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Butylamide-terminated poly(amidoamine) dendritic gelators

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ABSTRACT

Butylamide-terminated poly(amidoamine) dendrons with either a Boc group (**C-n** (**n** = 1, 2, 3)) or a carboxyl group (**E-n** (**n** = 1, 2)) at the focal point, as a new kind of dendritic gelators, were synthesized and their gelation properties were studied by TEM, WAXD, SAXS, NMR,and FTIR spectroscopy. It was found that the structure of focal groups impacted greatly on their gelation ability and the dendrons with higher generations facilitated the gel phase assembly. Hydrogen-bonding and hydrophobic interactions were proved to be the main driving forces responsible for the fibrous assembly with the diameter in the range of 30–100 nm. The molecular packing pattern of the xerogels of **C-2**, **C-3**, **E-1,** and **E-2** all showed a lamellar structure, which was revealed by WAXD and SAXS.

During the past two decades, dendritic gelators, as a novel kind of organogelators, have been developed into an active field. They have advantages of tunable structures, multiple peripheral functional groups, repeating branches, and favorable encapsulation characteristic. Since Newkome et al.[1] opened the research field of dendritic gelators in 1986, Aida,[2] Smith,[3] Majoral,[4] Kim,[5] Grinstaff,[6] and Stupp[7] groups have separately reported different kinds of dendritic gelators that could gel water or various organic solvents. Notably, the dendritic gelators with amide-bonded branches exhibited excellent gelation properties. For example, Smith et al.[3] have systematically investigated one-component and two-component dendritic gels from lysine-based peptide dendrimers. They claimed that the intermolecular and/or intramolecular hydrogen-bonding interactions among amide groups played a key role in the gel phase assembly. Chow and Zhang[8] reported a library of α-amino acids-based layer-block dendrons (G1-G3) and found that the composition of amino acid, the nature of focal-point group, and the layer-block sequence had great effects on their gelation ability. Kim et al.[5a,b] synthesized a series of dendrons based on amide-bonded branches and modified them with focal carboxyl group and peripheral alkyl tails (laurylamide-terminated) or polymerizable diacetylene moieties. These dendrons could gel organic solvents, such as chloroform and tetrahydrofuran, with hydrogen-bonding interaction as the main driving force. In addition, depending on the generation of the dendritic molecules, the gels from the dendrons with peripheral polymerizable diacetylene units showed either lamellar or hexagonal columnar structures that could be stabilized by photo-polymerization.[5b] It was found that the focal carboxyl group and the peripheral alkyl tails were the key factors responsible for the gel formation. The former constructed dimeric units as building blocks and the latter provided the aggregates with van der Waals interaction. More recently, Wang and co-workers[9] synthesized a series of amphiphilic diblock codendrimers consisting of PUA (poly(urethane amide)) and PMDC (poly(methallyl dichloride)) dendrons. These novel codendrimers could self-assemble into ribbon-like aggregates and further afforded gels in toluene, which was attributed to the high polarity and multiple molecular interactions, especially the hydrogen bonds between amide and hydroxyl groups. Although amide-bonded dendritic gelators have been reported by several groups, the poly(amidoamine) dendrons have not been involved so far.

Previously, we reported a series of natural amino acid-based dendritic gelators and found that the high generations of these dendrons facilitated the gel phase assembly in some organic solvents.[10–13] Herein, we reported the synthesis and gelation properties of butylamide-terminated poly(amidoamine) dendrons (from the first to third generation) with focal *t*-butyloxycarbonyl (Boc) (**C-n** (**n** = 1, 2, 3)) and carboxyl groups (**E-n** (**n** = 1, 2)). The gelation ability, morphology, molecular packing patterns of the gel phase assemblies, and the driving forces were investigated by the combined techniques of transmission electron microscopy (TEM), wide-angle X-ray diffraction (WAXD), small-angle X-ray scattering (SAXS), nuclear magnetic resonance (NMR), and Fourier transform infrared (FTIR) spectroscopy.

As shown in Scheme 1, butylamide-terminated dendrons **C-n** (**n** = 1, 2, 3) were synthesized by the coupling reaction of **B-n** with

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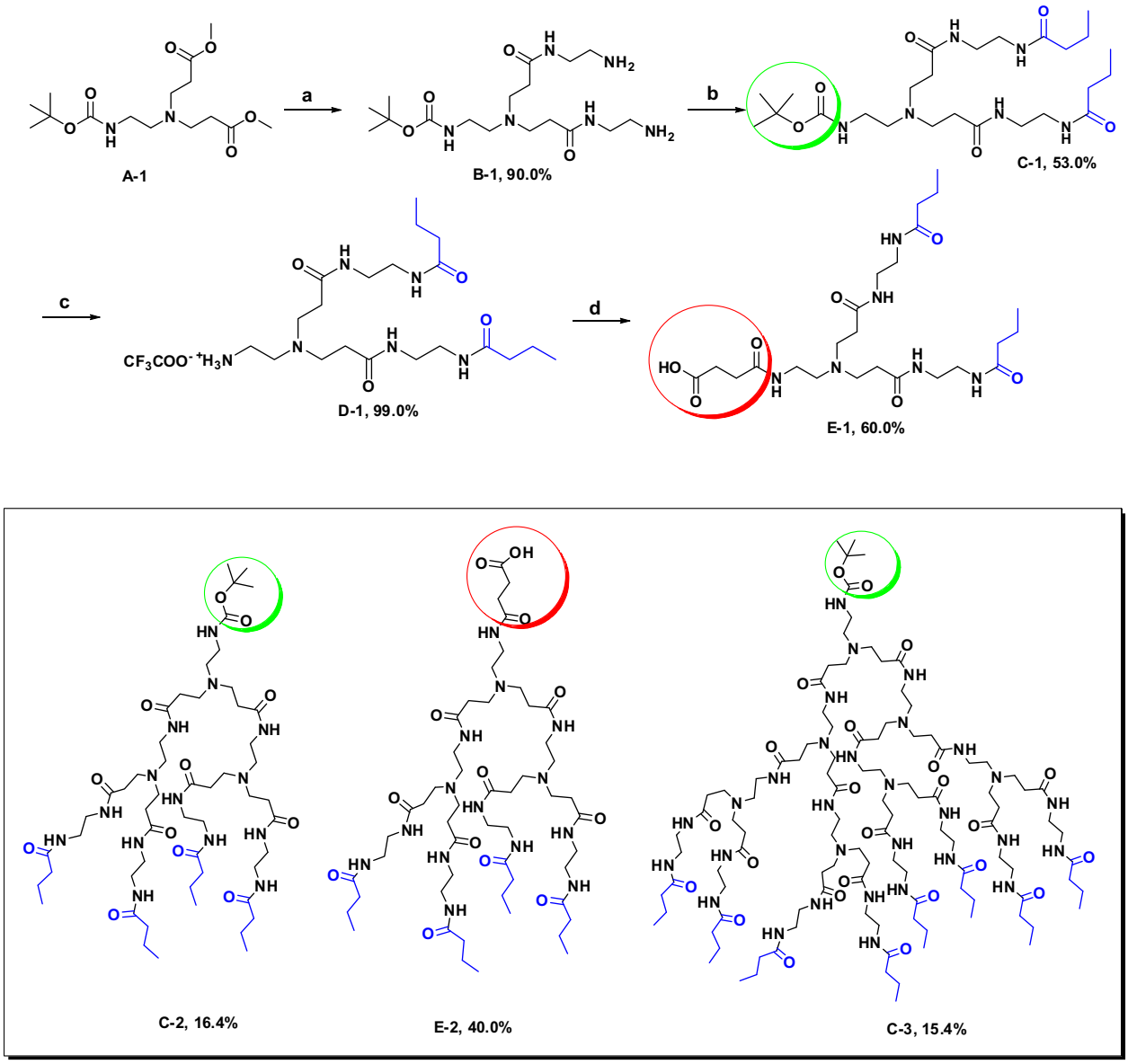


Scheme 1. Synthetic routes and structures of **C-n** and **E-n** (letters of **A**–**E** represent: **A**—dendrons with peripheral methyl ester group and focal Boc group; **B**—dendrons with peripheral amine group and focal Boc group; **C**—dendrons with peripheral butylamide group and focal Boc group; **D**—dendrons with peripheral butylamide group and focal $CF_3COO^-NH_3^+$ group; **E**—dendrons with peripheral butylamide group and focal carboxyl group. The suffix **n** denotes the generation of dendrons). Reagents and conditions: (a) excess ethylene diamine, methanol, 48 h; (b) butyric acid, DCC, $CHCl_3$, rt, 10 h; (c) CF_3COOH, $CHCl_3$, rt, 1 h; (d) succinic anhydride, Et_3N, 7 h, rt. rt = room temperature, DCC = dicyclohexylcarbodiimde.

excess butyric acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC). The yields of **C-1**, **C-2,** and **C-3** were 53.0%, 16.4%, and 15.4%, respectively. In addition, the focal carboxyl functionalized butylamide-terminated poly(amidoamine) dendrons (**E-n** (**n** = 1, 2)) were also prepared by removing the Boc group of **C-n** with trifluoroacetic acid (TFA), and subsequently via a ring-opening reaction with succinic anhydride. The chemical structures of **C-n** (**n** = 1, 2, 3) and **E-n** (**n** = 1, 2) were confirmed by ^{1}H NMR, ^{13}C NMR, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS and FTIR, while purity was identified by elemental analysis. Figure 1 shows the ^{1}H NMR spectra of **E-1** (Fig. 1a) and **C-1** (Fig. 1b). It can be seen that the proton signal of Boc group at 1.37 ppm disappears and the methylene protons corresponding to the focal succinic anhydride appear at 2.33–2.25 ppm as a carboxyl group replaces the Boc group. As the representatives, MALDI-TOF MS spectra of **C-2** and **E-2** are shown in Figure 2a and b, respectively. The results agreed with the proposed structures. The details of experimental procedures, synthesis, and characterization are described in Supplementary data.

The gelation behavior of **C-n** was studied in organic solvents and the results are shown in Table 1. The gelation ability showed generation dependence with the order of **C-3** > **C-2** > **C-1**. **C-1** did not gel in any tested solvents, while **C-3** displayed the lowest minimum gel concentration (MGC). For example, the MGC of **C-3** in chloroform was 3.6×10^{-3} mol/L. That means one **C-3** molecule could entrap about 3.4×10^3 chloroform molecules. This result is consistent with our previous study that the higher generation dendrons facilitate the gel phase assembly.[11,12] As reported by Smith and co-workers,[3d] the higher generation dendrons or dendrimers could accelerate the gel formation, which was attributed to positive dendritic effect. Structurally, **C-2** and **C-3** possess more branches with amide groups that can provide more sites to form hydrogen bonds, while more branches also enhance the hydrophobic and van der Waals force interactions. All of these non-covalent

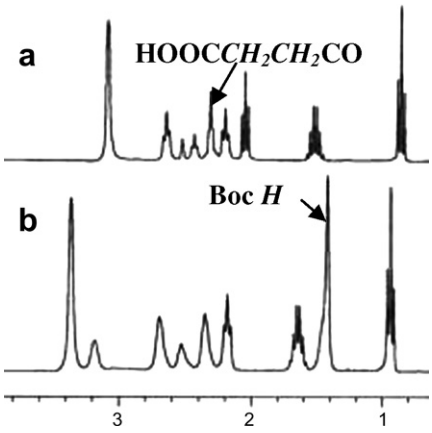


Figure 1. ^{1}H NMR spectra of (a) **E-1** and (b) **C-1** (DMSO-d_6 and $CDCl_3$ as solvents, respectively).

forces facilitate the gel phase assembly. To further access the gelation ability, the gel to sol transition temperature (T_{gel}) of **C-3** was determined under different concentrations and the result is shown in Figure 3. The T_{gel} value increased with increasing concentration of the gelator, and finally reached a plateau region with the concentration above 27 mg/mL, which was general for low molecular weight gelators.[14]

In addition, according to Kim's report,[5a,d] the amide-bonded dendrons without carboxyl units at the focal point could not self-assemble into fibrous network. However, **C-n** (**n** = 2, 3) dendrons with Boc group at the focal point could gel organic solvents, such as chloroform and acetone, indicating that the Boc group played an important role in the self-assembly due to enhancing the hydrophobic interaction. It is consistent with the result reported in our precious work.[12]

Interestingly, the gelation ability increased dramatically when a carboxyl group replaced the focal Boc group. For instance, **C-1** was unable to form gel in common solvents. In contrast, **E-1** formed gel in chloroform with the MGC of 2.1×10^{-2} mol/L. Moreover, the MGC of **E-2** decreased to 8.9×10^{-3} mol/L (the MGC of **C-2** was 2.2×10^{-2} mol/L), which clearly indicated that little change of focal structure had huge impact on the self-assembly behavior.

TEM images show that the dendrons with either a Boc or a carboxyl group at the focal point self-assemble into fibrous network structures (Fig. 4 and Fig. S-1). As the representatives, the morphologies of **C-2**, **3** xerogels are shown in Figure 4a and b, respectively. The diameter of single fiber was in the range of 30–100 nm, and

Table 1
Gelation behavior of **C-n** (**n** = 1, 2, 3) in various solvents at room temperature[a,b]

Dendrons	C-1	C-2	C-3
Cyclohexane	P	P	P
Benzene	P	CG (6.4)	P
Toluene	P	CG (6.4)	P
$CHCl_3$	S	TG (22.0)	CG (3.6)
CH_2Cl_2	S	OG (12.4)	TG (3.9)
Ethyl ether	P	P	P
THF	S	TG (9.8)	TG (6.0)
AcOEt	P	TG (11.6)	P
Acetone	P	OG (7.6)	OG (7.3)
Methanol	S	S	S
DMSO	S	S	S

[a] The value in parentheses is MGC, $\times 10^{-3}$ mol/L.
[b] S: solution; P: precipitation; OG: opaque gel; TG: translucent gel; CG: clear transparent gel.

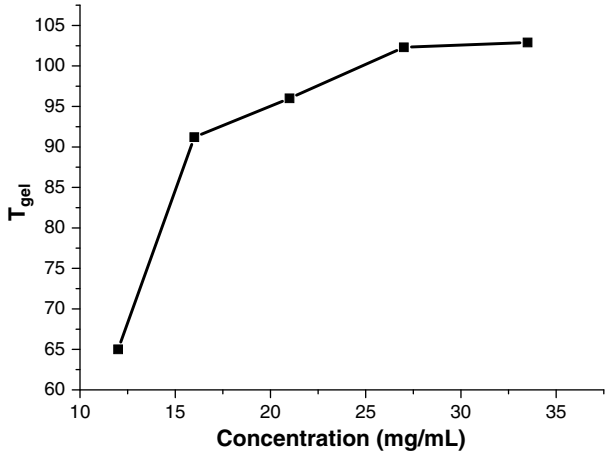


Figure 3. Concentration dependence of the gel to sol transition temperatures (T_{gel}) of **C-3**.

the fibers were inclined to tangle together and finally formed a network structure. This fibrous network morphology is coordinated with that of **G2** and **G3** Gly-Glu dendrons that we previously reported.[12]

In order to study the molecular packing pattern of the gel phase assemblies, WAXD and SAXS were performed on the xerogels. Figure 5 shows the WAXD patterns of **C-2** and **E-2** xerogels, respectively. It was found that the *d* values of the diffraction peaks of

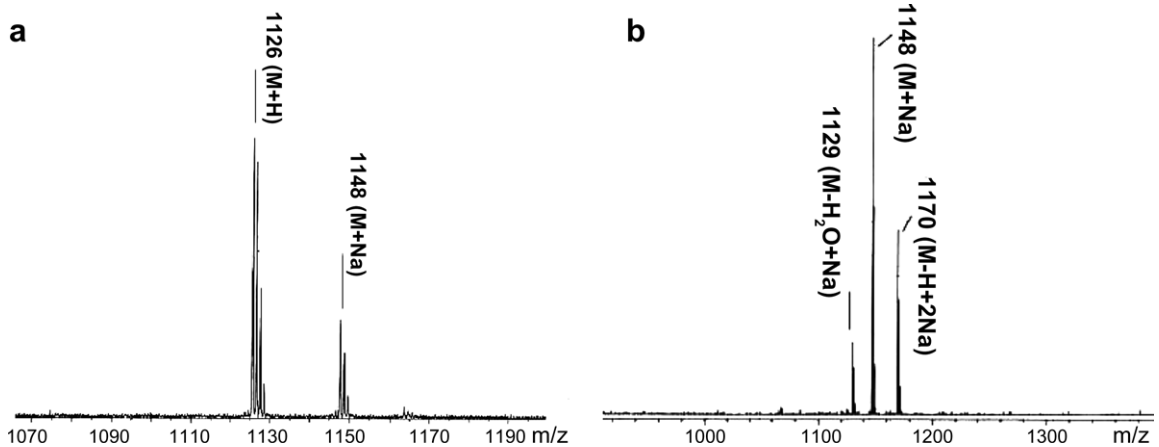


Figure 2. MALDI-TOF MS spectra of (a) **C-2** and (b) **E-2**.

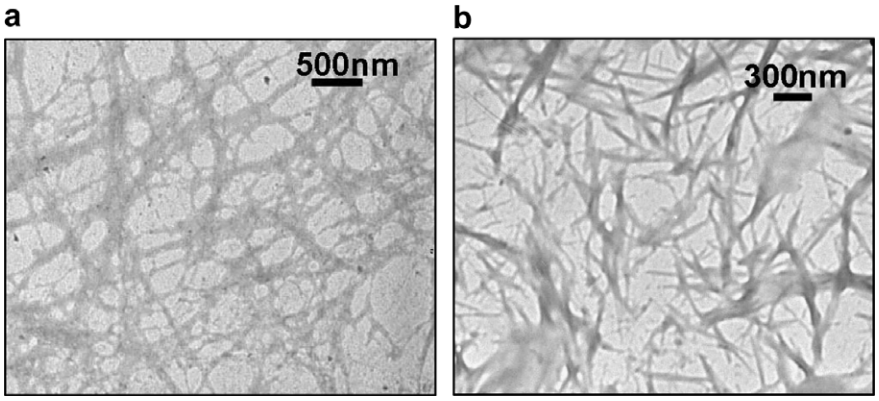


Figure 4. TEM images of xerogels prepared from (a) **C-2** in CH_2Cl_2; (b) **C-3** in $CHCl_3$.

WAXD patterns were in the ratio of 1:1/2:1/3:1/4, indicating that the xerogels of **C-2** and **E-2** self-assembled into a lamellar structure (Fig. 5). Same results were obtained from **C-3** and **E-1** (Fig. S-2). For example, the interlamellar spacing of **C-2** was calculated to be 4.90 nm (Fig. 5a). According to our preliminary computer modeling (MM2 method) of the **C-2** molecule, the size is estimated to be about 2.4 nm if the **C-2** molecule is in fully extended condition. Hence, we assumed that each lamella might consist of two layers of **C-2** molecules. Similar to **C-2**, other dendritic gelators reported herein also possessed a lamellar structure with dimeric species as building blocks. On the basis of the experimental data, we proposed a possible molecular packing model for the gel from **C-2** (Scheme 2). As shown in Scheme 2, two **C-2** molecules first form dimeric species that are the primary building blocks in the self-assembly. Then these dimeric species are arranged orderly to form a lamellar structure through hydrogen-bonding and hydrophobic interactions according to the WAXD result.

The main driving forces of gelation for these dendrons were hydrogen-bonding and hydrophobic interactions. The hydrogen-bonding interaction was proved by FTIR spectroscopy, and temperature- and concentration-dependent ^{1}H NMR spectra. Figure 6 shows the IR spectra of **C-2** in chloroform and the gel state of **C-2**. The characteristic bands of **C-2** in solution appeared at 3447 ($\nu_{N\text{-}H}$), 1649 (amide I, $\nu_{C=O}$) and 1526 cm^{-1} (amide II, $\delta_{N\text{-}H}$), while for **C-2** wet gel, these bands were shifted to 3299, 1644, and 1548 cm^{-1}, respectively. This indicated the presence of hydrogen-bonding interaction in the aggregates, which accorded well with the result reported by Kim and co-workers.[5a]

Variable-temperature ^{1}H NMR spectra were employed to further reveal the hydrogen-bonding interaction (Fig. 7). **C-2** was dissolved in $CDCl_3$ with the concentration of 25 mg/mL and self-assembled into fibrous network after sonification. ^{1}H NMR measurement was performed at 23, 30, 35, 40, 45, and 50 °C, respectively. In the ^{1}H NMR spectra, two broad peaks in the range of 7–9 ppm correspond to the protons of amide groups in the **C-2** molecule, except the sharp peak at 7.27 ppm that represents incompletely deuterium-replaced solvent $CDCl_3$. As Figure 7 shows, these two peaks shift to up-field with increasing temperature, indicating that hydrogen bonds among amide groups were weakened at high temperature and the hydrogen-bonding interaction plays an important role in the gel formation. The concentration-dependent ^{1}H NMR spectra of **C-2** were also provided to further prove the existence of hydrogen bonds (shown in Supplementary data as Fig. S-3.). The proton signals of amide groups at 7–9 ppm shifted to down-field when the concentration increased, which suggested that hydrogen bonds were strengthened at high concentration. Moreover, the gel from **C-2** could be easily destroyed by adding a drop of methanol, which also proved that hydrogen-bonding interaction was one of the main driving forces for gel phase assembly. In order to explore the contribution of hydrophobic interaction in gelation, **D-n** (**n** = 2, 3) (without Boc group at the focal point) were synthesized and their gelation behavior was investigated. It was observed that **D-n** (**n** = 2, 3) could not form gel in the tested solvents, indicating the important role of hydrophobic interaction in gelation.

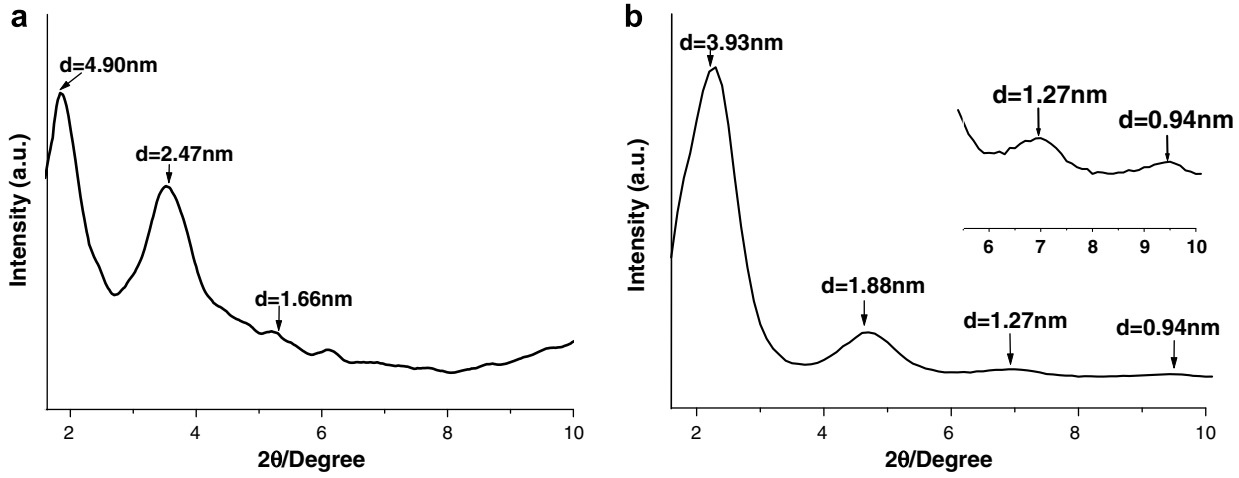
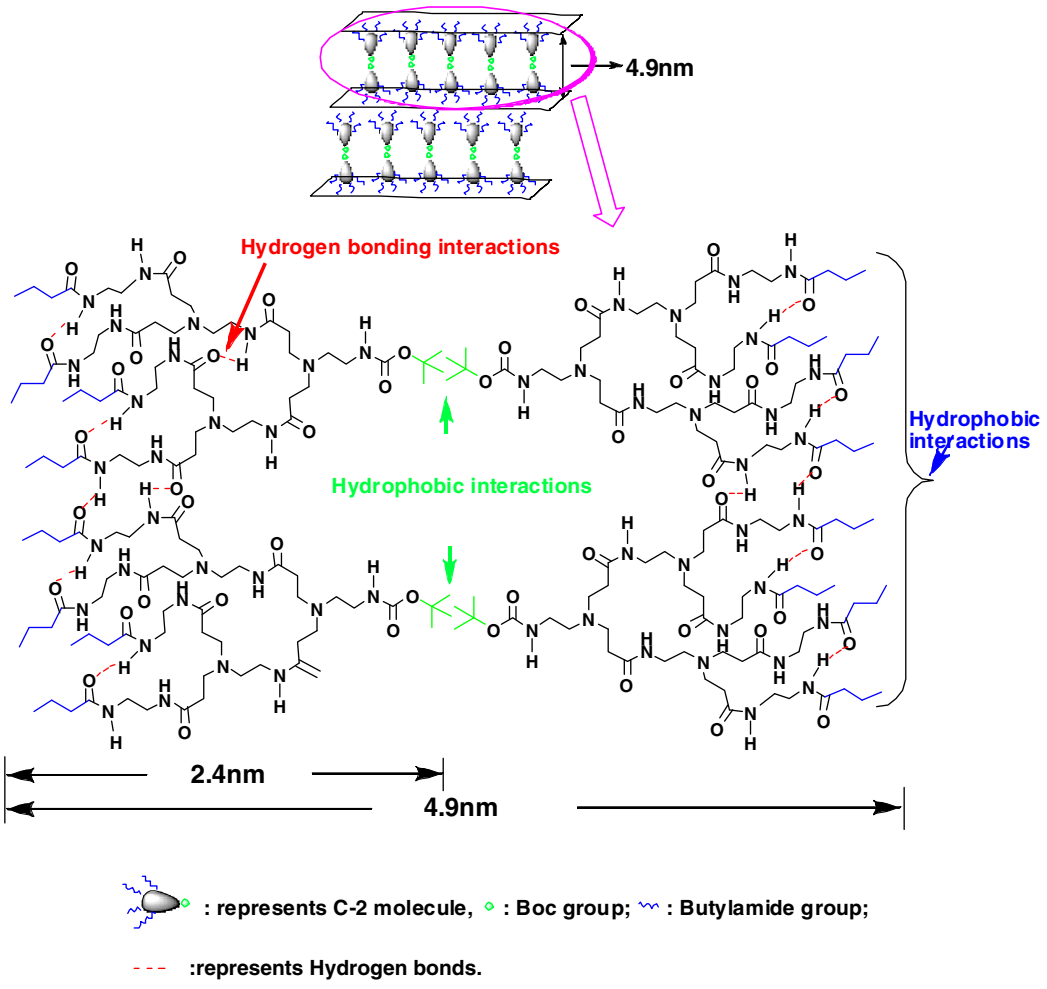


Figure 5. WAXD patterns of (a) **C-2** xerogel from $CHCl_3$; (b) **E-2** xerogel from $CHCl_3$ (inset: the enlarged photograph shows the third and fourth scattering peaks).



Scheme 2. A possible model of a lamellar structure for organogel from **C-2**.

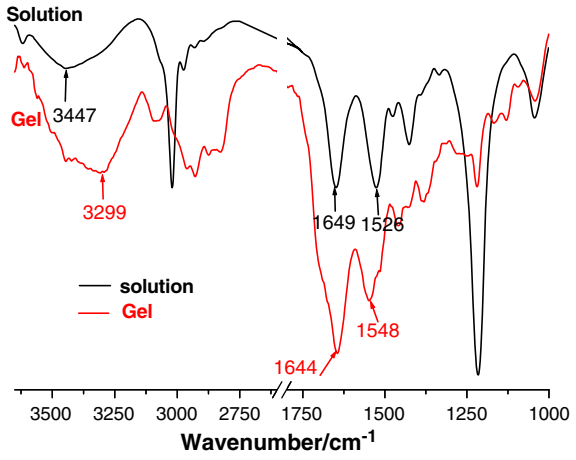


Figure 6. FTIR spectra of **C-2** solution (black line) and **C-2** gel from $CHCl_3$ (red line).

In summary, we synthesized a series of butylamide-terminated poly(amidoamine) dendrons with Boc (**C-n** (**n** = 1, 2, 3)) and carboxyl groups (**E-n** (**n** = 1, 2)) at the focal point and studied their gelation properties. The gelation ability of these dendrons increased with increasing generation due to the positive dendritic effect. For instance, **C-1** cannot gel any tested solvents, and **C-3** is more efficient than **C-2** in gelling organic solvents. It is believed

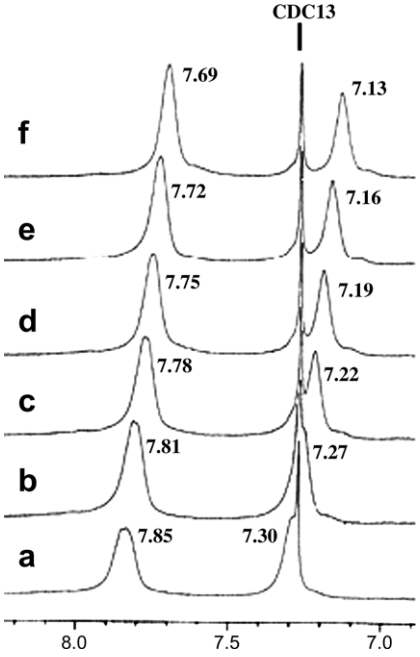


Figure 7. Variable-temperature ^1H NMR spectra of gel formed by **C-2** in $CDCl_3$ with concentration of 25 mg/mL measured at (a) 23; (b) 30; (c) 35; (d) 40; (e) 45; (f) 50 °C.

that hydrogen-bonding and hydrophobic interactions are the main driving forces responsible for the gelation. WAXD and SAXS measurements revealed that **C-2**, **C-3**, **E-1,** and **E-2** all self-organized into a lamellar structure. These modified poly(amidoamine) dendrons, as a new kind of dendritic gelators, not only provide a new strategy for design of supramolecular functional materials, but also have potential applications in the fields of drug delivery, cosmetics, food, and building nanostructured materials.

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Supplementary data

Details of experimental procedures, synthesis, and characterization of the dendrons **C-n** (**n** = 1, 2, 3) and **E-n** (**n** = 1, 2), TEM image of **E-1** xerogel, SAXS pattern of **C-3** xerogel, and the concentration-dependent ^{1}H NMR spectra of **C-2**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.008.

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