diethylenediamine as a monomer demonstrated that density and distribution of the nitrogen atoms and hence the positive charges along the polymer

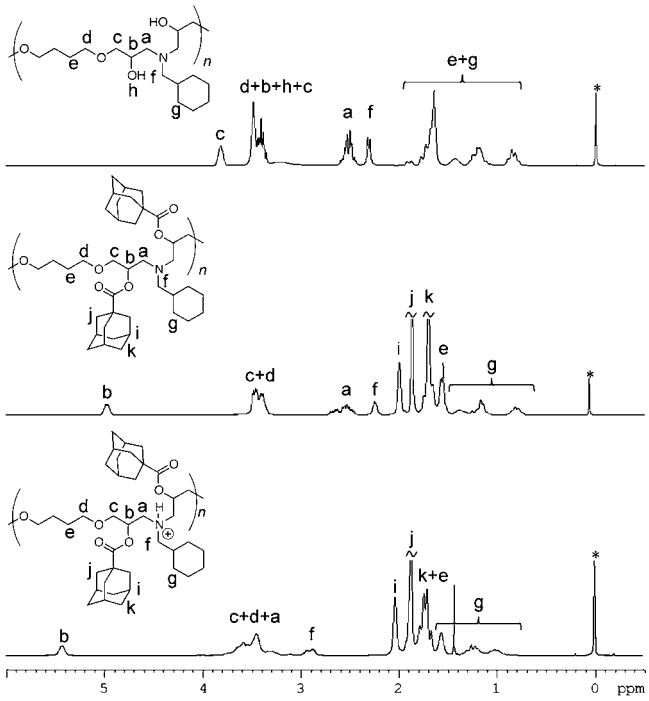
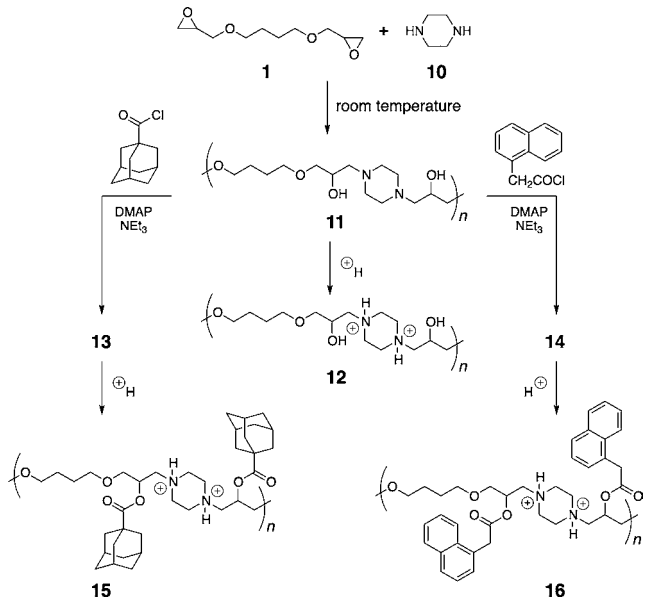


Figure 4. ^{1}H NMR spectra of polymers **3** (top), **6** (middle), and **8** (bottom) in $CDCl_3$. Tetramethylsilane signals are shown with an asterisk.

Scheme 2



backbone could be controlled by using an appropriate amine monomer. This in turn governs the physical properties of the polymer. Polymer **11** was transformed into functionalized polymers **13** and **14** upon esterification reaction and subsequently into ionic polymers **15** and **16**.

Since the amine–epoxy reaction is tolerant to the presence of free alkyne and alkene groups, functionalized primary amines could also be used as monomers. To demonstrate this, propargylamine, **17**, was employed as a monomer along with monomer **1** (Scheme 3). The polymerization reaction afforded alkyne and hydroxyl-substituted polymer **18**. Esterification of the hydroxyl groups furnished polymer **19**. The free acetylene

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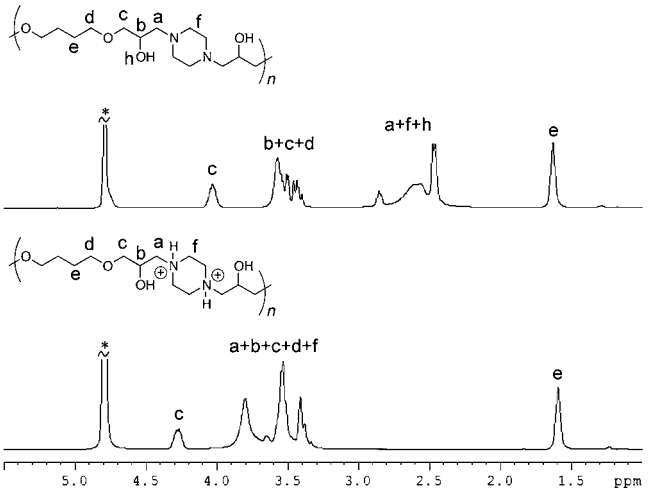
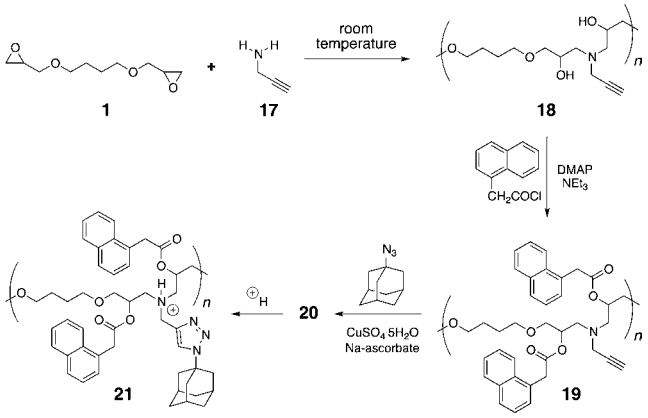


Figure 5. ^{1}H NMR spectra of polymers **11** (top) and **12** (bottom) in D_2O.

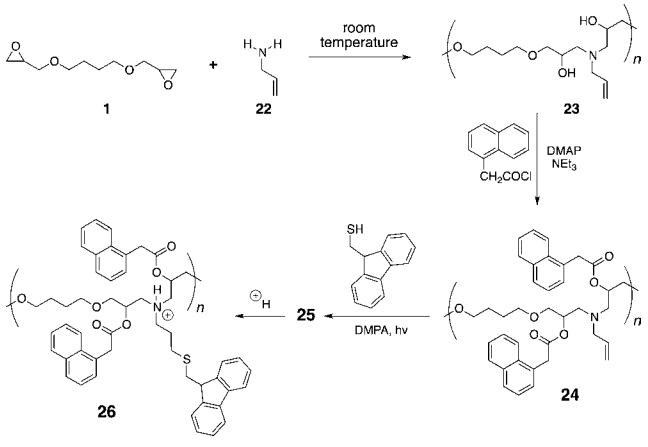
Scheme 3



moieties of **19** were subjected to a copper(I)-catalyzed alkyne–azide coupling reaction using adamantane azide.[5] The resulting polymer **20** carried naphthalene-esters as well as adamantane-triazoles and could be converted to its ionic form **21** upon protonation.

To examine the possibility of using an alkene-functionalized amine in the present polymerization system, allylamine, **22**, was employed as a monomer along with monomer **1** (Scheme 4).

Scheme 4



The polymerization yielded polymer **23**, which upon esterification, led to the formation of polymer **24**. The olefin groups in **24** could be subjected to a photochemical thiol–ene reaction by using fluorenylmethyl thiol in the presence of 2,2-dimethoxy-2-phenylacetophenone.[25] Amine quaternization of polymer **25** gave access to polymer **26**.

Encouraged by these results, multifunctional structures were targeted. For this, poly(ß-hydroxyl amine), **27**, with four chemically distinct reactive sites, (i) an alkyne, (ii) an alkene, (iii) a hydroxyl group, and (iv) a tertiary amine, was prepared by copolymerizing propargylamine, **17**, and allylamine, **22**, along with monomer **1** (Scheme 5). In polymer **27**, the alkyne can be reacted to a functional azide, the olefin can be coupled to a functional thiol, the hydroxyl group can be modified by an esterification reaction, and the tertiary amine can be protonated/alkylated to give cationic multifunctional backbones. The sequence of events can be altered so that the esterification reaction is performed first followed by alkyne–azide coupling, thiol–ene, and then, amine quaternization. Alternatively, an esterification reaction, a thiol–ene coupling, and an amine quaternization can follow the alkyne–azide coupling. The quaternization can be performed at any stage without disturbing the other reactive sites. To demonstrate these, the reactive scaffold **27** was allowed to react sequentially with adamantane azide, fluorenylmethyl thiol, naphthaleneacetyl chloride, and HCl to give polymers **28**–**31**, respectively (Scheme 5). The ^{1}H NMR spectrum of polymer **27** showed the alkyne proton signal at 2.2 ppm and the olefin signals at 5.15 and 5.8 ppm. Upon coupling to the adamantane azide, the akyne signal disappeared, and the signals from the adamantane moiety (1.8–2.2 ppm) and the newly formed triazole ring (7.6 ppm) could be observed (Figure 6). Upon coupling to the fluorenylmethyl thiol, the olefin signals disappeared, and signals from the aromatic rings of fluorene could be observed in the range 7.2–7.8 ppm. Moreover, a triplet and a doublet could be seen at 4.2 and 3.2 ppm, respectively. These signals belong to the protons present at the fluorene bridge and the adjacent methylene group. Upon esterification, due to the naphthalene rings, the aromatic area became broad, and a signal at 5 ppm was observed due to the proton located adjacent to the ester moiety. Alternatively, polymer **27** could also be esterified before carrying out the click reactions (Scheme 6). The alkyne and the olefin both remained intact after this functionalization step. Finally, polymers **27**–**29** could be converted into ionic structures without disturbing the other reactive sites (Scheme 6). Significantly, reactive ionic polymer **33** was soluble in water, whereas mono- and bifunctionalized ionic polymers **34** and **35** were soluble in water as well as chloroform.

In UV–vis absorption spectroscopy, polymers **27** and **28** did not show absorption above 250 nm (Figure 7). After the thiol–ene coupling, polymer **29** showed absorption in the range 250–320 nm due to the fluorene substitution. Naphthalene absorption dominated the absorption spectrum of polymer **30**. Protonation of polymer **30** did not influence the absorption properties of polymer **31**. IR spectroscopy further corroborated the ^{1}H NMR and UV–vis spectroscopic results by displaying the expected ether, ester, and aromatic vibrational stretches in this final series of polymers (Supporting Information, Figure S5).

In this modular way, a novel family of main-chain cationic polymers, poly(ß-hydroxyl amine)s, with 2–4 functional sites could be obtained in 3–5 simple synthetic steps from commercially available small molecular building blocks and

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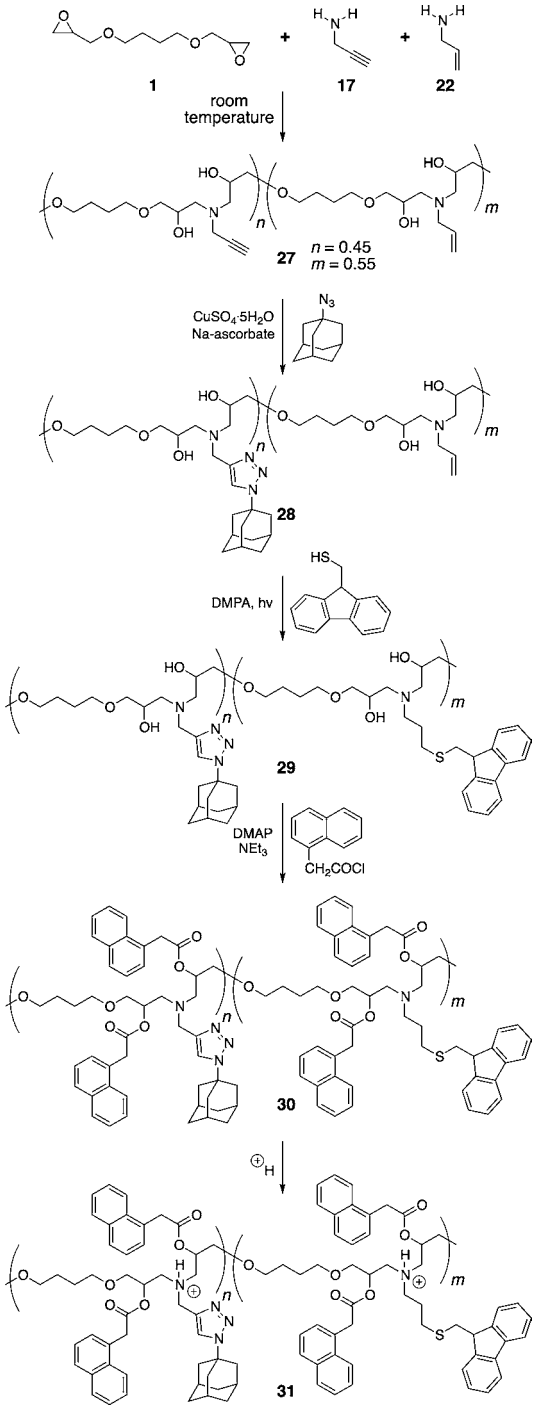
Scheme 5



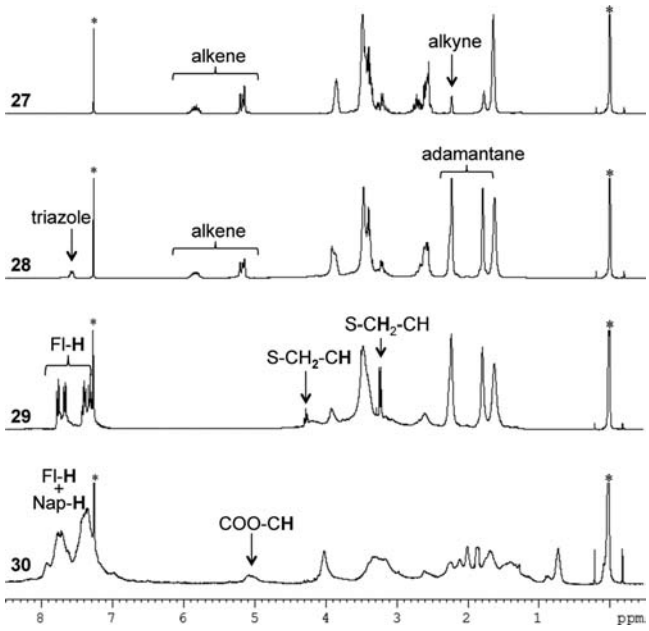
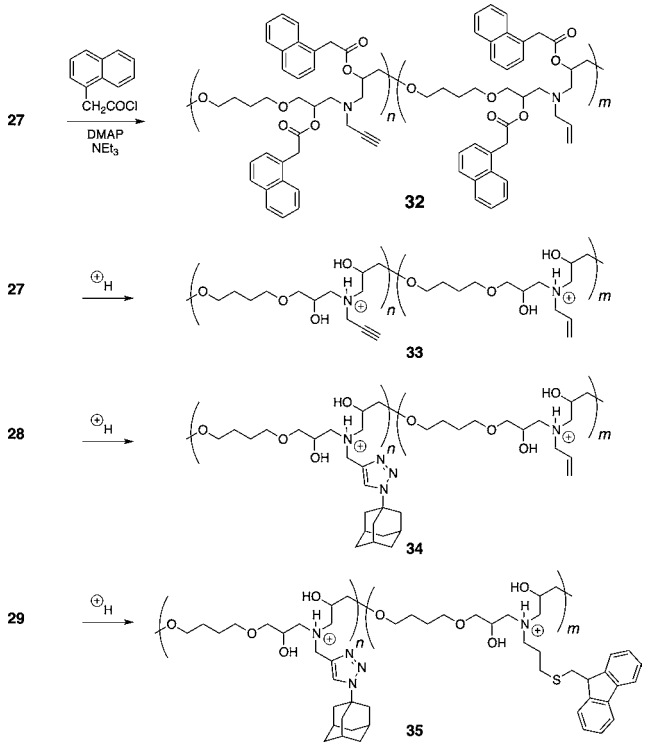


Figure 6. ^{1}H NMR spectra of polymers **27**−**30** in $CDCl_3$. Tetramethylsilane and chloroform signals are shown with an asterisk. ("Nap" stands for naphthalene whereas "Fl" stands for fluorene.)

Scheme 6



reagents. It should be noted that the epoxide monomer could also carry a functionalizable site, which may open doors to the synthesis of chemically precise penta- and hexafunctional structures. Moreover, instead of protonation, as presented in this work, the tertiary amine sites could also be alkylated using functional alkyl halides.[26]

CONCLUSIONS

A novel family of main-chain cationic polymers, poly(ß-hydroxyl amine)s, were prepared by the amine−epoxy click polymerization at ambient conditions and from readily available small molecular building blocks. By using the REO concepts, a number of chemically distinct reactive sites, in their chemically free form, could be incorporated during the construction of the polymer chains. Postpolymerization modifications of these reactive sites in a sequential manner afforded multifunctional cationic structures. The orthogonal nature of the applied chemistries allowed a protection/deprotection free synthetic scheme to be developed while the efficiency of the involved processes resulted in near quantitative modifications of the

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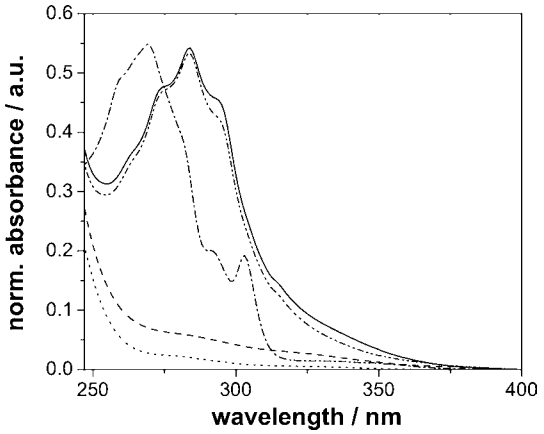

Figure 7. UV−vis absorption spectra of polymers **27** (dot line), **28** (dash line), **29** (dash-dot line), **30** (solid line), and **31** (dash-dot-dot line).

reactive sites.[27] The modification sequence could be altered due to the orthogonality of the selected set of reactions.

The opportunity of functionalization bodes well for various applications in which the cationic polymer chain has to be modified to achieve optimum properties. For example, hydrophobic modifications of the cationic polymers are shown to improve gene delivery efficiency by enhancing the cellular uptake of the modified polymer by lipophilic cell membranes.[28] The prospect of introducing more than one functional group in the present work suggests that not only can one add a hydrophobic site for better cellular uptake but also incorporate, for example, a targeting ligand and an imaging agent in a chemically well-defined manner.

In summary, the versatile, ambient, efficient, and practically simple synthetic strategy from commercially available inexpensive building blocks and the opportunity for multiple functionalizations of the presented new class of main-chain cationic polymers hold significant promise for the development of high-performance biomaterials for potential use in antimicrobial and gene delivery applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods and materials, synthesis and characterization details, ^{1}H NMR spectra of the polymers, solubility properties of the polymers, GPC profile of polymer **11**, and IR analysis of the polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

anzar.khan@mat.ethz.ch

Notes

The authors declare no competing financial interests.

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