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Incorporation of Conductive Internal Additives within Electrocurable Adhesives

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Aryl diazirine-grafted polyamidoamine (Dz-g-PAMAM) was recently investigated as an adhesive cured with low voltage potentials, leading to a concept of electrocuring adhesive. Ferrocene is a well-known redox active compound with a high degree of electron reversibility. Ferrocene is incorporated into the electrocuring adhesive as a conductive internal additive, attempting to improve the electron transfer efficiency. In this work, the synthesis of co-grafted Dz-g-Fc-g-PAMAM is confirmed by NMR and UV/Visible absorbance compares the optical properties with and without the ferrocene internal additive.

Introduction

Bioadhesives attempt to immobilize natural or synthetic materials through chemical fixation or molecular interlocking mechanisms (1-6). Bioadhesives are required to immobilize biomaterials, drug delivery depots, and other medical implants (7-17). In order to overcome current problems associated with today's commercial bioadhesives, new adhesive chemistries are required. Diazirine (Dz) moiety is a carbene precursor that has been observed to crosslink with high efficiencies (18, 19) and it is also an electro-active species (20, 21). Polyamidoamine (PAMAM) is a class of water-soluble and biocompatible dendrimers made of repetitively branched subunits of amide and amine functionality (22, 23). Due to the precise control of size, shape and placement of functional group, this dendrimer has led to applications such as drug delivery depots (24). The fifth generation PAMAM dendrimer (G5-PAMAM) was selected to be conjugated with an aryl-diazirine to develop an electrocuring adhesive (1). It can be activated on-demand to crosslink under low voltage (~ 2 V) in aqueous solutions. However, crosslinking efficiency remain low and further improvements are required in order to be comparable to it photocuring variants (1, 4).

To further improve the emerging electrocuring adhesive towards crosslinking efficiency and adhesive lap strength, we are attempting to modify the adhesive by incorporating conductive internal additive. Ferrocene (Fc) is a robust and versatile building block and a well-known redox-responsive compound with reversible one-electron redox behavior (25), furthermore, it allows the electron transfer occurs via electron hopping (26, 27). It is often incorporated in polymers, polymer brushes, and dendrimers to improve electron transduction (28-30). Herein, we selected Fc as conductive internal additive to modify the current electrocuring adhesive, expecting to promote the electrocuring material properties by improving its electron transfer efficiency.

Results and Discussion

Materials and Equipments

G5-PAMAM dendrimer (5th generation, 128 surface amine functional groups) was supplied by Dendritech, USA, stored in 0.5% w/v methonal. 3-[4-(bromomethyl)phenyl]-3-(trifluoromethyl)-diazirine (aryl-diazirine) was supplied by TCI, Tokyo. Chlorocarbonyl ferrocene was supplied by PICHEMICALS, China. Methonal (MeOH, anhydrous), and triethylamine (Et₃N) were obtained from Sigma, Singapore. Chloroform (CHCl₃), hexane, were obtained from TEDI, Singapore. Deuterated dimethyl sulfoxide (DMSO-d₆) used for nuclear magnetic resonance (NMR) was purchased from Merck, Singapore. NMR spectrum were recorded by Bruker Advance at 400 MHz, MestReNova software was applied for peak assignment and peak integration. Ultraviolet-Visible Spectroscopy (UV/Vis) were conducted by SHIMADZU UV-Vis Spectrometer UV-2700.

Design and Synthesis of The Cografted Conjugations

The conductive internal additive, Fc moiety, was first attached to the G5-PAMAM with the fixed 15% conjugation percentages, followed by attaching the carbene precursor, i.e., Dz moiety with a series of conjugation percentages ranging from 7% to 30% (**Figure 1**). The reaction stoichiometry is shown in **Table 1** with the feeding ratio of starting materials and predicted conjugation percentage indicated.

The general synthesis procedures are described as follow and displayed in **Figure 1**: vacuum-dried G5-PAMAM dendrimer was dissolved into anhydrous MeOH in 5% w/v. With the flow of N₂ gas, chlorocarbonyl ferrocene was dissolved in anhydrous MeOH in 5% w/v and added into G5-PAMAM dendrimer solution dropwise. Triethylamine was added into the reaction mixture as base. This whole reaction lasted for overnight and was protected under inert nitrogen gas. Crude product was obtained by precipitating in CHCl₃/Hexane (1 : 4 in v/v), yielding dark brown viscous gel. This Fc-containing G5-PAMAM (referred as “Fc-g-PAMAM” further in text) was dissolved in anhydrous MeOH in 5% w/v again for further grafting of Dz moiety. Aryl-diazirine was diluted by anhydrous MeOH and added into the Fc-g-PAMAM solution. This reaction lasted 12 h and crude product as obtained by precipitating in CHCl₃/Hexane (1 : 4 in v/v) mixed solvent, Dz-containing Fc-g-PAMAM (referred as “Dz-g-Fc-g-PAMAM” further in text) as dark brown solid was obtained. After drying under vacuum for overnight, all products were ready to basic characterizations.

Conjugation Percentages Estimated by NMR Analysis

Fc-g-PAMAM and Dz-g-Fc-g-PAMAM conjugates were analyzed with ¹H NMR spectroscopy and the results were compared to all the starting materials, including free Dz moiety, Fc moiety, and pure PAMAM. Diazirine-containing G5-PAMAM (referred as “Dz-g-PAMAM” further in text) was measured as reference. See **Figure 2**.

Five groups of protons in PAMAM dendrimer have been detected, and these peaks were assigned from **a** to **e**, according to the previous literature (4, 31, 32). After the conjugation,

whether the primary amine is substituted or not, peak **a** always shifts to same position ($\delta = 2.21 \pm 0.03$ ppm). Hence peak **a** was set as polymer standard. In Fc-g-PAMAM conjugates, Fc moiety shows a pair of peaks (g_1 and g_2) at $\delta = 4.61$ and 4.32 ppm, and a singlet peak (g_3) at $\delta = 4.16$ ppm, indicating the protons from cyclopentadiene (Cp) rings of Fc. In Dz-g-PAMAM conjugates, Dz moiety shows a pair of peaks (f_1 and f_2) at $\delta = 7.44$ and 7.19 ppm, indicating the protons from aromatic rings of Dz. Comparing with the starting material aryl-diazirine, the aromatic proton signals (f_1 and f_2) became broader and two split peaks merged together, suggesting appearance of a new chemical environment in the complex macromolecular system (4).

According to the previous assignments (4, 32), we are able to calculate the conjugation percentages for Fc and Dz moieties by integrating the aromatic proton peaks (f_1 and f_2) and the Cp proton peaks (g_1 , g_2 , and g_3). The calculation process is presented by a representative sample, 15%Dz-g-15%Fc-g-PAMAM (Table 2).

The terminal amine group has two reaction sites for nucleophilic substitution (can react either with bromo or acyl group or both), hence it is possible to form bi-substitution on single terminal amine group. Heteronuclear multiple quantum coherence (HMQC) 2D NMR spectrum analysis were applied to investigate the tertiary amine formation (4), and we have found in some cases, an extra pair of f_1 and f_2 peaks at $\delta = 7.62$ and 7.28 ppm (data not shown). This observation indicates that Dz moiety may form bi-substitution which may due to the fast addition of aryl diazirine to Fc-g-PAMAM reaction solution. To better control the substitution, we controlled the addition dropwise and tried to dilute the aryl diazirine starting material. However, due to the relatively large steric hindrance for Fc group (as spheres with a diameter of $6.6\text{\AA}$ (33)), it has less chance to form bi-substitution than Dz group (as planar structure), hence we did not observe the bi-substitution for Fc moiety. This is also the reason that we designed to attach the more bulky moiety first. In the chemical structure of PAMAM side chain shown in Figure 2, only the mono-substitution for both moiety on single peripheral is presented as example.

UV/Vis Measurements for Cografted Conjugates

Figure 3 displays the UV/Visible absorbance for cografted conjugates. All samples were dissolved in methanol with the concentration of 0.2 mM for UV/Visible measurements. The absorbance (ABS) spectra of PAMAM was measured as control (ABS peak at $\lambda = 280\text{ nm}$), the UV ABS spectra for three cografted conjugates were shown in main panel with the ABS peak assignment indicated accordingly. The UV ABS spectrum of 15%Fc-g-PAMAM is presented in inset panel, with all characteristic ABS peaks of Fc are assigned (34, 35): $\lambda = 348\text{ nm}$ and 440 nm present the symmetry forbidden transition from Fe ($a1g$) to Fe ($e1g$); $\lambda = 302\text{ nm}$ presents the charge transfer from Fe ($a1g$) to Cp ($e1g$); $\lambda = 263\text{ nm}$ could be the charge transfer from Fe ($e2g$) to Cp ($e1g$), or the shifted ABS peak of PAMAM, or just the combination of both. Since the UV extinction coefficient value for Dz moiety ($1009\text{ ml cm}^{-1}\text{ g}^{-1}$ at 360 nm) was larger than Fc moiety ($443\text{ ml cm}^{-1}\text{ g}^{-1}$ at 360 nm and $235\text{ ml cm}^{-1}\text{ g}^{-1}$ at 440 nm , which were measured separately), the ABS peak for Fc moiety was shielded by ABS peak for Dz moiety, therefore we can only observe a combined absorbance peak at 360 nm for Dz containing-15%Fc-g-PAMAM conjugates.

TABLE 1. Synthesis Recipe for a Series of Cografted PAMAM Conjugates.

Polyaddition Recipe for a Series of Conjugated PAMAM Conjugates:			
Targets	Feeding Ratios (in mol)		Predicted Conjugation Percentage
15%Fc-PAMAM	Internal Additive Attachment		
	Surface Group (%)	Fc (%)	
	100	18	15%
7%Dz-g-15%Fc-PAMAM	Carbene Precursor Attachment		
	Surface Group (%)	Dz (%)	
	100	10	7%
15%Dz-g-15%Fc-PAMAM		20	15%
30%Dz-g-15%Fc-PAMAM		35	30%

(A) Internal additive attachment **(B) Carbene precursor attachment**

Figure 1. Schematic illustration of the synthesis for cografted Dz-g-Fc-g-PAMAM conjugations. (A) Synthesis route of grafting Fc internal additive to G5-PAMAM. (B) Synthesis route of grafting Dz carbene precursor to Fc-g-PAMAM. Remarks: only one of each moiety is presented to simplify the structure, while in reality, there are more functional groups clustering but the distribution of each moiety is unknown.

(A) Dz-g-Fc-g-G5-PAMAM side chain structure **(B) Stacked NMR traces**

Figure 2. (A) Chain structure of Dz and Fc moieties attached G5-PAMAM dendrimer (only mono-substitution for both moieties on single peripheral is presented as example). (B) Stacked NMR traces for all starting materials and synthesized conjugates.

TABLE 2. Calculation Process of Conjugation Percentages for Sample 15%Dz-g-15%Fc-g-PAMAM by ^1H NMR Method.

Peak	Refer to	Integral (<i>I</i>)	Corresponding Proton Number	Calculated Conjugations
a	total -NH ₂	$I_a = 100$	508	---
$f_1 + f_2$	substitution of Dz	$I_f = 17.2$	4	17.1%
$g_1 + g_2 + g_3$	Substitution of Fc	$I_g = 44.5$	9	19.6%

Figure 3. UV absorbance spectra of PAMAM (black dot line, as control), 7% Dz-g-15%Fc-g-PAMAM (red solid line), 15%Dz-g-15%Fc-g-PAMAM (blue solid line) and 30%Dz-g-15%Fc-g-PAMAM (green solid line). Inset: UV absorbance spectra of 15%Fc-g-PAMAM as reference.

Conclusions

The current electrocuring adhesive, i.e., aryl diazirine grafted PAMAM conjugates with both redox-active conductive moiety Fc and carbene precursor moiety Dz was synthesized and investigated. NMR and UV/Vis measurements of the synthesized conjugates were conducted, and we successfully applied the NMR results to calculate the conjugate percentage for each moiety. The potential application for incorporation the Fc moiety as the conductive internal additives to electrocuring adhesive is about to improve its electron transfer efficiency via the electron hopping feature of Fc moiety.

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