Synthesis of Poly(amidoamine) Dendrimer with Redox-Active Spacers

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Dendrimers, well-defined hyperbranched polymers, consist of a central core, radiated branches ending in multivalent terminal groups, and internal cavities within the branched structure, arousing great interest in the past two decades due to their unique chemical and physical performances toward various applications.[1] Synthesis of dendrimers usually involves a series of repetitive steps via either divergent or convergent pathway, on which the exploration of versatile dendritic structures with special core, interior, and exterior functionalities is achieved.[2] For the divergent process, either 1 → 2 or 1 → 3 branching motifs are iteratively introduced to a multiple functional core, and more layers of the branching units lead to a higher generation of dendrimer.

Among the dendrimers prepared by this manner, PPI and PAMAM dendrimers (denoting poly(propylenimine) and poly(amidoamine), respectively) are two noteworthy examples based on 1 → 2 *N*-branched structure, achieved by a Michael reaction of terminal multiple amines and α,β-unsaturated carbonyl monomers, i.e., acrylonitrile for PPI and methyl acrylate for PAMAM dendrimer. Then the amino end groups are regenerated for the cascade construction of PPI and PAMAM dendrimers through a catalytic hydrogenation of the multiple nitrile terminals and an amidation of multiple methyl ester terminals with diamines, respectively.[3] By using the facile synthetic protocols, both PPI and PAMAM dendrons could be easily conducted to numerous functional core molecules to demonstrate a site isolation effect.[4] In addition, the multivalent characteristics of PPI and PAMAM dendrimers toward target substrates could be carried out by covalently modifying the surface amino or carboxyl groups into versatile specific functional molecules.[5]

The interior building blocks for both PPI and PAMAM dendrimers are composed of the alkylamine as the spacer and tertiary amine as the branch juncture. Therefore, one special feature of PPI and PAMAM dendrimers is the interior affinity toward small organic molecule through hydrophobic interaction, based on the less polar spacer of alkylamine.[6] For example, water-insoluble organic compounds, e.g., pyrene and polycyclic aromatic hydrocarbons, can be effectively encapsulated inside the interior cavities of PPI and PAMAM dendrimers.[5,7] Moreover, because of the cationic characteristic of the tertiary amino branching sites (pK_a = 6.1 and 6.65, respectively) in water,[8] anionic organic dyes and surfactants also can be trapped by the microcavities via electrostatic association.[9]

It is noted that PPI dendrimers have a shorter repetitive spacer as propyleneimine (−$CH_2CH_2CH_2N$⟨), whereas the spacer of PAMAM dendrimer could be more extended due to the amidation process, in which diamine with longer alkyl spacer is allowed to react with methyl ester terminals to yield an amidoamine group.[10] Furthermore, from the synthetic consideration, the amidation process also provides a quite convenient route to create the tailor-made spacer functionality only by the incorporation of diamine to be versatile functional spacer. However, compared to the exploration of internally modified poly(benzyl ether) dendrimer derivatives,[11] the case regarding either post- or premodified interior of aliphatic dendrimers such as PPI and PAMAM dendrimers is limited. Jayaraman and coworkers[12] demonstrated a four-step iterative protocol on which alkyl ether is embedded as the internal linkage for the formation of poly(propyl ether imine) dendrimer. Another example involving 1,2-propanediamine as the spacer for the construction of internally branched PAMAM dendrimer was recently reported by Pittelkow and Christensen.[13] However, a tedious protection/deprotection procedure was usually involved in the consecutive synthesis of the internally modified dendrimer.

In the present study, spacer-modified PAMAM dendrimer with internal isopropanol (IPA) groups was synthesized straightforwardly without fancy protection/deprotection procedure (Supporting Information). As shown in Scheme 1, 1,3-diamino-2-propanol, a known AB_2 building block for the synthesis of carbamate dendrimer,[14] was directly utilized as the core molecule and the building block for each amidation process on the synthesis of PAMAM dendrimer analogue without preprotection of the secondary alcohol moieties, based on a simple principle that amine selectively reacts with terminal methyl ester at ordinary reaction temperature than hydroxyl group does. Moreover, the internal IPA group was capable of the postmodification through various chemical reactions, and either chemical or electrochemical oxidation of these internal secondary alcohol to corresponding ketone functionality was also demonstrated.

In our strategy, the IPA groups were directly embedded as the spacer component of PAMAM dendrimer during the amidation process. As shown in Scheme 1, 1,3-diamino-2-propanol instead of alkyldiamine was allowed to react with methyl acrylate to give model compound **1** in a quantitative yield, serving as a precursor for the cascade construction of spacer-modified dendrimers **2** and **3** with methyl ester surface groups in 70% and 42% yield, respectively. On the basis of a simple fact that amine could selectively react with those methyl ester groups to form an amide linkage through transamidation,

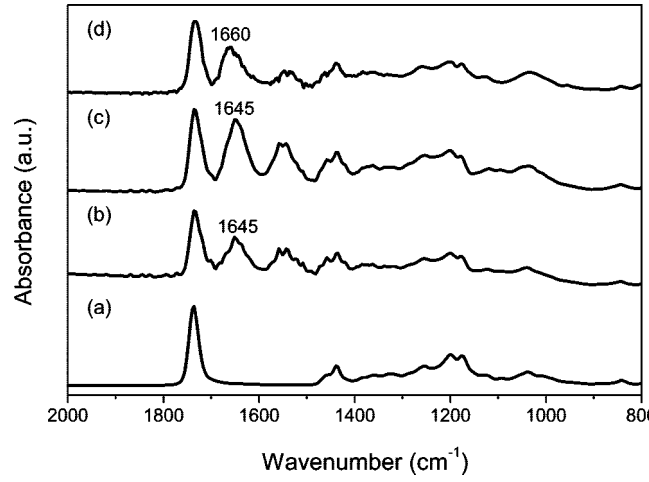

Figure 1. FT-IR spectra of (a) alcohol **1**, (b) dendrimer **2**, (c) dendrimer **3**, and (d) dendrimer **5**.

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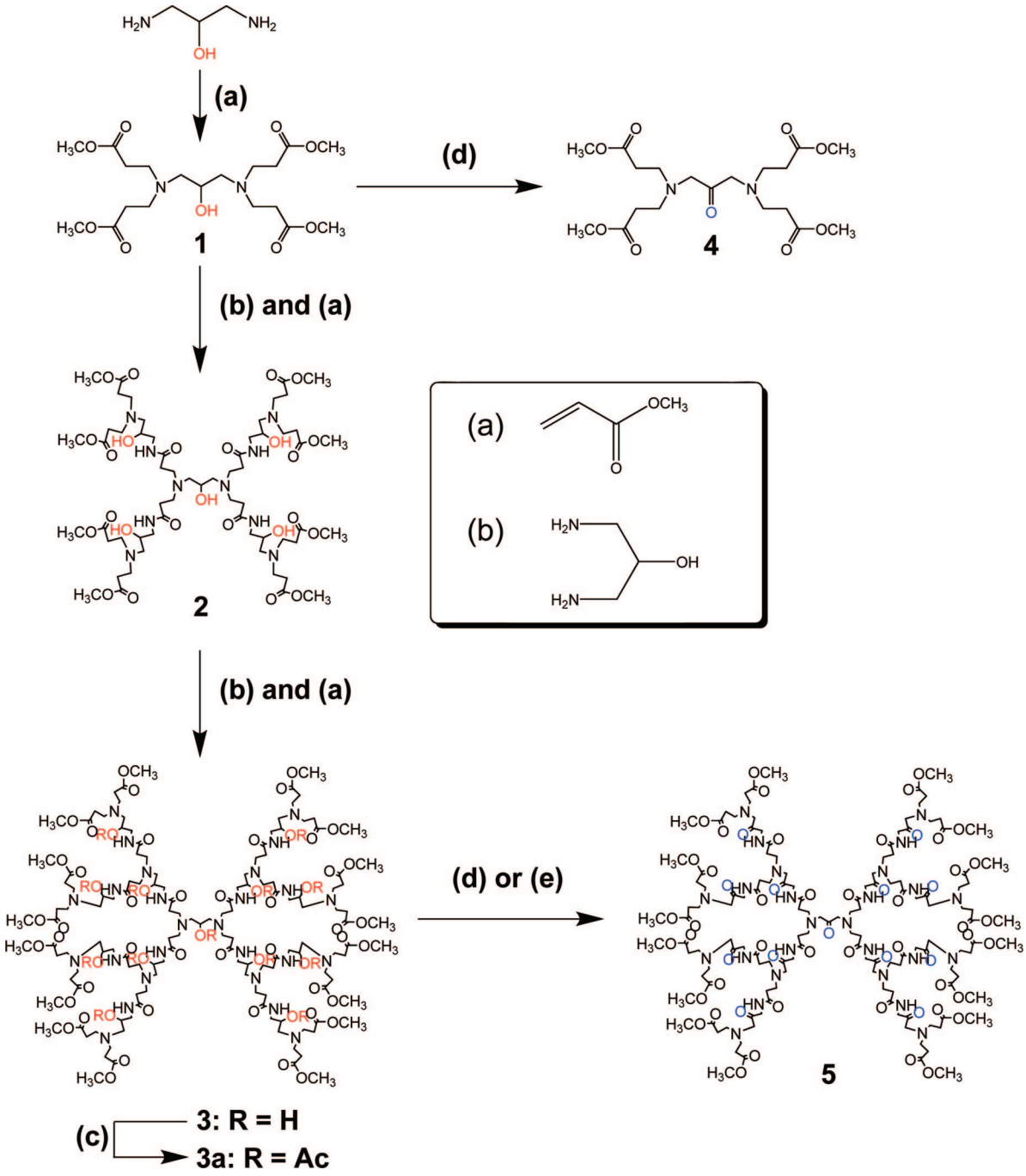
Scheme 1. Divergent Synthesis of Spacer-Modified PAMAM Dendrimer[a]



[a] Reagents and conditions: (a) methyl acrylate, MeOH, 2 days, rt; (b) 1,3-diamino-2-propanol, MeOH, 7 days, rt; (c) acetic anhydride, Et_3N, CH_2Cl_2, overnight, rt; (d) DMSO, oxalyl chloride, CH_2Cl_2, 2 h, −78 °C; (e) Pt-catalyzed electrochemical oxidation.

the preprotection of the secondary hydroxyl group during the synthesis was evitable.

The chemical structures of the embedded IPA group on dendrimer **2** and **3** were confirmed by NMR analyses (Figures S1 and S2). The appearance of $\delta = 3.81$ ppm on the ^{1}H NMR spectra corresponds to the "−C*H*OH−" proton resonance on the secondary alcohol moiety, and the methylene protons adjacent to the amide linkage show the diastereotropic signals at 3.09 and 3.45 ppm due to the insertion of additional hydroxyl group in the spacer. Moreover, ^{13}C NMR spectra also distinctly show $\delta = 67.6$ and 58.0 ppm, corresponding to the "−*C*HOH−" and "−CHOH*C*H_2N⟨" carbon resonances, respectively. These results all suggest successful construction of spacer-modified PAMAM dendrimers until the second and half-generation, in which IPA groups are embedded as the spacer component.

Except the vibration mode of terminal ester groups at 1735 cm^{-1} just like compound **1** (Figure 1a), FT-IR analyses of dendrimers **2** and **3** (Figure 1b,c) show the characteristic vibration modes of amides I and II at 1645 and 1550 cm^{-1}, respectively, confirming the amide linkage of the spacer-modified PAMAM dendrimer. Moreover, the fact that decreasing in the relative intensity of ester to amide follows the propagation of dendrimer supports that the ratio of terminal methyl ester group to internal amide decreases from dendrimer **2** (2/1) to **3** (4/3). Therefore, the result supports a consecutive growth of spacer-modified PAMAM dendrimer.

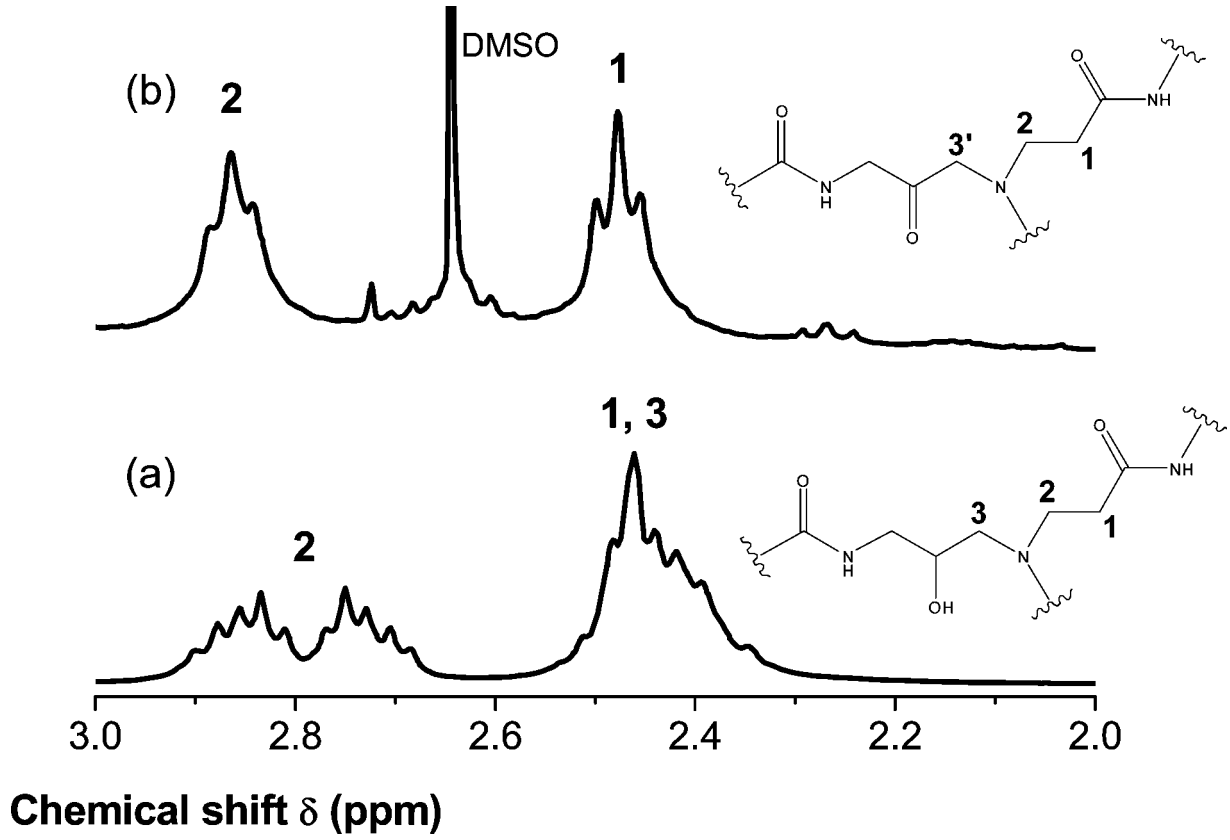


Figure 2. ^{1}H NMR spectra for 10 mg/cm^3 $CDCl_3$ solutions of (a) dendrimer **3** and (b) dendrimer **5** at 25 °C. A DMSO signal is the trace of the solvent for carrying out the Swern oxidation, being trapped in the internal void of dendrimers.

To double-check the existence of the internal hydroxyl groups on spacer-modified dendrimer, a simple examination by acetylation of those hydroxyl groups was carried out by coupling the spacer-modified dendrimer with acetic anhydride under basic promotion (process c in Scheme 1). NMR spectra of internally acetylated dendrimer **3a** clearly show the characteristic proton and carbon resonances of methyl group at 1.89 and 20.7 ppm, respectively. In addition, the proton and carbon resonances of "−CHOH−" group on the IPA spacer shift downfield from 3.81 and 67.6 ppm to 4.75 and 70.6 ppm, respectively, because of the electron-withdrawing capacity of the acetyl group. The spectroscopic data not only confirm the internal secondary hydroxyl groups but also demonstrate the postesterification ability of these interior functional groups.

A clean and facile chemical reaction, named Swern oxidation, was introduced to examine the oxidation ability of the internal IPA groups on spacer-modified dendrimers. An active reagent of dimethylchlorosulfonium chloride, prepared by a mixing of dimethyl sulfoxide and oxalyl chloride at low temperature, is able to oxidize the secondary alcohol, giving the desired ketone. A model reaction shown in process d of Scheme 1 was carried out by in situ reaction of thus-prepared active reagent and alcohol **1** to give ketone **4** with quantitative yield. The successful oxidation reaction is directly confirmed by ^{13}C NMR spectra. Appearance of distinct carbon resonance at 208.3 ppm corresponds to the formation of desired ketone, chemically oxidized from the IPA moiety, leading to the result that methylene carbon resonance adjacent to the central carbonyl group also shifts downfield from 58.7 to 60.9 ppm due to electron-withdrawing effect of the carbonyl group. On the basis of this successful model reaction, the chemical oxidation of the internal IPA moieties on dendrimer **3** was also executed in the same manner to give the oxidized dendrimer **5**, in which the multiple ketone groups are embedded as the alternative internal functionality (process d in Scheme 1), except the hydroxyl and acetyl groups.

^{13}C NMR spectra clearly confirmed the effective oxidation of the internal IPA moieties on spacer-modified dendrimer based on the appearance of carbonyl resonance at 206.5 ppm and on the downfield shifts of the methylene carbon resonances adjacent to the central ketone from 43.4 and 58.0 ppm to 47.5 and 61.9 ppm, respectively (Figure S3). Moreover, the entire disappearance of the carbon resonance at 67.6 ppm indicates a complete transformation of functional groups from internal secondary alcohols into corresponding ketones. Although the formation of the ketone is unable to be monitored by FT-IR spectrum (Figure 1d), because of the spectroscopic overlap of internal carbonyl and terminal carboxyl stretching bands, it is noticeable that the characteristic amide I shifts from 1645 to 1660 cm^{-1}, being attributed to the conformational change of the spacer-modified dendrimer, owing to the oxidation of the IPA moiety to ketone and the succeeding variation of interaction among hydrogen bonding sites (e.g., amide, *sec*-alcohol/ketone, and ester).

In addition, comparing the ^{1}H NMR spectra of dendrimers **3** and **5** (before and after oxidation), it is noticed that a multiplet splitting pattern of the CH_2 protons adjacent to the tertiary amino-branching site (Figure 2, $\delta \sim 2.8$ ppm) converts to a simplified triplet one after oxidation. The result indicates that the spin−spin coupling of these internal CH_2 protons with neighboring nucleus is more complicated in the case of spacer-modified dendrimer **3** than oxidized dendrimer **5**, obviously suggesting that the conformation of spacer-modified dendrimers before and after oxidation is not necessarily the same because the internal IPA groups on each spacer moiety may provide different hydrogen-bonding sites from internal ketone groups.

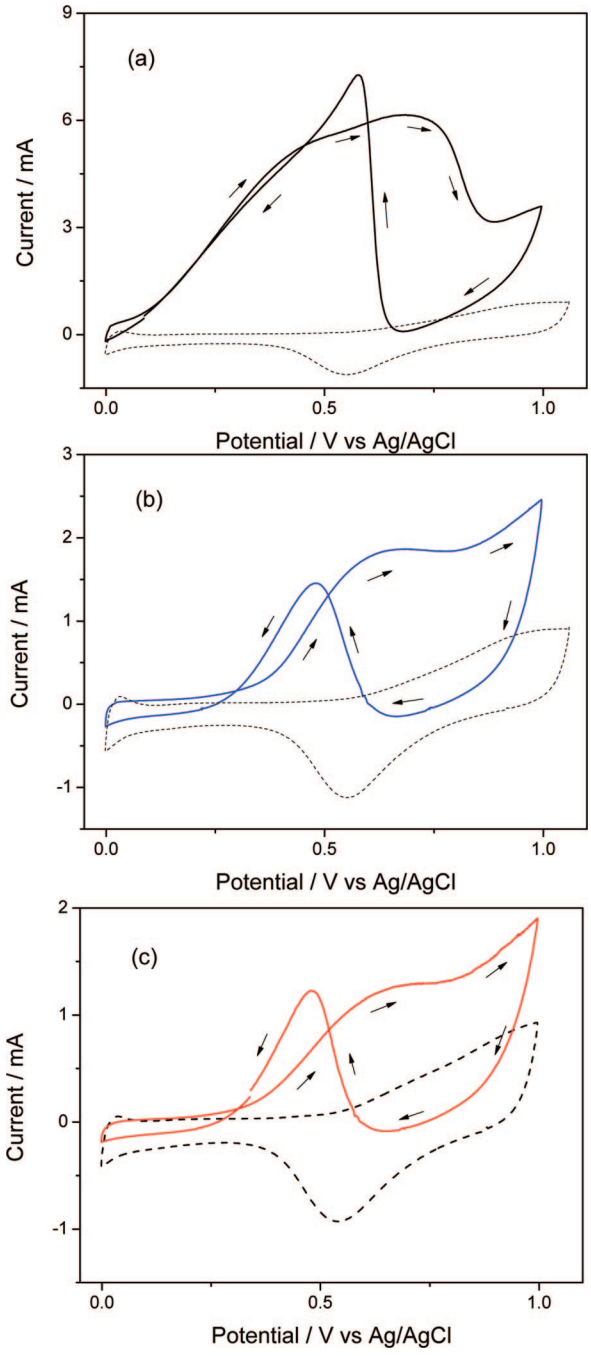


Figure 3. Cyclic voltammograms of (a) 50 mM isopropanol, (b) 4.6 mM alcohol **1**, and (c) 2.5 mM dendrimer **3**. Electrolytes: 0.1 M $HClO_4$ (---); scan rate: 10 mV s^{-1}.

It is known because of nanosized structure that dendrimer conformation responds to either the stimuli from surroundings (solvent, pH, ionic strength, and temperature) or the dynamics of multivalent surface groups to give a tightly packed or an extended conformation.[15] Within this consideration, the spacer modification of PAMAM dendrimer also provides a noticeable strategy for the preparation of dendrimers with different conformations because additional internal spacer functionality, such as an IPA group beyond the amide and tertiary amine, could result in a remarkable conformational change presumably due to more hydrogen-bonding sites.[16]

Since the formation of acetone through oxidation of IPA involves a dehydrogenation process, alternatively metal-catalyzed electrochemical oxidation of spacer-modified dendrimer was also examined (process e in Scheme 1). The *n*th generation of spacer-modified dendrimer internally contains $2^{n+2}-3$ IPA groups. Therefore, it is expected that electrochemical treatment of a single dendrimer could generate abundant hydrogen molecules because metal-catalyzed oxidation process may lead to the loss of two protons on each IPA moiety accompanied by the formation of ketone-containing spacer.

Figure 3a exhibits a typical cyclic voltammogram of IPA molecules, which was obtained on a working electrode deposited electrochemically by platinum (Pt). The electro-oxidation of IPA was characterized by two anodic peaks on the forward and reverse scans. On the forward scan, the peak is attributed to the oxidation of freshly chemisorbed species coming from adsorption of alcohol. The reverse scan peak is primarily associated with removal of carbonaceous species, which is not completely oxidized in the forward scan.[17]

Meanwhile, Figure 3b,c demonstrates cyclic voltammograms of alcohol **1** and dendrimer **3**, showing a similar redox behavior with the oxidation of IPA; two distinct anodic peaks were clearly observed in the forward (>0.65 V) and reverse scans (~0.48 V). The result implies the oxidation of the internal IPA moieties because PAMAM dendrimer is regarded as a redox-nonactive species, unless dendrimers are premodified with redox-active probes predominantly functionalized from the terminal groups of dendrimer.[18] In the case of the spacer-modified dendrimer, 1,3-diamino-2-propanol with a central IPA group was simply embedded through amidation process and served not only as the linking spacer but also as the internal redox probe under the promotion of Pt catalyst.

In summary, we have demonstrated a newly synthetic route for the preparation of internally modified PAMAM dendrimers. The functional diamines were synthetically embedded as the linking spacer through the amidation process on the divergent construction of dendrimer. NMR analyses supported the covalent incorporation of multiple IPA moieties inside the dendrimer by the appearance of carbon and proton signals on the secondary alcohol, and postacetylation was also successfully carried out to confirm the existence of these internal hydroxyl functionalities. Moreover, based on the oxidation capability of IPA into corresponding ketone through dehydrogenation process, spacer-modified dendrimer successfully demonstrated a redox-active property by either chemical or electrochemical oxidation method. Potentially, one spacer-modified PAMAM dendrimer molecule can be regarded not only as the "fuel carrier", containing multiple IPA molecules, but also as the "hydrogen donor" for further applications such as fuel cells and biosensors. These concerning topics are now under investigation.

Supporting Information Available: Experimental details, NMR spectra for the synthesis of spacer-modified PAMAM dendrimers, and XPS and SEM characterizations for Pt foil and electrodeposited Pt film. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Bosa, U.; Christensen, J. B.; Heegaard, P. M. H. *Dendrimers in Medicine and Biotechnology*; RSC Publishing: Cambridge, 2006. (b) Vögtle, F.; Richardt, G.; Werner, N. *Dendrimer Chemistry: Concepts, Syntheses, Properties, Applications*; Wiley-VCH: New York, 2009.
(2) (a) Inoue, K. *Prog. Polym. Sci.* **2000**, *25*, 453. (b) Moorefield, C. N.; Newkome, G. R. *C. R. Chim.* **2003**, *6*, 715.
(3) Newkome, G. R.; Shreiner, C. D. *Polymer* **2008**, *49*, 1.
(4) Tomalia, D. A. *Prog. Polym. Sci.* **2005**, *30*, 294.
(5) Imae, T.; Funayama, K.; Nakanishi, Y.; Yoshii, K. *Encycl. Nanosci. Nanotechnol.* **2004**, *3*, 685.

(6) (a) Richter-Egger, D. L.; Landry, J. C.; Tesfai, A.; Tucker, S. A. *J. Phys. Chem. A* **2001**, *105*, 6826. (b) Richter-Egger, D. L.; Tesfai, A.; Tucker, S. A. *Anal. Chem.* **2001**, *73*, 5743.
(7) (a) Arkas, M.; Tsiourvas, D.; Paleos, C. M. *Chem. Mater.* **2003**, *15*, 2844. (b) Arkas, M.; Eleades, L.; Paleos, C. M.; Tsiourvas, D. *J. Appl. Polym. Sci.* **2005**, *97*, 2299. (c) Arkas, M.; Tsiourvas, D.; Paleos, C. M. *Chem. Mater.* **2005**, *17*, 3439.
(8) (a) Kabanov, V. A.; Zezin, A. B.; Rogacheva, V. B.; Gulyaeva, Z. G.; Zansochova, M. F.; Joosten, J. G. H.; Brackman, J. *Macromolecules* **1998**, *31*, 5142. (b) Leisner, D.; Imae, T. *J. Phys. Chem. B* **2003**, *107*, 13158.
(9) (a) Cooper, A. I.; Londono, J. D.; Wignall, G.; McClain, J. B.; Samulski, E. T.; Lin, J. S.; Dobrynin, A.; Rubinstein, M.; Burke, A. L. C.; Fréchet, J. M. J.; DeSimone, J. M. *Nature (London)* **1997**, *389*, 368. (b) Maurice, W. P. L. B.; Froehling, P. E.; Meijer, E. W. *Chem. Commun.* **1997**, 1959. (c) Nakanishi, Y.; Imae, T. *J. Colloid Interface Sci.* **2005**, *285*, 158. (d) Nakanishi, Y.; Imae, T. *J. Colloid Interface Sci.* **2006**, *297*, 122. (e) Chu, C. C.; Ueno, N.; Imae, T. *Chem. Mater.* **2008**, *20*, 2669.
(10) (a) Yemul, O.; Ujihara, M.; Imae, T. *Trans. Mater. Res. Soc. Jpn.* **2004**, *29*, 165. (b) Ujihara, M.; Mitamura, K.; Torikai, N.; Imae, T. *Langmuir* **2006**, *22*, 3656.
(11) Hecht, S. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1047.
(12) (a) Krichna, T. R.; Jayaraman, N. *J. Org. Chem.* **2003**, *68*, 9694. (b) Jayamurugan, G.; Umesh, C. P.; Jayaraman, N. *Org. Lett.* **2008**, *10*, 9.
(13) Pittelkow, M.; Christensen, J. B. *Org. Lett.* **2005**, *7*, 1295.
(14) Lee, J.-K.; Suh, Y.-W.; Kung, M.-C.; Downing, C. M.; Kung, H. H. *Tetrahedron Lett.* **2007**, *48*, 4919.
(15) (a) Murat, M.; Grest, G. S. *Macromolecules* **1996**, *29*, 1278. (b) Imae, T.; Funayama, K.; Aoi, K.; Tsutsumiuchi, K.; Okada, M.; Furusaka, M. *Langmuir* **1999**, *15*, 4076. (c) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (d) Ramzi, A.; Scherrenberg, R.; Joosten, J.; Lemstra, P.; Mortensen, K. *Macromolecules* **2002**, *35*, 827. (e) Lee, I.; Athey, B. D.; Wetzel, A. W.; Mexiner, W.; Baker, J. R. *Macromolecules* **2002**, *35*, 4510.
(16) (a) Huang, B.; Parquette, J. R. *Org. Lett.* **2000**, *2*, 239. (b) Huang, B.; Parquette, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 2689.
(17) (a) Manoharan, R.; Goodenough, J. B. *J. Mater. Chem.* **1992**, *2*, 875. (b) Pastor, E.; González, S.; Arvia, A. *J. Electroanal. Chem.* **1995**, *395*, 233. (c) Huang, J.; Liu, Z.; He, C.; Gan, L. M. *J. Phys. Chem. B* **2005**, *109*, 16644. (d) Ye, J.; Liu, J.; Xu, C.; Jiang, S. P.; Tong, Y. *Electrochem. Commun.* **2007**, *9*, 2760.
(18) (a) Goldsmith, J. I.; Takada, K.; Abruña, H. D. *J. Phys. Chem. B* **2002**, *106*, 8504. (b) Cooke, G.; Sindelar, V.; Rotello, V. M. *Chem. Commun.* **2003**, 752. (c) Ong, W.; McCarley, R. L. *Chem. Commun.* **2005**, 4699. (d) Nijhuis, C. A.; Yu, F.; Knoll, W.; Huskens, J.; Reinhoudt, D. N. *Langmuir* **2005**, *21*, 7866. (e) Berduque, A.; Scanlon, M. D.; Collins, C. J.; Arrigan, D. W. M. *Langmuir* **2007**, *23*, 7356.

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