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Chemically and Electrochemically Mediated Release of Dendrimer End Groups

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ABSTRACT: Generations 1−5 of poly(propyleneimine) dendrimers (**1**−**5**) terminated with redox-labile, trimethyl-locked quinone (TLQ) end groups were shown to release the TLQ units as lactone **6** upon chemical or electrochemical redox action. Sodium dithionite was used as a chemical reducing agent to instantly convert the TLQ units to their deuteroquinone analogues (TLDQ), which were subsequently liberated from the dendrimers following zero-order kinetics in both DMSO-d_6−D_2O (85:15, v/v, $k_{obs} = 7 \times 10^{-6}$ M s^{-1}, $t_{1/2} = 9$ min) and THF-d_8−D_2O (76:24, v/v, $k_{obs} = 4 \times 10^{-6}$ M s^{-1}, $t_{1/2} = 15$ min). Cyclic voltammetry of **1**−**5** in DMSO/0.1 M n-Bu_4PF_6 revealed that the reduction peak potential (E_{pc}) values for the formation of TLQ^{2-} were generally invariant (−1.85 V vs Fc/Fc$^+$) with dendrimer generation. Thus, bulk electrochemical reduction of **1**−**5** at an overpotential of −0.3 V vs the E_{pc} of TLQ^{2-} produced PPI dendrimers containing dianionic TLQ^{2-} termini. Protonation of the electrochemically generated TLQ^{2-} end-group units with H_2O produced the transient and structurally labile hydroquinone (TLHQ) intermediates, which were liberated from the dendrimers as lactone **6** in a similar fashion as in the sodium dithionite-induced approach. In both the chemically and electrochemically mediated routes, ^{1}H NMR spectroscopy verified that the redox-promoted disconnection of TLQ from the dendrimers was quantitative.

Introduction

The hosting properties of high-generation poly(propyleneimine), PPI,[1] and poly(amidoamine), PAMAM,[2] dendrimers are actively being investigated due to the utility of these dendrimers for guest containment and, hence, potential delivery applications. In principle, guest molecules can be covalently and noncovalently loaded in the termini and void interior locations, respectively, of these two dendrimer families.[3] Therefore, studies that target the guest-containment ability of these dendrimers, such as loading capacity and kinetics of guest release, are necessary in order to fully explore the promising carrier properties of these macromolecules.

In this article, we strictly focus our attention on the liberation of covalently linked termini residues from PPI dendrimers. We demonstrate that electron-transfer (et) events are utilized to induce the covalent disconnection of the end-group residues from the dendrimers and that such events can be effected by homogeneous (chemical) and heterogeneous (electrochemical) redox activation. The potential applications of each of these two routes are widespread. For example, redox-promoted release of dendrimer end groups using chemical agents will find applications in redox-mediated[4] drug delivery,[5] provided that the kinetic and thermodynamic requirements for et between the physiological redox cofactors (e.g., redox proteins, ascorbic acid, thiols) and dendrimers are met. For et events that are induced by electrochemical means, the general end-group-release strategy can be applied to the engineering of dendritic structures on electroactive and microscopic surfaces[6] (e.g., microfluidic devices, high-surface-area reactors).

Dendrimers that are able to release their end-group units in response to external stimuli can be generally classified into two distinct classes. The first is known as self-immolative dendrimers[7] (SIDs), wherein an external chemical or enzymatic stimulus triggers the structural disassembly of the dendrimers to release the end-group moieties. The second class is composed of dendrimers that are able to release their end groups while maintaining the integrity of the dendrimer architecture (i.e., without "detonating" the central dendrimer structures, as in the case of the SIDs).[8,9] The common goal of these two classes of end-group liberation motifs is motivated by two factors. First, the polycovalent capacity of the dendrimer termini generally allows augmented loading of target residues. Second, external stimuli action is needed in order for the end-group residues to be liberated. In line with the general strategy of developing end-group-releasing dendrimers that belong to the second class, we[8] and others[9] reported the use of various stimuli sources to induce the liberation of dendrimer end groups. In particular, our current interest in this area lies in a redox-responsive approach, wherein the oxidation states of the dendrimer structures are expected to manipulate their end-group-releasing property. Thus, it becomes apparent that the general design of the aforementioned redox-responsive dendrimers makes an et event a convenient and effective strategy to gate the liberation of covalently attached target residues. Hence, it is necessary to explore the liberation motif of dendrimer end groups.

We initially reported that the release of the trimethyl-locked quinone (TLQ) end groups from the PPI dendrimers in Chart 1, PPI-x-TLQ ($x = 4$−64), is regulated by redox control.[8] To our knowledge, these dendrimers and those of de Groot[7a] are the only dendritic systems capable of liberating their end-group units upon redox action. In both cases, chemical reducing agents are needed to homogeneously activate the dendrimers to their unstable forms, which leads to the eventual release of the end groups. Dendrimers **1**−**5** contain the redox-sensitive TLQ end groups that can be reduced to their hydro(deutero)quinone (TLH(D)Q) intermediates, which dissociate into the pentamethyl lactone **6** and free amines (Scheme 1). Herein, we report the chemical and electrochemical characterization of these dendrimers, and we demonstrate that the chemically and electro-

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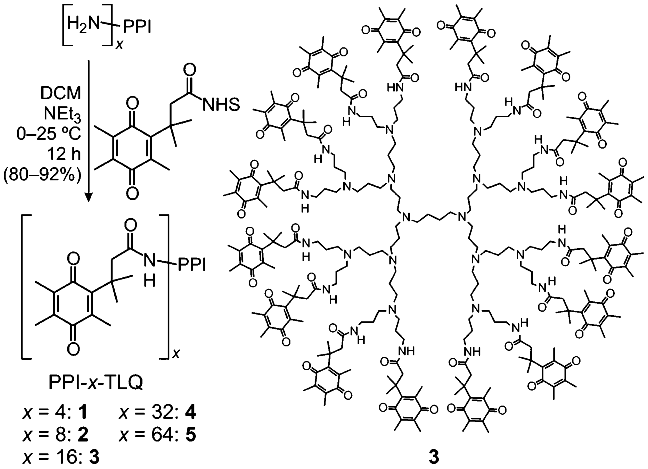
Chart 1. Synthesis of PPI Dendrimers (1−5) That Are Terminated with TLQ End Groups[a]



[a] The structure of third-generation **3** is shown.

chemically induced release of the TLQ units occurs in a facile manner. The results of this investigation provide valuable insights into the versatility of such redox-mediated methodology in controlling the architectures of electroactive dendrimers.

Results and Discussion

Synthesis and Characterization of Dendrimers. Dendrimers **1**−**5** were prepared by condensing the parent PPI-*x*-NH_2 dendrimers ($x = 4$, 8, 16, 32, and 64) with the NHS-activated lactone[10] (Chart 1). The reactions for all dendrimers reached completion after 12 h, but the isolated yields were in the 80−92% range because some materials were lost during the precipitation steps in the purification. Nonetheless, the high symmetry of the ^{1}H NMR resonances and the values of the apparent M^+ peaks in the MALDI-TOF mass spectra (Table 1 and Figures S1 and S2) of **1**−**5** indicate that these dendrimers are of reasonably high purity.

Diffusion coefficient (D) measurements in DMSO-d_6 on these dendrimers by pulsed-gradient spin-echo (PGSE) ^{1}H NMR generated D and hydrodynamic radii (r_H) values that monotonically decreased and increased, respectively, with increasing dendrimer generation (Figure 1 and Table 1). When compared to the known r_H values of their commercial PPI-*x*-NH_2 (x = 4−32) precursors in D_2O, the experimentally determined values

Table 1. Spectrometric and Diffusion Data for Dendrimers 1−5: Calculated M^+ and Observed Values (in amu), Diffusion Coefficients (D, in cm^2 s^{-1}, at 25 °C), and Hydrodynamic Radii (r_H, in nm, at 25 °C)

dendrimer	MS (calcd, M^+)	MS (obsd)	D	r_H
1	1245.7	1245.8	1.5	0.73
2	2631.6	2632.6	1.3	0.84
3	5403.4	5406.9	0.92	1.2
4	10947	10949	0.69	1.6
5	22034	22041	ND[a]	n/a

[a] The D value of **5** was not determined because the nonlinearity of its PGSE data indicated evidence of dendrimer aggregation in DMSO-d_6.

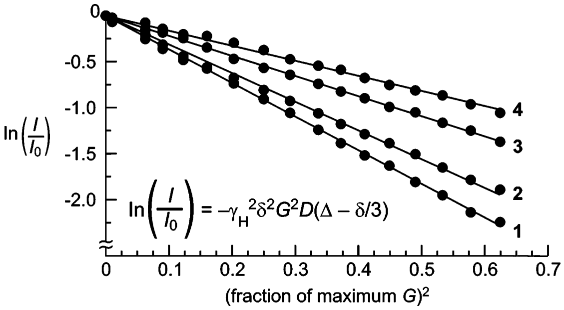
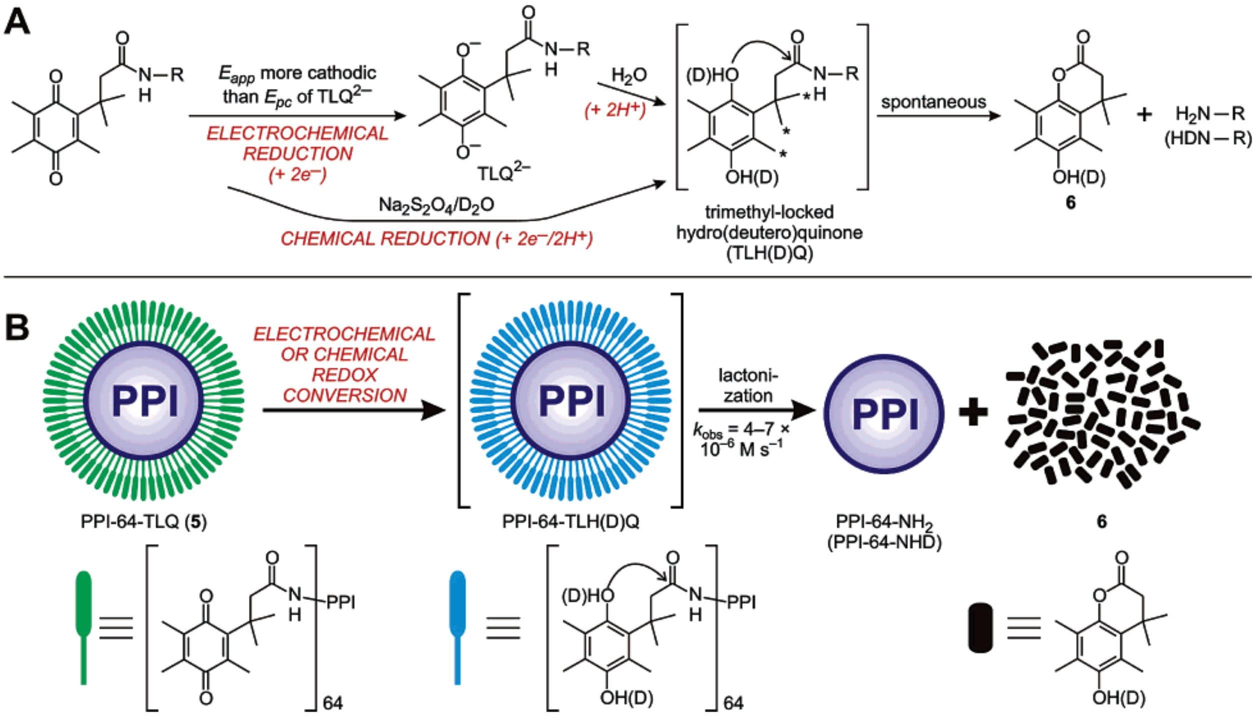


Figure 1. PGSE ^{1}H NMR plots for **1**−**4** in DMSO-d_6 at 25 °C (Δ = 55 ms, δ = 5 ms). Lines show the best fits (correlation > 0.99) of the attenuated ^{1}H echoes to the inset equation. The echo attenuation of 5 vs G^2 is nonlinear (not shown). 100% G corresponds to 0.51 T m^{-1}.

Scheme 1[a]



[a] (A) Chemically and electrochemically induced routes for the reduction of TLQ to form the structurally labile TLH(D)Q intermediate, which eventually releases the free amine from lactone **6**. The three methyl groups of the TLH(D)Q intermediate that are marked with an asterisk comprise the "trimethyl-locked" conformation. (B) Graphical illustration showing the release of the 64 TLQ end groups from fifth-generation dendrimer **5**.

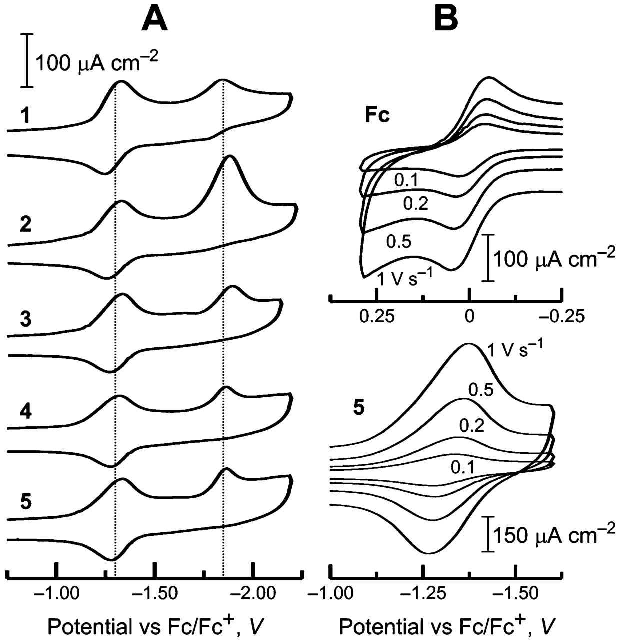


Figure 2. (A) Cyclic voltammetric responses of dendrimers **1**−**5** at a glassy carbon electrode in DMSO/0.1 M *n*-Bu_4PF_6 at 25 °C. In all measurements, the [end group TLQ] was fixed at 1.0×10^{-3} M. Scan rate = 0.1 V s^{-1}. Dotted lines at −1.30 and −1.85 V reveal the steady behavior of the half-wave potential of the TLQ/$TLQ^{\bullet-}$ couple relative to the E_{pc} of TLQ^{2-}. (B) Voltammetric responses of the internal ferrocene reference (Fc, top) and the TLQ/$TLQ^{\bullet-}$ couple of **5** (bottom) as a function of sweep rates.

of **1**−**4** in DMSO-d_6 fall within the range expected for these dendrimers.[11] However, the growth of the r_H values with increasing dendrimer generation is more pronounced for the parent PPI-*x*-NH_2 dendrimers in D_2O than for **1**−**4** in DMSO-d_6. This observation is not too surprising, considering that the degree of end-group backfolding between the parent PPI-*x*-NH_2 and the title dendrimers is unlikely to be similar in different media. On the basis of the diffusion data, it is reasonable to assume that dendrimers **1**−**4** are predominantly monomeric (i.e., nonaggregated) at the millimolar concentration levels used in the PGSE experiments.

Electrochemistry of Dendrimers. In aprotic organic media, the voltammetry of quinones (Q) generally exhibits two consecutive one-et processes that are associated with the redox responses of the Q/$Q^{\bullet-}$ and $Q^{\bullet-}$/Q^{2-} couples. The cyclic voltammograms of **1**−**5** in DMSO/0.1 M *n*-Bu_4PF_6 (Figure 2A) display these expected characteristics.[12] For the TLQ/$TLQ^{\bullet-}$ redox couple, the half-wave potential values (−1.30 V vs Fc/Fc^+) are invariant with dendrimer generation, suggesting that there is no generation-dependent, thermodynamic preference for heterogeneous et. In other words, dendrimer growth does not appear to thermodynamically favor or disfavor the reduction of Q to $Q^{\bullet-}$. Interestingly, at a fairly long voltammetric time scale of 0.1 V s^{-1}, the diffusive shape of the reduction peaks for the high-generation dendrimers **3**−**5** implies the absence of electrode precipitation/adsorption.[13] Although DMSO is a relatively polar solvent, this observation is rather remarkable considering that the electrogenerated and highly polyanionic intermediates (negative charge of up to 64 for the one-electron reduction of **5**) remain soluble upon the redox conversion of the dendrimers.[14] Though we are unable to provide a rationale for the unexpected solubility of the high-generation polyanionic dendrimers, it is plausible that the predominantly monomeric nature of their neutral forms (vide supra) helps explain this surprising behavior.

Table 2. Kinetic Data for the Release of the TLDQ Intermediates from Dendrimers 1−5 as Lactone 6

medium[21]	k_{obs} (M s^{-1})	$t_{1/2}$ (min)
DMSO-d_6−D_2O (85:15, v/v)[8]	7×10^{-6}	9
THF-d_8−D_2O (74:26, v/v)	4×10^{-6}	14

It is also evident from Figure 2A that the general behavior of the voltammetric responses of the TLQ/$TLQ^{\bullet-}$ couple in all generations is electrochemically reversible in DMSO/0.1 M *n*-Bu_4PF_6. Other solvents such as CH_2Cl_2, CH_3CN, and DMF produced complicated voltammetric responses. Examination of the voltammograms in DMSO/0.1 M *n*-Bu_4PF_6 at scan rates up to 1 V s^{-1} led to the observation that the TLQ/$TLQ^{\bullet-}$ couple retained its reversible behavior in all generations (Figure 2B). The fact that the separation of the peak-to-peak potential values of the TLQ/$TLQ^{\bullet-}$ couple remained comparable to those of the internal Fc/Fc^+ reference at all scan rates[15] indicates that the rates for heterogeneous et of these two redox couples remain fast and indistinguishable from each other at the time scales surveyed in the experiments. Observation of such fast et events is indirect evidence that the TLQ end groups are kinetically accessible for heterogeneous et, which may suggest that the end groups are unlikely to be severely backfolded. The absence of significant backfolding events is imperative for the dendrimer systems presented here because the accessibility of the redox cofactors (chemical and electrochemical redox stimuli) to the dendrimer exterior has kinetic and thermodynamic consequences on the et events that are required to release the TLQ end groups (vide infra).

The voltammetric responses of the $TLQ^{\bullet-}$/TLQ^{2-} couple are irreversible and complicated in all generations. For example, no anodic currents were observed for the reoxidation of TLQ^{2-} to $TLQ^{\bullet-}$. In addition to the slightly unsteady reduction peak potential values (E_{pc}) at approximately −1.85 V vs Fc/Fc^+, the nonuniform cathodic peak current (i_p) intensities for this couple are consistently observed in all of the voltammograms (Figure 2A). This observation is most likely a reflection of the chemically unstable nature of Q^{2-}, whose voltammetric behavior is known to be very sensitive to solvation energy, ion pairing, and protonation equilibria.[16]

Release of TLQ End Groups from the Dendrimers. Scheme 1A depicts the reductive lactonization of a masked amine,[17,18] where formation of the reactive hydro(deutero)-quinone (TLH(D)Q)[19] intermediate eventually liberates lactone **6** from the amine. It is believed that the presence of the so-called “trimethyl-locked”[10,20] configuration is responsible for promoting the reductive lactonization process. We extend this concept to dendrimers **1**−**5** and demonstrate that the outright liberation of their TLQ end groups can indeed be activated via chemical (case A) and electrochemical (case B) redox action.

Case A: Activation via Chemical Redox Action. We initially showed by ^1H NMR spectroscopy that the homogeneous and chemically induced removal of the TLQ units of **1**−**5** by $Na_2S_2O_4$ in DMSO-d_6/D_2O (85:15, v/v) is completed in under 20 min.[8] We find here that similar experiments in THF-d_8/D_2O (74:26, v/v) also produced the expected products, but under these conditions, the rate for the zero-order appearance of pentamethyl lactone **6** is slightly slower than in the DMSO-d_6/D_2O system (Table 2 and Figure 3).[21] Because the chemical reduction of TLQ and the deuterium ion uptake by TLQ^{2-} proceed instantaneously (<2 s), the rate-limiting step for the eventual release of TLQ from the PPI dendrimers as lactone **6** in both DMSO-d_6/D_2O and THF-d_8/D_2O media is practically governed by the lactonization of the TLDQ intermediate. That is, following the reduction of TLQ to TLDQ, the TLDQ intermediates are slowly

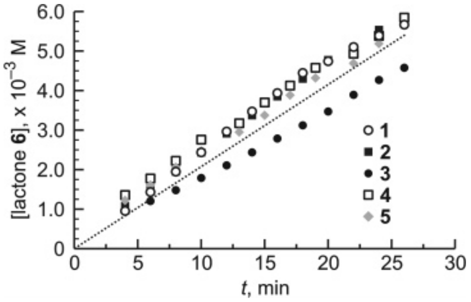


Figure 3. Kinetic profiles exhibiting the zero-order appearance of **6** in THF-d_8−D_2O (74:26, v/v) following the chemical reduction of the TLQ end groups in **1**−**5** by $Na_2S_2O_4$ to TLDQ intermediates; i.e., the dendrimer end groups are all in TLDQ forms at $t = 0$ min. The end-group concentration of the TLQ units prior to chemical reduction is 7.2×10^{-3} M. The dotted line corresponds to a k_{obs} value of 4×10^{-6} M s^{-1}.[21] The data points correspond to the resonance intensities of the geminal dimethyl groups of lactone **6**.

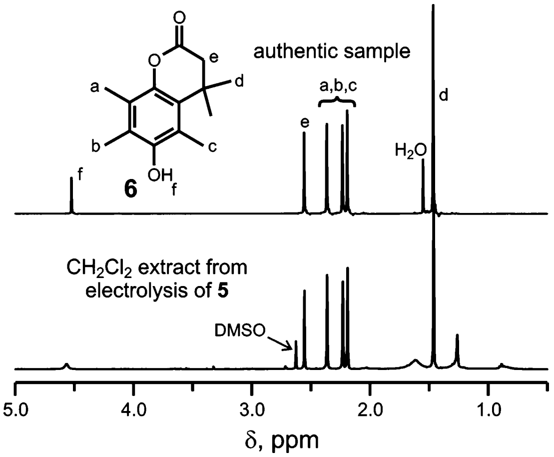


Figure 4. ^1H NMR spectra (400 MHz, $CDCl_3$) of an authentic sample of **6** (top) and the electrolyzed product of **5** (bottom). The resonances at δ 0.88 and δ 1.26 ppm (bottom) originate from the unremoved hexanes in **5**. The postelectrolysis products of dendrimers **1**−**4** produced identical spectral features as those of the electrolyzed product of **5**.

released from the dendrimers as lactone **6** following zero-order kinetics (Scheme 1). We were unable to identify other binary solvent systems that are compatible with both the high-generation TLQ dendrimers and $Na_2S_2O_4$ (primarily due to solubility issues). Thus, no general conclusion can be made at this time regarding the media effect on the k_{obs} values. Nonetheless, it must be noted that the redox-promoted release of lactone **6** from dendrimers **1**−**5** in both DMSO-d_6/D_2O and THF-d_8/D_2O media share the following similarities: (1) despite the complexities of the dendrimer structures (up to 64 TLQ end groups for **5**), release of lactone **6** follows simple zero-order kinetics, and (2) there is no generation-dependent trend for the liberation of lactone **6**. Within the sensitivity limits of ^1H NMR spectroscopy, quantitative conversion of the dendrimers' TLDQ units to lactone **6** was observed.

Case B: Activation via Electrochemical Redox Action. Having demonstrated the homogeneous and chemically activated release of the TLQ end groups in case A, we now show that the structurally labile TLHQ end groups can also be formed by the heterogeneous electrochemical reduction of TLQ followed by protonation. On the basis of the voltammetric results in Figure 2, the TLQ end groups were electrolyzed in DMSO/0.1 M KPF_6 at an overpotential of −0.3 V vs the E_{pc} of TLQ^{2-} (i.e., at −2.15 V vs Fc/Fc^+) until the residual electrolytic current reached less than 3% of its initial value.[22,23] This condition is in slight contrast to the homogeneous reduction experiments, where the dendrimers were chemically reduced by $Na_2S_2O_4$ in the binary DMSO-d_6−D_2O and THF-d_8−D_2O media. In protic media, TLQ^{2-} uptakes two H^+ ions to generate its fully protonated and neutral form, TLHQ. At the conclusion of the electrolysis, when the TLQ units have been quantitatively converted to TLQ^{2-}, H_2O was added to the electrolyzed solution to instantly protonate TLQ^{2-} to TLHQ.[24] Judging from the kinetic data in Table 2 and Figure 3, the lactonization process was assumed to have reached completion in under 30 min. Following lactonization, the DMSO−H_2O solution was extracted with CH_2Cl_2, and the combined organic extracts were analyzed by ^1H NMR spectroscopy. From Figure 4, it is evident that aside from the nearly coalesced resonances of the acidic −OH (δ 4.57 ppm) and H_2O (δ 1.62 ppm) protons, the CH_2Cl_2 extract only contained the released lactone **6**. Considering that no tedious purification was performed on the electrolyzed solution, the ^1H NMR results in Figure 4 further indicate that electrolysis of the dendrimer end groups did not produce byproducts other than lactone **6**. Thus, under the conditions of the electrolysis experiments, and as predicted in Figure 2A, the TLQ units surrounding the exterior of dendrimers **1**−**5** are converted to TLQ^{2-} anions (Scheme 1A).[25]

To quantify the conversion efficiency of TLQ to lactone **6**, the postelectrolyzed DMSO−H_2O solution was evaporated to dryness under vacuum, and the obtained oily residues were suspended in $CDCl_3$. An equal volume of D_2O was added to extract the residual DMSO that interferes with the ^1H NMR analysis of lactone **6**. The ^1H resonances of interest in the $CDCl_3$ layer (Figure S3B) were identical to those shown in Figure 4, while the spectrum of the D_2O layer reveals only a resonance that is associated with the DMSO/KPF_6 medium (Figure S3C). Similar to case A, the ^1H NMR spectra for the solutions described in case B indicate that the TLQ end groups were quantitatively converted to lactone **6**.[26,27]

In both the chemically and electrochemically initiated routes for end-group removal, the liberation of lactone **6** from the high-generation dendrimers is not hampered by precipitation/adsorption effects that are oftentimes encountered with various dendrimers containing multiple redox-active sites.[14] Because such unwanted effects are absent in the dendrimers presented here, the true polycovalent carrier properties of the dendrimer structures can be exploited without compromising any chemical and redox limitations resulting from dendritic growth. We believe that the excellent solubility of the dendrimers' various oxidation states positively addresses a critical concern regarding the compatibility of such design in many practical applications. For instance, water-soluble carriers (dendritic or polymeric) bearing TLQ trigger points can find applications that are suitable for in-vivo conditions, such as redox-mediated therapeutic delivery.[4] In addition, the independence of the heterogeneous approach from chemical reagents for end-group removal makes such method suitable for applications that are not strictly based on solution chemistry, and it may have implications on the eventual integration of redox-cleavable dendrimers on microscopic structures and electroactive surfaces.

Conclusions

We have prepared generations 1−5 of PPI dendrimers that are terminated with redox-cleavable TLQ end groups. It was shown that these dendrimers are electron sinks that drive the removal of the TLQ units as lactone **6**. The outright liberation of the end groups can be induced chemically (homogeneous et) and electrochemically (heterogeneous et). By using $Na_2S_2O_4$

as the chemical reducing agent, it was demonstrated by ^{1}H NMR spectroscopy that the TLQ moieties of **1**−**5** were reduced to the structurally labile TLDQ units, which liberated from the dendrimers as lactone **6** under apparent zero-order kinetics. The reductive lactonization process occurred regardless of the solvent system used and was complete in under 30 min ($k_{obs} = (4-7) \times 10^{-6}$ M s^{-1}, $t_{1/2} < 15$ min). Similar observations were recorded when the removal of TLQ from the dendrimers was effected by electrochemical means. Bulk electrolysis of **1**−**5** at an overpotential of −0.3 V relative to the E_{pc} of TLQ^{2-} followed by protonation with H_2O generated the TLHQ intermediates, which were released from the dendrimers in a similar manner as in the chemically induced case. In both the chemically and electrochemically induced routes for the removal of the TLQ end groups, precipitation/adsorption effects associated with the drastic change of dendrimer polarities and oxidation states were not observed.

Experimental Section

Materials. All reagents, including generations 1−5 of amine-terminated PPI dendrimers (PPI-*x*-NH$_2$, x = 4, 8, 16, 32, and 64), were purchased from Sigma Aldrich (Milwaukee, WI). NHS-activated quinone was prepared as previously reported.[10] ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer. MALDI-TOF mass spectra were obtained from an Applied Biosystems QStar XL QTOF mass spectrometer using dithranol as matrix.

Standard Procedure for the Synthesis of Dendrimers 1−5. The respective generation of PPI-*x*-NH$_2$ (0.100 mmol of end group −NH$_2$) oil was stripped with dry toluene (2 × 25 mL) in a 50 mL round-bottom flask to remove traces of H_2O. Dry CH_2Cl_2 (25 mL) was charged into the round-bottom flask to dissolve PPI-*x*-NH$_2$. The reaction mixture was cooled to 0 °C before the NHS-activated quinone[10] (0.105 mmol) was added. The reaction vessel was covered with aluminum foil, allowed to warm to room temperature, and left overnight for the reaction to proceed to completion. Note: reaction workup must be performed with minimal exposure to light (in darkness if possible) because dendrimers **1**−**5** are sensitive to ambient light. The crude mixture was diluted with CH_2Cl_2 (25 mL) and extracted with 5% $NaHCO_3$ (2 × 50 mL). The organic layer was dried with Na_2SO_4 and concentrated under vacuum, and the desired TLQ-terminated dendrimer was precipitated out of solution by the slow addition of hexanes. The light yellow solid was redissolved in CH_2Cl_2, and the precipitation process was repeated two more times using the same hexanes/CH_2Cl_2 combination. The yellow solid was filtered and dried under vacuum to produce the title dendrimers. **1**: yield = 86%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (s, 28 H), 1.55 (m, 8H), 1.95 (s, 12 H), 1.97 (s, 12 H), 2.13 (s, 12 H), 2.32 (m, 4 H), 2.36 (t, 8 H), 2.78 (s, 8 H), 3.18 (m, 8 H), 6.5H (t, 4H). MS calculated for M$^+$: 1245.7; found (MALDI): 1245.8. **2**: yield = 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (s, 52 H), 1.51 (m, 8 H), 1.60 (m, 16 H), 1.95 (s, 24 H), 1.97 (s, 24 H), 2.12 (s, 24 H), 2.35 (m, 36 H), 2.77 (s, 16 H), 3.15 (m, 16 H), 6.67 (t, 8 H). MS calculated for M$^+$: 2631.6; found (MALDI): 2632.6. **3**: yield = 80%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.39 (s, 100 H), 1.52 (m, 56 H), 1.94 (s, 48 H), 1.96 (s, 48 H), 2.11 (s, 48 H), 2.34 (m, 84 H), 2.77 (s, 32 H), 3.14 (m, 32 H), 6.82 (bs, 16 H). MS calculated for M$^+$: 5403.4; found (MALDI): 5406.9. **4**: yield = 92%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 196 H), 1.52 (m, 120 H), 1.94 (s, 96 H), 1.96 (s, 96 H), 2.11 (s, 96 H), 2.33 (m, 180 H), 2.77 (s, 64 H), 3.13 (m, 64 H), 7.00 (bs, 32 H). MS calculated for M$^+$: 10947; found (MALDI): 10949. **5**: yield = 83%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (s, 388 H), 1.51 (m, 248 H), 1.93 (s, 192 H), 1.95 (s, 192 H), 2.10 (s, 192 H), 2.32 (m, 372 H), 2.76 (s, 128 H), 3.11 (m, 128 H), 7.19 (bs, 64 H). MS calculated for M$^+$: 22034; found (MALDI): 22041. ^{1}H NMR and MALDI-TOF mass spectra for **1**−**5** are shown in Figures S1 and S2, respectively.

Translational Diffusion and Hydrodynamic Radii Measurements. Translational diffusion measurements were performed on a Bruker DPX 400 spectrometer equipped with a pulsed gradient unit capable of producing *z*-gradients of up to 0.51 T m^{-1}, which was calibrated by using the self-diffusion coefficient of HDO in D_2O.[28] Pulse sequence for the standard Stejskal−Tanner/PGSE experiment was used.[29] Dendrimer solutions in DMSO-d_6 containing millimolar amounts of TLQ end groups ((3−5) × 10^{-3} M) were used in all measurements. Seventeen data points ranging from $G = 0$ to 0.32 T m^{-1} were sampled at 25 °C using $\Delta = 55$ ms and $\delta = 5$ ms. Natural logarithmic plots of the relative ^{1}H echo intensities at various G values ($\ln(I/I_0)$ vs G^2) yielded a linear correlation from which the diffusion coefficient (D) values were extracted using the Stejskal−Tanner equation, $\ln(I/I_0) = -\gamma_H{}^2\delta^2G^2(\Delta - \delta/3)D$,[29] where I and I_0 are echo intensities at $G > 0$ and $G = 0$, respectively, γ_H is the gyromagnetic ratio of ^{1}H (2.675 × 10^8 T^{-1} s^{-1}), G is the gradient amplitude, Δ is the delay between *z*-gradient pulses, and δ is the rectangular gradient pulse length. Trial measurements for independently prepared dendrimer solutions yielded D values that were generally within 10% of the values listed in Table 1. Hydrodynamic radii (r_H) values were extracted from the D values using the Stokes−Einstein relation $D = kT/6\pi\eta r_H$, where k is the Boltzmann constant, T the temperature, and η the solvent viscosity (for DMSO, $\eta = 2.0$ cP at 25 °C).

Voltammetry of Dendrimers. Cyclic voltammograms of dendrimers **1**−**5** (end group [TLQ] = 1.0 × 10^{-3} M) in DMSO containing 0.1 M *n*-Bu$_4$PF$_6$ as supporting electrolyte and trace amounts of ferrocene (Fc) as internal reference were recorded on a Princeton Applied Research EG&G 273A potentiostat (Princeton, NJ) using a traditional three-electrode cell configuration. Glassy carbon ($d = 3$ mm, CH Instruments, Austin, TX), Ag/AgCl (CH Instruments), and Pt wire (99.9%, $d = 0.5$ mm, Refining Systems, Las Vegas, NV) were used as working, reference, and counter electrodes, respectively. The dendrimer solutions were kept in the dark at all times and were deoxygenated by bubbling a stream of N_2 prior to the voltammetric measurements.

Reduction of Dendrimers. (A) Chemical Reduction. Protocol for the chemical reduction of the dendrimers by $Na_2S_2O_4$ in DMSO-d_6/D_2O (85:15, v/v) is described elsewhere.[8] A similar methodology was employed for the reduction of the dendrimers in THF-d_8/D_2O (74:26, v/v). The results in Figure 3 required 4−5 equiv of $Na_2S_2O_4$ per TLQ end group. The resonance intensities of the geminal dimethyl groups of lactone **6** (THF-d_8/D_2O) shown in Figure 3 were monitored with time.

(B) Electrochemical Reduction. For the electrolysis experiments, a reticulated vitreous carbon ($A \sim 410$ cm^2, Bioanalytical Systems, West Lafayette, IN) was used as the working electrode, a homemade Pt coil (99.9%, $d = 0.5$ mm, Refining Systems) that was isolated in a fritted compartment was used as the counter electrode, and a standard Ag/AgCl (CH Instruments) reference was used. A DMSO solution (70 mL) containing one of the title dendrimers (5 mg of dendrimer, ∼1.5 × 10^{-5} mol of TLQ end groups) and KPF_6 supporting electrolyte (300 mg, 1.6 × 10^{-3} mol) was electrolyzed at −2.15 V vs Fc/Fc$^+$ until the residual current reached 3% of the initial value, which typically lasted for at least 2 h. In the entire course of the electrolysis experiment, convection was achieved by continuously purging the solution with N_2, while the cell was completely isolated from ambient light. Following electrolysis, triply distilled/deionized H_2O (12 mL) was immediately added to the cell, and the resulting DMSO−H_2O solution was continuously purged with N_2 for 30 min. (Note: after the addition of H_2O to the cell, which instantly protonates TLQ^{2-} to the light-stable TLHQ, the DMSO−H_2O solution can now be safely exposed to ambient light.) The solution was separated into two portions. The first portion was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic fractions were reextracted with H_2O (25 mL), dried with Na_2SO_4, and concentrated in a vacuum to produce an oil. ^{1}H NMR analysis (Figure 4) suggests that the oily consistency of the electrolysis product is due to residual DMSO. The second portion was evaporated under vacuum to produce a white (precipitated KPF_6) and oily suspension, which was further stripped with H_2O (20 mL). The final oily suspension was partitioned between $CDCl_3$ and D_2O (1:1 v/v, 2 mL) to reduce the amount of unremoved/

excess DMSO and KPF_6 suspension in $CDCl_3$, which otherwise interferes with the ^1H NMR analysis of lactone **6**. The $CDCl_3$ layer was separated from D_2O and was eluted through a plug of Na_2SO_4. The ^1H resonances of interests in the $CDCl_3$ layer (Figure S3B) are identical to those of the spectra shown in Figure 4. The ^1H NMR spectrum of the D_2O layer shows only a peak corresponding to DMSO and an unassigned resonance at δ 2.99 ppm. From control electrolysis experiments, this unassigned resonance was shown to arise from the DMSO/KPF_6 media (Figure S3C).

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Supporting Information Available: ^1H NMR and MALDI-TOF mass spectra of **1**−**5** and ^1H NMR data for the electrolysis products of **5**, **1**, and the control DMSO/0.1 M KPF_6 medium. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Electrolysis experiments in H_2O/THF (26:74, v/v) and H_2O/DMSO (15:85, v/v) media were also conducted for dendrimer **1**, which cleanly released lactone **6.** The ^1H NMR spectrum for this sample is practically identical to those shown in Figure 4.

(25) Coulometric analysis of the electrolysis yielded n values (>3−5) that were larger than expected for the two-electron reduction (i.e., $n = 2$) of a quinone unit. This observation is most likely due to the unstable i_p levels of the TLQ$^{\bullet -} \rightarrow$ TLQ^{2-} reduction (see Figure 2A).

(26) Additional evidence for the quantitative conversion is stated in ref 21, wherein the conversion efficiency of TLDQ to lactone **6** was practically quantitative.

(27) The structural integrity of PPI-*x*-NH_2 after electrolysis cannot be verified. The ^1H NMR resonances associated with the PPI-*x*-NH_2 dendrimer byproducts were not observed in the CH_2Cl_2 extract of the electrolysis product. It is expected that the highly ionic nature of the electrochemical experiments (100-fold excess KPF_6 per TLQ unit) produced polycationic PPI-*x*-$NH_2 \cdot K^+$ complexes that are insoluble in CH_2Cl_2. In addition, the high K^+-to-PPI-*x*-NH_2 ratio prevented the analysis of the postelectrolyzed aqueous solution by mass spectrometry. Together with the high salt content, the low absolute [PPI-*x*-NH_2] (end group [NH_2] before extraction by $H_2O < 2 \times 10^{-4}$ M) and the high residual DMSO content of the leftover H_2O mixture, analysis of the byproducts by ^1H NMR spectroscopy was inappropriate. However, it is reasonable to assume that the electron-rich structure of PPI-*x*-NH_2 is not expected to undergo reductive degradation at the cathodic potentials employed in the electrolysis experiments.

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