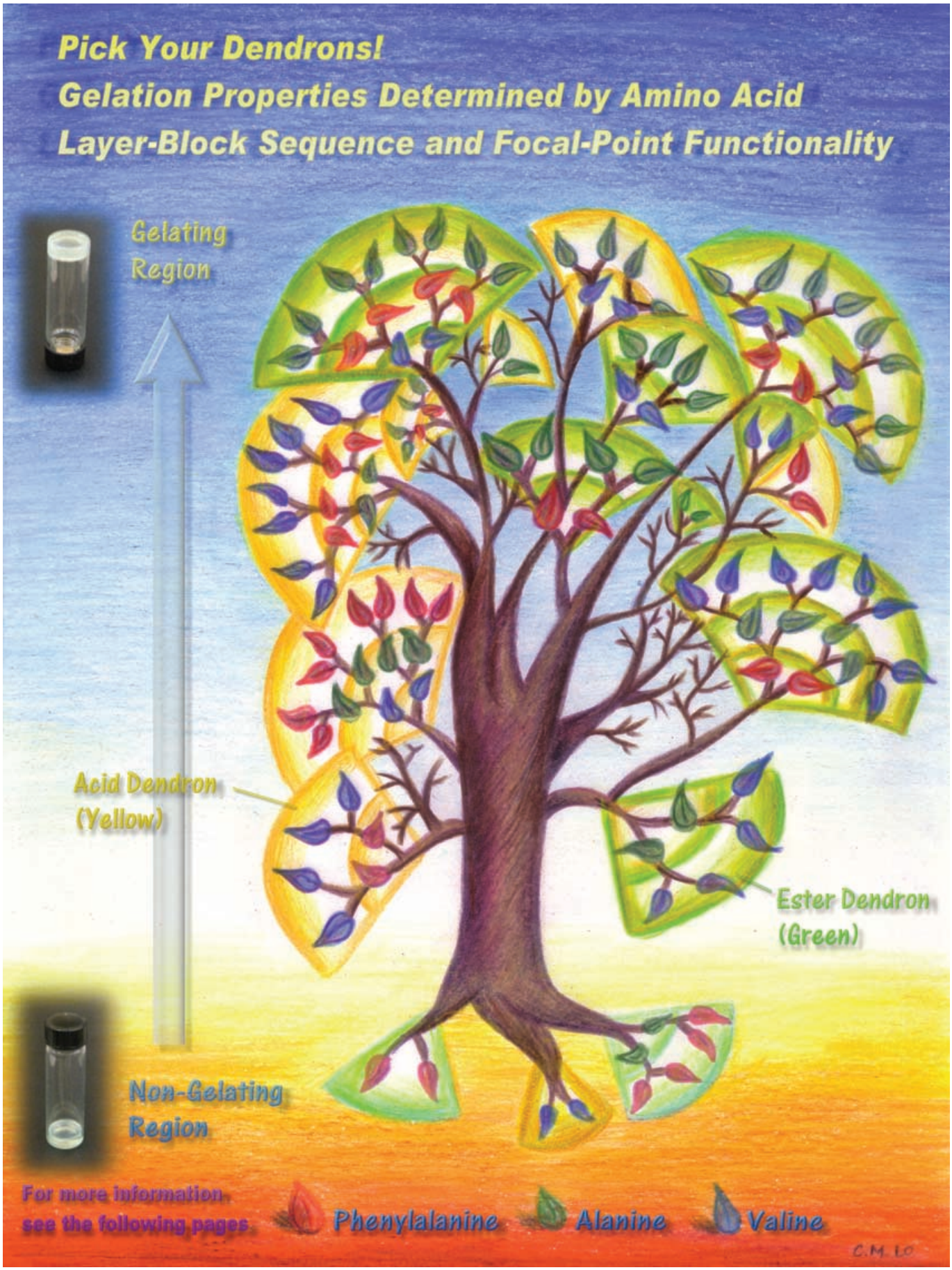

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Structural Diversity of α-Amino Acid Based Layer-Block Dendrons and Their Layer-Block Sequence-Dependent Gelation Properties

Hak-Fun Chow* and Jie Zhang[a]

Abstract: A library of G1–G3 α-amino acid based layer-block dendrons **1–6** containing different amino acid residues in the different concentric layers was prepared by solution-phase peptide synthesis. The structures of these dendrons were characterized by ^{1}H and ^{13}C NMR spectroscopy and, except for the G3 series of compounds, by mass spectrometry. The purities of these compounds were also determined by size-exclusion chromatography. Owing to the presence of a large number of amide groups, these dendrons exhibit unusually strong self-aggregating properties in both polar and nonpolar solvents. Some of these dendrons are found to be extremely good organogelators towards aromatic solvents with minimum gel concentrations approaching 4 mg mL^{-1}. Their gelation ability is found to be highly dependent on the nature of the amino acid compositions, the amino acid layer-block sequence within the dendritic architecture and the nature of the focal-point functionality. IR spectroscopic analysis indicates that gelation is induced by intermolecular hydrogen bonds. Circular dichroism studies suggest the formation of hierarchical chiral structures in the gel state, although the existence of chiral morphologies could not be observed by scanning electron microscopy.

Keywords: aggregation · amino acids · dendrimers · gels · protein models

Introduction

There has been an increasing interest in the use of natural α-amino acids as components in the construction of peptide-based[1,2] or amino acid based dendrimers[3] owing to their structural resemblance to proteins and enzymes. Such dendrimers are also potentially useful molecules in catalysis and biomedical applications because of their perceived biocompatibility.[4] One particular appealing attribute of this research is that dendrimers with extremely broad structural diversities can be generated by varying the α-amino acids used in their construction. Yet another equally important aspect lies in the establishment of whether the properties of such amino acid derived dendrimers can be controlled by the constituent amino acid residues residing within the dendritic structure. This critical issue is closely related to the doctrine that the amino acid sequence determines the properties of protein and enzyme molecules. Indeed, Reymond et al. recently reported that the esterolysis reactivity of a library of layer-block or segment-block peptide-based dendritic catalysts was dependent on their amino acid composition.[1f–i] Smith also disclosed that the two-component gelation property of lysine-containing peptide-based dendrimers with aliphatic diamines was dependent on the dendrimer generation.[2] Although no structural diversity could be realized with this series of compounds, as lysine was the only amino acid component used, the study nonetheless revealed that the number of lysine repeating units, and hence the amino acid composition, of such peptide-based dendrimers was an important determinant of the gelation properties. We earlier disclosed the synthesis of β-alanine based dendrimers and reported their self-aggregation properties in polar organic solvents.[5] However, owing to their poor solubility, we were unable to study their properties in nonpolar solvents. Here we report the synthesis of a new library of G1–G3 α-amino acid based layer-block dendrons **1–6** by replacing the β-alanine moieties with alanine, phenylalanine, or valine residues. We show here that the α-amino acid side chains have an important influence on the properties of these dendrons and that they form dendritic physical gels in nonpolar aromatic solvents. Moreover, their gelation properties are also determined by their layer-block sequence[6] and their amino acid composition. This finding further supports the observa-

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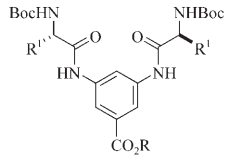
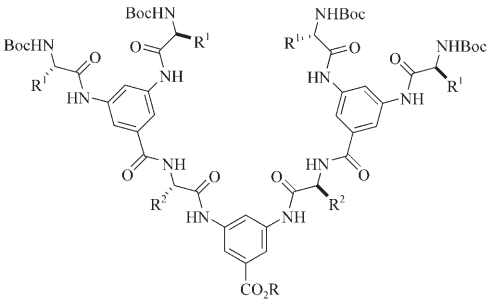
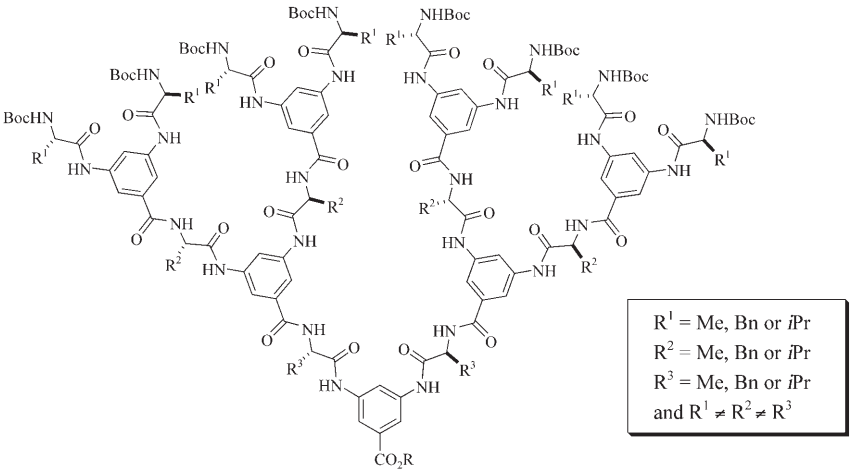


1 R = Et, [G1-(aa^1)$_2$-CO$_2$Et]
2 R = H, [G1-(aa^1)$_2$-CO$_2$H]
(aa^1 = A, F, V)



3 R = Et, [G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$Et]
4 R = H, [G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$H]
(aa^{1}aa^2 = AF, AV, FA, FV, VA, VF)



R^1 = Me, Bn or *i*Pr
R^2 = Me, Bn or *i*Pr
R^3 = Me, Bn or *i*Pr
and R^1 ≠ R^2 ≠ R^3

5 R = Et, [G3-(aa^1)$_8$(aa^2)$_4$(aa^3)$_2$-CO$_2$Et]
6 R = H, [G3-(aa^1)$_8$(aa^2)$_4$(aa^3)$_2$-CO$_2$H]
(aa^{1}aa^{2}aa^3 = AFV, AVF, FAV, FVA, VAF, VFA)

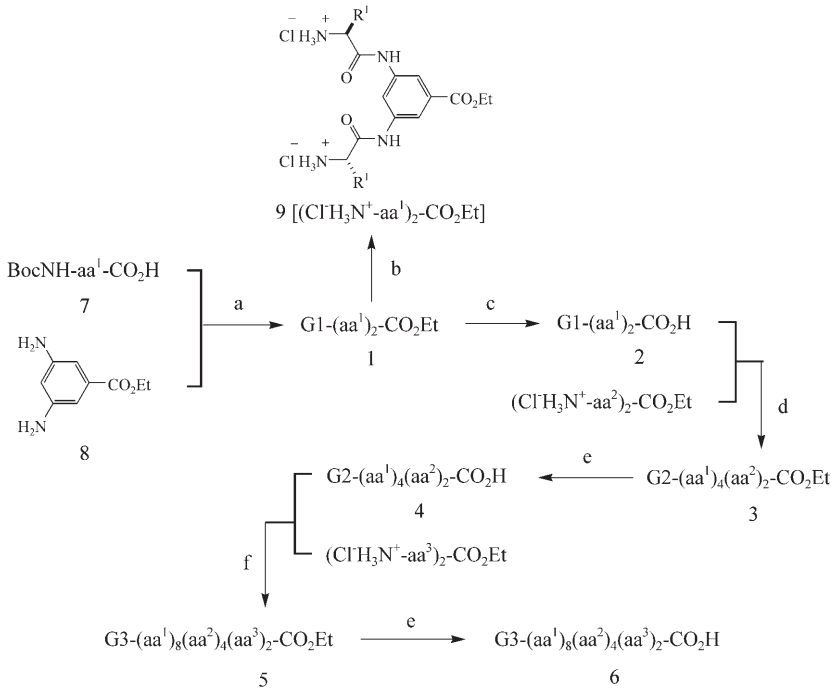
tion that the amino acid side chains not only confer the structural diversity, but also play a very important role in determining the physico-chemical properties of this interesting class of biomimetic dendrimers.

Results and Discussion

Synthesis: The syntheses of the Boc-*N*-protected α-amino acid dendrons **1–6** were similar to those of the β-alanine dendrons reported earlier by us.[5] Only nonpolar amino acids (L-alanine = A; L-phenylalanine = F; L-valine = V) were chosen in the present study. They were connected by amide linkages to a 3,5-diaminobenzoic acid branching unit using liquid-phase peptide coupling methods by a convergent synthesis methodology. The G1–G3 layer-block dendrons **1–6** of all possible layer sequences were prepared. Hence, reaction of BocNH-aa^1-CO$_2$H (**7**) with ethyl 3,5-diaminobenzoate (**8**) in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in THF afforded the various ester dendrons G1-(aa^1)$_2$-CO$_2$Et[7] **1** in 82–90% yields (Scheme 1). The Boc groups in compounds **1** were then removed in the presence of HCl to give the diammonium salts (Cl$^-$H$_3$N$^+$-aa^1)$_2$-CO$_2$Et (**9**) in quantitative yields. Alternatively, the focal point ethyl ester group was removed by alkaline hydrolysis to furnish the various acid dendrons G1-(aa^1)$_2$-CO$_2$H (**2**) in 76–99% yields. The G1 acid dendrons containing aa^1 amino acid residues were then coupled to another diammonium salt (Cl$^-$ H$_3$N$^+$-aa^2)$_2$-CO$_2$Et to give the G2 ester dendrons G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$Et (**3**) having a layer-block sequence of aa^{1}aa^2 in the presence of HOBt, DCC, and 4-methylmorpholine in 69–93% yields. Six different G2 ester dendrons were thus prepared and then subjected to alkaline hydrolysis to give the corresponding G2 acid dendrons **4** in 84–92% yield. For the syntheses of the G3 ester dendrons **5**, the more reactive 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDCI) was used instead of DCC as the coupling reagent and the product yields were slightly inferior (38–62%). Finally, the G3 acid dendrons **6** were obtained by alkaline hydrolysis from the G3 ester dendrons **5**.

Characterization

NMR spectroscopy: The structures of all compounds were characterized by ^{1}H NMR spectroscopy. The presence of a pseudo-C_2 symmetry axis in these molecules greatly simplified their spectral peak assignments. The ^{1}H NMR spectra of the different dendrons of the same generation are very similar because they all possess the same dendrimer backbone and branching skeleton. The only notable differences were the signals due to the side groups belonging to the different amino acid residues. For example, the ^{1}H NMR spectra of the three G1-(aa^1)$_2$-CO$_2$Et dendrons all gave a sharp singlet ($\delta \sim 1.3$ ppm) due to the *tert*-butyl protons, a triplet ($\delta \sim 1.3$ ppm) and a quartet ($\delta \sim 4.3$ ppm) due to the ethyl ester protons, two singlets ($\delta \sim 7.9$ and ~ 8.2 ppm) for aromatic protons of the branching aromatic unit, an NH doublet for the carbamate ($\delta \sim 7.2$ ppm), and a broad singlet ($\delta \sim 10.2$ ppm) for the anilide NH (Figure 1). On the other hand, the chemical identities of the different G1-(aa^1)$_2$-CO$_2$Et dendrons could be confirmed by the "fingerprint" peaks due to the different amino acid side chains. Hence, G1-A$_2$-CO$_2$Et



Scheme 1. Reagents and conditions: a) HOBt, DCC, THF, −10 °C to 25 °C, 11 h; b) HCl, EtOH, 25 °C, ~10 h; c) KOH (2.0 M), MeOH, H_2O, 25 °C, ~10 h; d) HOBt, DCC, 4-methylmorpholine, DMF, −10 °C to 25 °C, 50 h; e) KOH (2.0 M), MeOH, THF, H_2O, 25 °C, ~10 h; f) HOBt, EDCI, 4-methylmorpholine, DMF, −10 °C to 25 °C, 62 h.

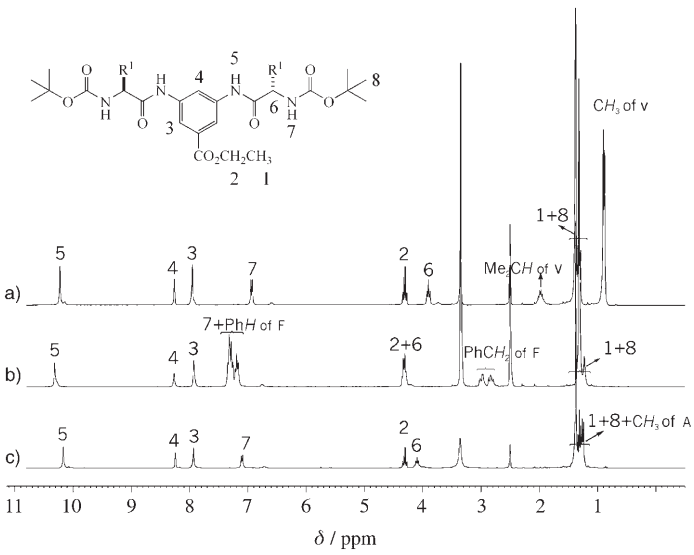


Figure 1. ^{1}H NMR (300 MHz) spectra of G1-(aa^1)$_2$-CO_2Et: a) aa^{1}V (R = *i*Pr), b) aa^1 = F (R = Bn), and c) aa^{1}A (R = Me) in [D_6]DMSO.

could be distinguished from the other ester dendrons by the presence of a doublet (δ = 1.25 ppm) from the side chain methyl groups. For G1-F_2-CO_2Et, the side chain benzyl groups appeared as three separate signals (δ = 2.75–2.90, 2.90–3.05, and 7.17–7.35 ppm) in its ^{1}H NMR spectrum. Finally, the isopropyl signals in compound G1-V_2-CO_2Et showed up as a doublet (δ = 0.89 ppm) and a multiplet (δ = 1.90–2.05 ppm). The presence of ^{1}H signals due to the minor carbamate rotamers, as in the case of the β-alanine dendrimers,[5] was also found.

For the various G2-(aa^1)$_4$(aa^2)$_2$-CO_2Et dendrons, the positions and patterns of the resonance peaks pertaining to the aa^1 amino acid side chain protons located on the outer layer were nearly unchanged when compared to those of the corresponding G1-(aa^1)$_2$-CO_2Et dendrons having the same amino acid residue. On the other hand, the resonance positions for protons in the inner layer aa^2 amino acid side chains were shifted downfield as compared with those of the G1-(aa^2)$_2$-CO_2Et dendrons. As an example, the relevant proton resonance signals of the two dendrons having F residues in the outer layer—G2-F_4A_2-CO_2Et and G2-F_4V_2-CO_2Et and the two dendrons having F in the inner layer—G2-A_4F_2-CO_2Et and G2-V_4F_2-CO_2Et were tabulated and compared with those of the G1-F_2-CO_2Et dendron (Table 1). A closer examination of the data revealed that the chemical shift values of the benzylic protons and the α protons of the F residues were shifted downfield by δ ~ 0.2 and ~0.5 ppm, respectively, when the F residues were moved from the outer to the inner layer. This is due to a difference of the linker group connecting to the α-amino residues. For those groups located in the outer layer, the amino ends of the F residues are connected to a carbamate functionality, while for those situated in the inner layer the amino moieties are linked to the aromatic branching unit by an amide bond. Such an apparent upfield shift of ^{1}H resonance positions, when the amino acid residue is located on the outer layer, can be used as a convenient tool to identify the nature of the amino acid located on the outer layer of the G2 and G3 layer-block dendrons.

Table 1. ^{1}H NMR (300 MHz, [D_6]DMSO) chemical shift values (δ) of proton signals relating to the F residues when placed in different layers inside the dendrons.

	G1-F_2-CO_2Et	G2-F_4A_2-CO_2Et	G2-F_4V_2-CO_2Et	G2-A_4F_2-CO_2Et	G2-V_4F_2-CO_2Et
NCHC*H*$_2$Ph	2.75–3.05	2.68–3.08	2.72–3.07	3.07–3.21	3.05–3.21
NC*H*CH$_2$Ph	4.25–4.38	4.16–4.39	4.21–4.40	4.78–4.88	4.77–4.88

The ^{13}C NMR spectra of these dendrons also share the same spectral characteristics as those of the ^{1}H NMR spectra. The chemical shift values of the carbon nuclei arising from the dendritic backbone and the aromatic branching unit are nearly the same. Hence, the primary and tertiary carbon atoms of *tert*-butyl groups resonate at $\delta = 29$ and 79 ppm, respectively. The peaks for the ethyl ester group appeared at $\delta = 15$ and 61 ppm, while the four aromatic carbon signals of branching units were found around $\delta = 115$–140 ppm. Three carbonyl ^{13}C signals appeared in the most downfield area of the spectra. The carbonyl ^{13}C signal at $\delta \sim 156$ ppm corresponded to the carbamate C=O group, while the signal at $\delta \sim 166$ ppm was assigned to the C=O ester moiety. The third signal, located at $\delta \sim 172$ ppm, originated from the anilide C=O group. Similarly, the chemical identities of the amino acid residues could be differentiated, as in the case of ^{1}H NMR spectroscopic analysis, by the "fingerprint" peaks from the different side chain functionalities.

Mass spectrometry: The structures of the G1 and G2 dendrons were also characterized by FAB-or L-SIMS mass spectrometry. For the G1 series, molecular ions appeared in forms of M^+, $[M+Na]^+$, or $[M+K]^+$. For the G2 dendrons, a molecular ion peak corresponding to $[M+Na]^+$ and/or $[M+K]^+$ is always present, as well as a series of fragmentation ion peaks due to the sequential cleavage of up to four Boc groups. For example, in addition to the molecular ion peak signals at *m/z* 1657.8 $[M+Na]^+$ and 1674.4 $[M+K]^+$, four fragment ion peaks at *m/z* 1535.9, 1436.4, 1335.7 and 1236.4, corresponding to $[M-Boc]^+$, $[M-2Boc]^+$, $[M-3Boc]^+$ and $[M-4Boc]^+$, respectively, were also found in the mass spectrum of G2-$F_4V_2CO_2Et$ (Figure 2). Unfortunately, we were unable to obtain satisfactory mass spectral data for the G3 series of dendrons.

Size-exclusion chromatography: The purities of the target dendrons were further determined by size-exclusion chromatography (SEC). All ester dendrons, irrespective of dendrimer generation, produced a symmetrical peak with a narrow polydispersity (≤ 1.03) in the SEC chromatogram in DMF. No peaks due to the presence of defective dendrons were detected. Surprisingly, the SEC chromatograms of all acid dendrons were broad and unsymmetrical in DMF, suggesting the presence of aggregates (Figure 3). However, upon addition of 5% acetic acid to the eluting solvent, the SEC peaks became sharper and symmetrical. The positions of the peaks were shifted to longer retention times that were nearly identical to that of their corresponding dendritic

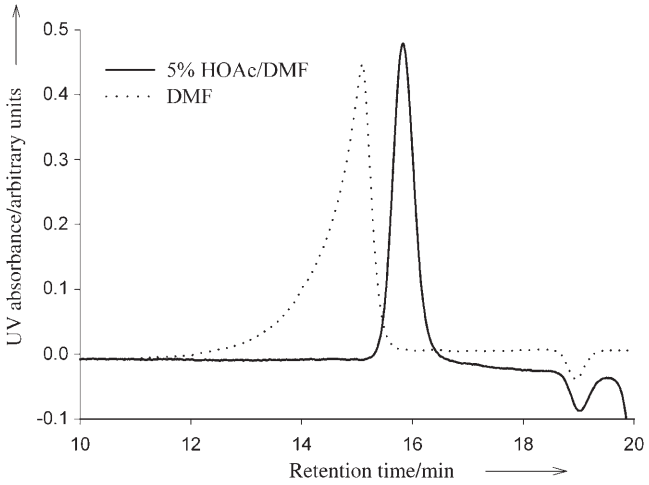


Figure 3. SEC chromatograms of G2-A_4V_2-CO_2H in different solvent systems (flow rate: 1 mL min^{-1}; temperature: 40 °C; columns: Waters Styragel HR1 and HR3 in serial). The negative absorption peaks are due to signals of water and acetic acid.

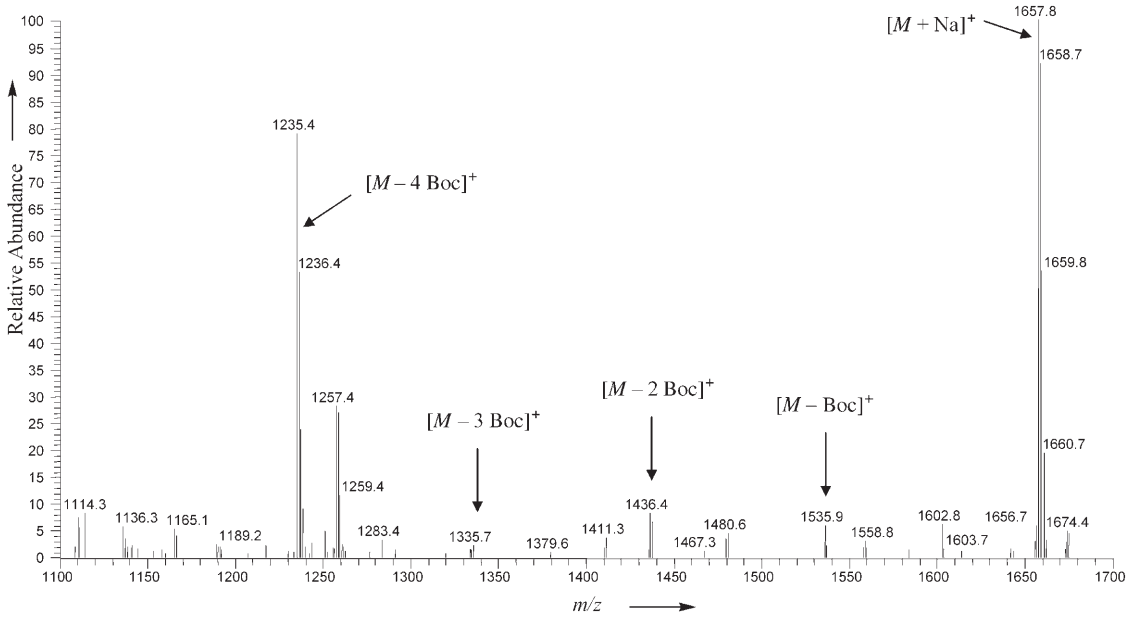


Figure 2. FAB mass spectrum of G2-F_4V_2-CO_2Et.

ester precursors, indicating the breaking down of the aggregates in a stronger hydrogen bonding solvent. Furthermore, a linear relationship can be established between the SEC retention time and the logarithm of the theoretical molecular weight of the dendrons (Figure 4). Hence, dendrons of the same generation are found in close proximity in the figure. As a result, three separate clusters were found in the plot, with the G3 cluster located near the top left corner and the G1 cluster situated at the bottom right corner. This finding also suggests that dendrons of the same generation all possess similar hydrodynamic radii, irrespective of the amino acid composition and the focal-point functional group.

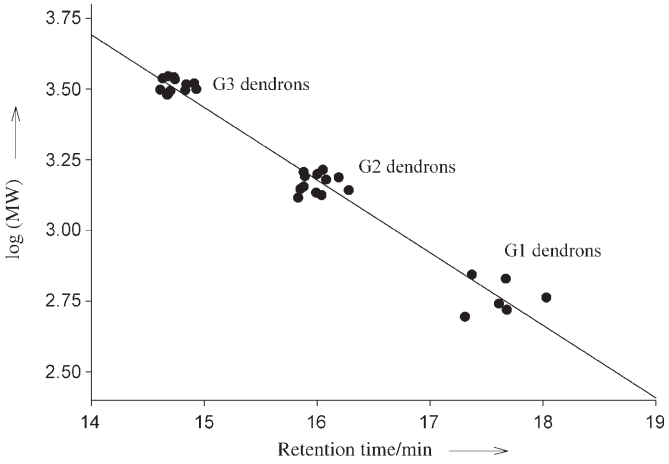


Figure 4. A plot of SEC retention time versus log(MW) of the G1–G3 dendrons (solvent: 5% HOAc/DMF).

Optical polarimetry: The chiroptical data of the dendrons were measured in 5% HOAc in 1,2-dichloroethane to avoid complications due to aggregation (Table 2). One notable feature is that the sign of the specific rotation does not change from the dendritic esters to their corresponding carboxylic acids. This suggests that the nature of the focal-point functionality has little influence on the chiral conformation. Another point of interest is that the molar rotation of the higher generation dendrons can be roughly estimated from summation of the molar rotations of all the smaller constituent chiral components. For example, the molar rotations of G1-A_2-CO_2R (R = Et or H) and G1-V_2-CO_2R dendrons are negative, while those of the G1-F_2-CO_2R are positive. As a result, the signs of the molar rotations of G2-A_4V_2-CO_2R and G2-V_4A_2-CO_2R dendrons, which can be considered to consist of G1-A_2-CO_2R and G1-V_2-CO_2R dendrons, are also negative. However, the sign of molar rotations for G2 dendrons consisting of a combination of A and F, or F and V residues are difficult to predict, because the chiroptical effects of A and F, or F and V, are counteracting each other, but not in an exact or quantitative manner. Thus, G2-F_4V_2-CO_2R, a dendron that can roughly be considered as consisting of two (+)-G1-F_2-CO_2R and one (−)-G1-V_2-CO_2R fragments, has a negative molar rotation value. On the other hand, G2-F_4A_2-CO_2R has a positive molar rotation, even though the molar rotation of G1-A_2-CO_2R is more negative than that of G1-V_2-CO_2R. Obviously this simple dissection of higher generation dendrons into smaller lower generation dendritic fragments is an over-simplified analysis, because the *N*-termini of the outer layer amino acids are linked to Boc moieties while those of the inner layer amino acids are connected to the 3,5-diaminobenzoic acid branching unit. It has been noted that a slight change in the chemical environment of chiral units could lead to dramatically different chiroptical properties.[8] It is therefore not surprising to see that an exact quantitative relationship cannot be formulated by using such a simplified structural dissection approach. Nevertheless, a qualitative statement claiming that the molar rotation of these dendrons is the simple sum of the rotations of its constituted chiral units, as in the case of sterically non-congested chiral dendrimers,[9] is possibly valid.

Table 2. Chiroptical data of G1 and G2 dendrons[a]

Dendron	$[\alpha]_D$[b]	$[M]$[c]	Dendron	$[\alpha]_D$	$[M]$
G1-A_2-CO_2Et	−66.9	−350	G1-A_2-CO_2H	−60.7	−300
G1-F_2-CO_2Et	+15.2	+103	G1-F_2-CO_2H	+8.8	+57
G1-V_2-CO_2Et	−30.5	−177	G1-V_2-CO_2H	−56.9	−313
G2-A_4F_2-CO_2Et	−52.6	−751	G2-A_4F_2-CO_2H	−73.5	−958
G2-A_4V_2-CO_2Et	−74.8	−996	G2-A_4V_2-CO_2H	−58.9	−768
G2-F_4A_2-CO_2Et	+26.1	+412	G2-F_4A_2-CO_2H	+141.7	+2199
G2-F_4V_2-CO_2Et	−0.6	−10	G2-F_4V_2-CO_2H	−48.4	−778
G2-V_4A_2-CO_2Et	−19.6	−272	G2-V_4A_2-CO_2H	−1.8	−25
G2-V_4F_2-CO_2Et	+13.3	+204	G2-V_4F_2-CO_2H	+45.1	+682

[a] In 1,2-dichloroethane/HOAc = 95/5 (v/v) solutions at 25 °C. [b] Specific rotation (10^{-1} deg cm^2 g^{-1}). [c] Molar rotation (10 deg cm^2 mol^{-1}).

Self-aggregation properties: In contrast to the poor solubility properties of the β-alanine dendrons reported earlier,[5] these α-amino acid dendrons, owing to the presence of the nonpolar alkyl amino acid side chains, are reasonably soluble in aromatic and chlorinated solvents. As a result of this change of amino acid composition, the α-amino acid dendrons exhibit aggregation properties that were not revealed previously as in the case of the β-alanine dendrimers. Most of the α-amino acid dendrons prepared here were found to have a tendency to form self-organized species in the solid and solution states. For example, X-ray crystallographic analysis of a G1-V_2-CO_2Et crystal (from ethyl acetate) shows that the compound crystallizes as a dimer of approximate C_2 symmetry (Figure 5). Each molecule in the dimer embraces the other with its two longer, pincer-like arms, such that the pair of aromatic rings are mutually nearly parallel and arranged in a staggered manner (dihedral angle between ring planes = 8.1°, distance between ring centers = 3.553 Å). The molecular association in the dimer is further consolidated by four intermolecular hydrogen bonds of the type N–H···O=C (N1···O7′ 2.947, N3···O4′ 2.977, N1′···O7 2.968, N3′···O4 2.996 Å).

The formation of dimeric species from G1-V_2-CO_2Et can also be revealed from a ^{1}H NMR investigation. In $CDCl_3$ solution, the chemical shift value of the NH anilide protons

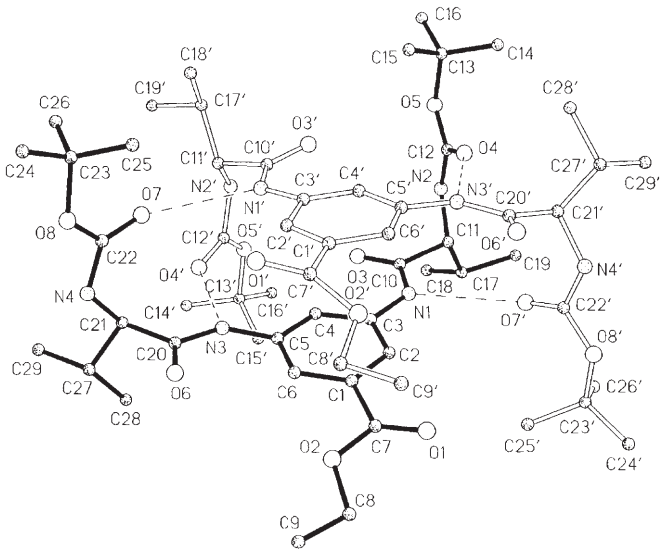


Figure 5. Structure of G1-V_2-CO_2Et showing the dimeric nature in the solid state, as obtained by X-ray crystallography. Hydrogen atoms and atoms from ethyl acetate are omitted for clarity.

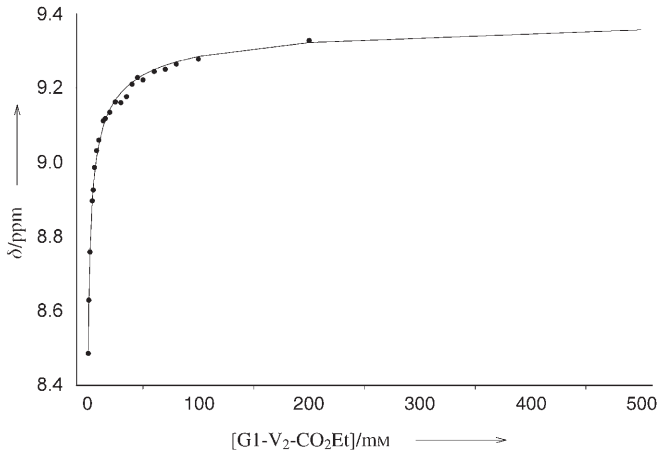


Figure 6. Concentration dependent ^{1}H NMR (300 MHz) chemical shift of the NHAr protons in G1-V_2-CO_2Et in $CDCl_3$.

was shown to be dependent on the sample concentration (Figure 6). The data could be fitted into a dimerization model reported by Hunter[10] and the dimerization constant was estimated to be $350 \pm 50\,\text{M}^{-1}$. Interestingly, the presence of the dimeric (*m*/*z* 1156.7) and trimeric species (*m*/*z* 1736.1) could also be detected in the L-SIMS mass spectrum of G1-V_2-CO_2Et.

Gelation properties: *Minimum gelation concentration* (mgc): The self-assembling properties of the α-amino acid based dendrons were further exemplified by their tendency to form physical gels[2,11] in a solvent and layer-block sequence-dependent manner. Gel formation was not observed in non-polar hydrocarbon solvents or alcohols, and only weak gels were formed in chlorinated solvents. On the other hand, gelation was noted in a wide range of aromatic solvents (Figure 7). The focal-point carboxylic acid or ethyl ester functionality also played an important role in gel formation. Hence, the lower generation G1 and G2 acid dendrons have a stronger tendency than the ester dendrons to form very stable transparent gels (mgc < 2–100 mg mL^{-1}), while for the G3 series the ester dendrons are the better gelators. Most interestingly, the nature of the amino acid side chains in the various layers also exhibited an intriguing effect on the gelation efficiency. Hence, among the three G1 acid dendrons, only G1-F_2-CO_2H is capable of producing strong transparent gels (mgc = 5 mg mL^{-1}) (Table 3). On the other hand, the corresponding G1-F_2-CO_2Et ester dendron is a poor organogelator and is highly soluble in aromatic solvents. To our surprise, the strongest organogelator amongst the six G2

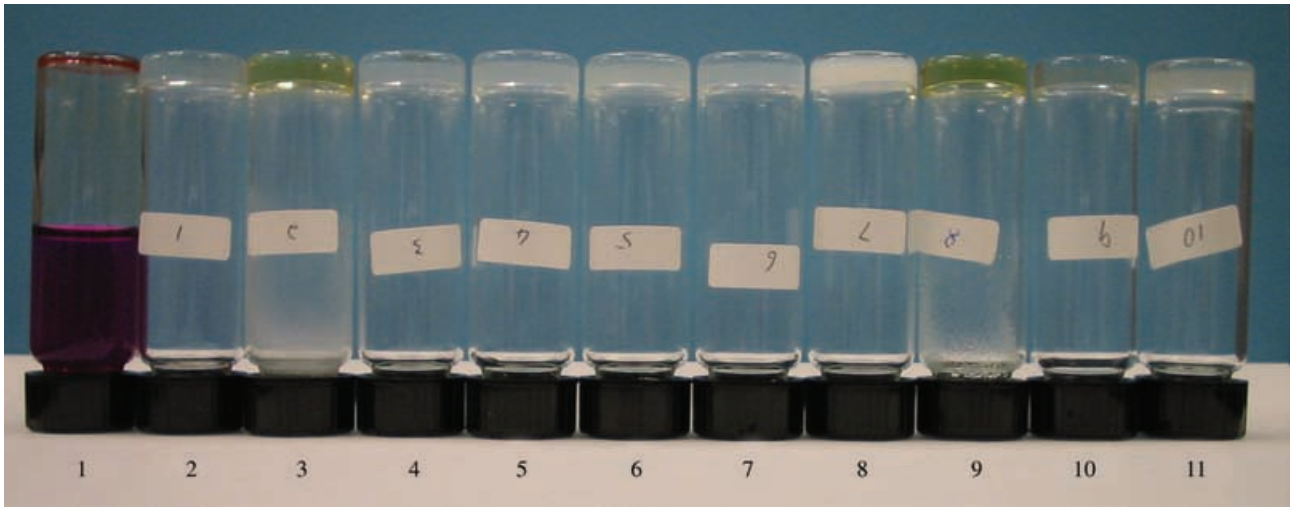


Figure 7. Photographic images of amino acid based dendritic gels (concentration = 10 mg mL^{-1}). From left to right: 1) aqueous $KMnO_4$ solution; 2) G1-F_2-CO_2H in benzene; 3) G1-F_2-CO_2H in nitrobenzene; 4) G1-F_2-CO_2H in toluene; 5) G1-F_2-CO_2H in *o*-xylene; 6) G1-F_2-CO_2H in *p*-xylene; 7) G1-F_2-CO_2H in *m*-xylene; 8) G1-F_2-CO_2H in CH_2Cl_2; 9) G3-$A_8V_4F_2$-CO_2Et in nitrobenzene; 10) G2-V_4A_2-CO_2H in toluene; 11) G2-V_4A_2-CO_2H in benzene.

Table 3. Minimum gelation concentrations of G1 dendrons in various organic solvents at 25 °C.[a]

	G1-A_2-CO_2Et	G1-F_2-CO_2Et	G1-V_2-CO_2Et	G1-A_2-CO_2H	G1-F_2-CO_2H	G1-V_2-CO_2H
hexane	I	I	I	I	I	I
diethyl ether	P	I	P	I	I	I
THF	S	S	S	S	S	P
dichloromethane	S	S	S	I	OG (10)	I
chloroform	S	S	S	I	S	I
ethyl acetate	S	S	C	S	S	I
acetone	S	S	S	S	S	PG
acetonitrile	C	C	C	P	P	P
methanol	S	S	S	S	S	PG
ethanol	S	S	S	S	S	PG
1-propanol	S	C	S	S	S	P
benzene	PG	S	TG (100)	TG (100)	**CG (3)**	I
toluene	PG	S	TG (80)	PG	**TG (3)**	I
o-xylene	OG (60)	S	TG (80)	TG (30)	**CG (4)**	I
p-xylene	PG	S	TG (80)	TG (100)	**CG (4)**	I
m-xylene	PG	S	TG (80)	TG (100)	**CG (4)**	I
anisole	PG	S	TG (90)	TG (70)	PG	PG
chlorobenzene	PG	S	TG (80)	TG (100)	CG (10)	OG (70)
o-dichlorobenzene	OG (100)	S	PG	CG (40)	TG (20)	S
nitrobenzene	S	S	TG (90)	S	**CG (2)**	PG

[a] CG: clear transparent gel; PG: partial gelation; TG: translucent gel; OG: opaque gel; S: soluble ($>100\,mg\,mL^{-1}$); I: insoluble upon heating; C: crystallization; P: precipitation. The value given in parentheses is the mgc in $mg\,mL^{-1}$ to achieve gelation at 25 °C.

dendrons is G2-V_4A_2-CO_2H (mgc ~ 4–50 $mg\,mL^{-1}$)—a compound that is deprived of F residues (Table 4). On the other hand, the G2 dendron with the 'reverse' layer-block structure G2-A_4V_2-CO_2H turned out to be a less-efficient gelator, and mainly formed translucent or opaque gels. The G3 dendrons, in contrast to their lower generation analogues, produced mainly translucent or weakly opaque gels with most aromatic solvents (Table 5). Of the 12 possible G3 dendrons, only G3-$A_8V_4F_2$-CO_2Et produced strong transparent gels (mgc = 6 $mg\,mL^{-1}$) in nitrobenzene, while the corresponding acid dendron G3-$A_8V_4F_2$-CO_2H was an inferior organogelator. Hence, both the focal-point functional group and the amino acid side chains in the various dendritic layers played a pivotal role in determining the gelation process.

Gelation mechanism: The gelation process is mostly likely induced by both hydrogen-bonding and aromatic π–π stacking interactions, since it is observed mainly in aromatic solvents. Furthermore, the electron-deficient nitrobenzene was the most effective aromatic solvent for gel formation. This solvent was expected to interact more strongly with the electron-rich 3,5-diaminobenzamide branching moiety. We therefore studied the gelation mechanism by IR spectroscopy. Our initial attempt was to compare the IR spectral changes between the solution and gel states of G1-F_2-CO_2H in *p*-xylene. However, this compound rapidly formed gels in the sample cell and we were unable to obtain a clear, homogeneous solution in *p*-xylene, even at very low organogelator concentration ($<0.2\,mg\,mL^{-1}$). On the other hand, the FT-IR signals were too weak to be observed at much lower concentration, therefore the solution IR was recorded in $CHCl_3$ for comparison. Peak assignments of N–H and C=O absorptions were based on the IR data obtained from model compounds BocNH-phenylalanine benzyl ester (BocNH-F-CO_2Bn) and G1-F_2-CO_2Bn, both of which formed clear solutions in $CHCl_3$ and in *p*-xylene. The IR spectrum of a nongelled sample of G1-F_2-CO_2H ($10\,mg\,mL^{-1}$) in $CHCl_3$ exhibited typical carbamate N–H, anilide N–H, acid/carbamate C=O and anilide C=O stretchings at 3436, 3322, 1710 and 1685 cm^{-1}, respectively (Figure 8). These signals were red-shifted by 100, 70, 19 and 24 cm^{-1}, respectively, in the *p*-xylene gels ($10\,mg\,mL^{-1}$), revealing the presence of intermolecular hydrogen bonds in the gelled sample.

To investigate the chiral structure of the gel, circular dichroism (CD) spectra of G1-F_2-CO_2H ($10\,mg\,mL^{-1}$) in *p*-xylene were recorded at different temperatures (Figure 9). Prior to gelation, the solution sample showed only weak CD signals. After gelation, a large CD band from the aromatic chromophore was observed at 310 nm, the intensity of which decreased gradually with increasing temperature. These results strongly indicate the formation of hierarchical chiral aggregates in the gelled state. Scanning electron microscopic (SEM) studies of a freeze-dried gel sample of G1-F_2-CO_2H ($10\,mg\,mL^{-1}$) in *p*-xylene showed the presence of fibrous structures with diameters ranging from 50 to 100 nm (Figure 10).However, the existence of a chiral morphology could not be

Table 4. Minimum gelation concentrations of G2 dendrons in various aromatic solvents at 25 °C.[a]

	Toluene	*o*-Xylene	Anisole	Nitrobenzene	*o*-Dichlorobenzene
G2-A_4F_2-CO_2Et	OG (40)	OG (70)	CG (20)	TG (100)	CG (30)
G2-A_4V_2-CO_2Et	OG (100)	PG	CG (50)	CG (60)	PG
G2-F_4A_2-CO_2Et	S	S	S	S	S
G2-F_4V_2-CO_2Et	OG (90)	TG (70)	TG (30)	TG (50)	OG (70)
G2-V_4A_2-CO_2Et	PG	PG	PG	S	S
G2-V_4F_2-CO_2Et	PG	PG	S	CG (40)	CG (100)
G2-A_4F_2-CO_2H	OG (40)	OG (40)	TG (100)	OG (50)	TG (50)
G2-A_4V_2-CO_2H	OG (100)	TG (100)	OG (50)	CG (30)	TG (30)
G2-F_4A_2-CO_2H	TG (100)	OG (100)	CG (100)	PG	PG
G2-F_4V_2-CO_2H	OG (50)	OG (50)	CG (100)	CG (30)	TG (30)
G2-V_4A_2-CO_2H	**CG (4)**	CG (20)	CG (30)	CG (50)	CG (30)
G2-V_4F_2-CO_2H	TG (100)	TG (100)	PG	PG	PG

[a] CG: clear transparent gel; PG: partial gelation; TG: translucent gel; OG: opaque gel; S: soluble (> 100 $mg\,mL^{-1}$). The value given in parentheses is the mgc in $mg\,mL^{-1}$ to achieve gelation at 25 °C.

Table 5. Minimum gelation concentrations of G3 dendrons in various aromatic solvents at 25 °C.[a]

	Toluene	*o*-Xylene	Anisole	Nitrobenzene	*o*-Dichlorobenzene
G3-$A_8F_4V_2$-CO_2Et	OG (50)	OG (50)	PG	TG (100)	TG (40)
G3-$A_8V_4F_2$-CO_2Et	OG (50)	OG (60)	TG (50)	**CG (6)**	PG
G3-$F_8A_4V_2$-CO_2Et	OG (100)	OG (100)	S	S	TG (100)
G3-$F_8V_4A_2$-CO_2Et	OG (20)	OG (30)	PG	PG	TG (70)
G3-$V_8A_4F_2$-CO_2Et	TG (20)	TG (50)	PG	TG (50)	TG (20)
G3-$V_8F_4A_2$-CO_2Et	OG (40)	OG (30)	PG	TG (100)	TG (60)
G3-$A_8F_4V_2$-CO_2H	OG (60)	OG (50)	TG (90)	TG (100)	TG (50)
G3-$A_8V_4F_2$-CO_2H	PG	PG	TG (60)	TG (30)	TG (30)
G3-$F_8A_4V_2$-CO_2H	OG (50)	OG (50)	S	S	OG (100)
G3-$F_8V_4A_2$-CO_2H	TG (100)	PG	PG	CG (30)	S
G3-$V_8A_4F_2$-CO_2H	PG	PG	TG (50)	TG (40)	TG (100)
G3-$V_8F_4A_2$-CO_2H	TG (100)	OG (60)	TG (100)	TG (50)	TG (100)

[a] CG: clear transparent gel; PG: partial gelation; TG: translucent gel; OG: opaque gel; S: soluble ($>100\,mg\,mL^{-1}$). The value given in parentheses is the mgc in $mg\,mL^{-1}$ to achieve gelation at 25 °C.

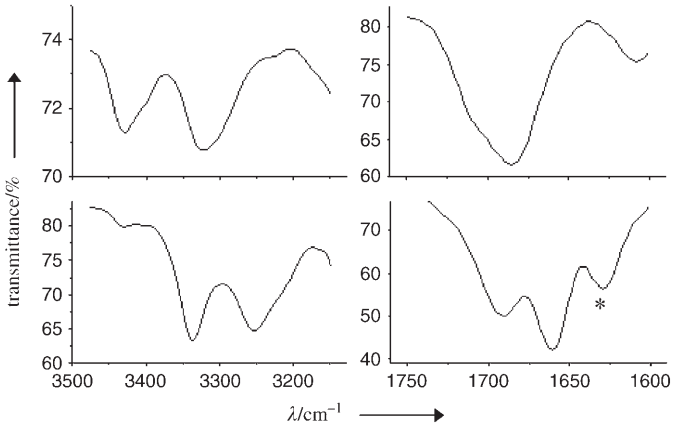


Figure 8. FT-IR spectra of G1-F_2-CO_2H ($10\,mg\,mL^{-1}$) in $CHCl_3$ solution (top two spectra) and in *p*-xylene gel (bottom two spectra). The peak labeled with an asterisk (*) is due to the presence of *p*-xylene.

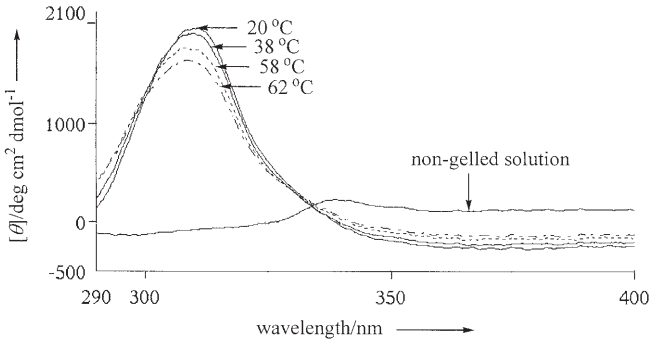


Figure 9. Stacked CD spectra of G1-F_2-CO_2H in *p*-xylene gels ($10\,mg\,mL^{-1}$) at different temperatures and in a non-gelled *p*-xylene solution.

observed. These fibers were likely to be supramolecular bundles formed from the intertwining of smaller chains resulting from the intermolecular hydrogen bonding of individual dendrons. On the other hand, the SEM image of the G2-V_4A_2-CO_2H ($10\,mg\,mL^{-1}$) dried gel sample in toluene showed the presence of dense structures with no clear, well-defined microscale architecture. These findings suggest that the degree of branching also determines the aggregation process. Unfortunately, we were unable to obtain satisfactory dried gel samples of the G3 dendrons for SEM investigations. Thin transparent films were always formed and hence the microscopic morphology of the samples must have been modified during sample preparation.

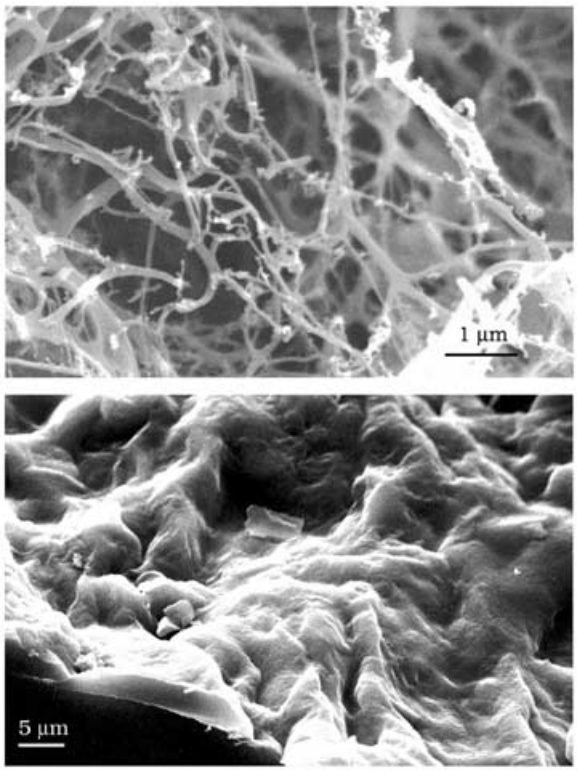


Figure 10. SEM images of freeze-dried gel samples of (top) G1-F_2-CO_2H from *p*-xylene ($10\,mg\,mL^{-1}$) and of (bottom) G2-V_4A_2-CO_2H from toluene ($10\,mg\,mL^{-1}$).

Conclusion

We report here the synthesis of a new library of α-amino acid based layer-block dendrons based on three nonpolar amino acid residues. Such dendrons are capable of forming very strong, transparent physical gels (mgc down to $2\,mg\,mL^{-1}$) with aromatic solvents through intricate interactions between the aromatic, amino and carbonyl functionalities. It is believed that the solubility properties and structural rigidities of the nonpolar amino acid side chains as well as those of the focal-point functionality play an important role in the gelation process. Only dendrons with the optimal

amino acid composition and the appropriate focal-point functional group can prevent dissolution into or crystallization from the solvent medium and exhibit such good gelation properties. In other words, their gelation ability is highly dependent on the amino acid layer-block sequence of the dendrons, even though we are unable to clearly define the structure–gelation relationship at the present moment. Such α-amino acid based dendritic gels are potentially useful molecules for biocompatible drug-delivery materials. We envisage that the introduction of other amino acid residues of different polarity and hydrogen-bonding capabilities will further enrich the structural diversity, physico-chemical and biological properties of such amino acid based dendritic molecules, the results of which will be reported in the near future.

Experimental Section

THF was distilled from sodium benzophenone ketyl prior to use. DMF was stirred with calcium hydride overnight and distilled in vacuo. Macherey Nagel 60M (230–400 mesh) silica gel was used for flash chromatography. *N*-Boc-protected L-amino acids (BocNH-aa^1-CO_2H) and other chemical reagents were used as received from Aldrich. All NMR spectra were recorded in [D_6]DMSO (dried over molecular sieve 4 Å) on a Brüker DPX spectrometer at 300 MHz (^{1}H) and 75.5 MHz (^{13}C) at 25 °C unless otherwise indicated. The residual proton or carbon signals of [D_6]DMSO ($\delta_H = 2.50$ ppm; $\delta_C = 40.5$ ppm) were used as internal references. All chemical shifts are reported in ppm (δ) and coupling constants in Hz. Positive-ion L-SIMS and FAB spectra were carried out on a Bruker APEX 47E FTMS spectrometer, a Hewlett Packard 5989B or a Thermo Finnigan MAT 95XL mass spectrometer. Melting points were measured on an Electrothermal IA9100 Digital Melting Point Apparatus and were uncorrected. Melting temperatures (T_m) were collected on a Perkin-Elmer DCS6 differential scanning calorimeter and are referred to as the temperature at the onset of the transition. Optical rotations were taken on a Perkin Elmer 341 Polarimeter at 589 nm and at 20 °C, in a solvent mixture of 1,2-dichloroethane/HOAc (v/v 95/5). Size-exclusion chromatography (SEC) analyses were performed on Waters Styragel columns (HR 1 and HR 3 in serial) at 40 °C in 5% HOAc/DMF as eluent (flow rate = 1.0 mL min^{-1}) using a Waters HPLC 515 pump equipped with a Waters 486 tunable UV absorbance detector. Molecular weights obtained from SEC measurements were based on a calibration curve derived from polystyrene standards. Elemental analyses were performed either at the Shanghai Institute of Organic Chemistry, Academic Sinica, China or at MEDAC LTD, Brunel Science Center, Cooper's Hill Lane, Englefield Green, Egham, Surrey TW20 0JZ, UK.

General procedure for the synthesis of G1-(aa^1)$_2$-CO_2Et: Dicyclohexyl carbodiimide (DCC) (2.2 equiv) was added to a stirred mixture of BocNH-aa^1-CO_2H (2.2 equiv), ethyl 3,5-diaminobenzoate (1.0 equiv), and 1-hydroxybenzotriazole (HOBt) (2.2 equiv) in dry THF under a nitrogen atmosphere at −10 °C. The mixture was kept at −10 °C for 1 h and then at 25 °C for 10 h. The insoluble dicyclohexyl urea (DCU) produced was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in EtOAc (300 mL) and washed successively with saturated $NaHCO_3$ solution (100 mL), 10% citric acid solution (2 × 75 mL), saturated $NaHCO_3$ solution (2 × 75 mL), and water (2 × 75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give the target compound that was purified by flash chromatography on silica gel.

G1-A$_2$-CO_2Et: Starting from BocNH-A-CO_2H (8.32 g, 44.0 mmol), ethyl 3,5-diaminobenzoate (3.60 g, 20.0 mmol), HOBt (5.94 g, 44.0 mmol) and DCC (9.06 g, 44.0 mmol), compound G1-A$_2$-CO_2Et was obtained as a white crystalline solid (9.41 g, 90%) after flash chromatography (eluent: EtOAc/hexane = 2/3). M.p. 147–149 °C. $[\alpha]_D^{20} = -66.9$ ($c = 0.68$). SEC retention time: 17.68 min. ^{1}H NMR: $\delta = 1.25$ (d, $J = 7.1$ Hz, 6H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.38 (s, 18H), 4.05–4.16 (m, 2H), 4.31 (q, $J = 7.0$ Hz, 2H), 7.10 (d, $J = 7.0$ Hz, 2H), 7.95 (s, 2H), 8.24 (s, 1H), 10.17 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.8, 29.2, 51.4, 61.8, 79.0, 115.1, 115.6, 131.5, 140.6, 156.1, 166.4, 173.2 ppm; MS (FAB): m/z (%): 545 ([M+Na]$^+$, 21); elemental analysis calcd (%) for $C_{25}H_{38}N_4O_8$: C 57.46, H 7.33, N 10.72; found: C 57.35, H 7.47, N 10.83.

G1-F$_2$-CO_2Et: Starting from BocNH-F-CO_2H (11.68 g, 44.0 mmol), ethyl 3,5-diaminobenzoate (3.60 g, 20.0 mmol), HOBt (5.94 g, 44.0 mmol), and DCC (9.06 g, 44.0 mmol), compound G1-F$_2$-CO_2Et was obtained as a white crystalline solid (11.33 g, 84%) after flash chromatography (eluent: EtOAc/hexane = 1/2). M.p. 158–159 °C. $[\alpha]_D^{20} = +15.2$ ($c = 0.66$). SEC retention time: 17.67 min. ^{1}H NMR: $\delta = 1.26$–1.37 (m, 3H), 1.32 (s, 18H), 2.75–2.90 (m, 2H), 2.90–3.05 (m, 2H), 4.25–4.38 (m, 4H), 7.17–7.35 (m, 12H), 7.93 (s, 2H), 8.27 (s, 1H), 10.32 ppm (s, 2H); ^{13}C NMR: $\delta = 15.2$, 29.1, 38.2, 57.7, 61.9, 79.1, 115.2, 115.7, 127.3, 129.0, 130.2, 131.5, 138.9, 140.5, 156.4, 166.4, 172.1 ppm; MS (FAB): m/z (%): 675 ([M+H]$^+$, 1); elemental analysis calcd (%) for $C_{37}H_{46}N_4O_8$: C 65.86, H 6.87, N 8.30; found: C 65.84, H 6.88, N 8.27.

G1-V$_2$-CO_2Et: Starting from BocNH-V-CO_2H (9.55 g, 44.0 mmol), ethyl 3,5-diaminobenzoate (3.60 g, 20.0 mmol), HOBt (5.94 g, 44.0 mmol), and DCC (9.06 g, 44.0 mmol), compound G1-V$_2$-CO_2Et was obtained as a white crystalline solid (9.48 g, 82%) after flash chromatography (eluent: EtOAc/hexane = 2/5). M.p. 149–150 °C. $[\alpha]_D^{20} = -30.5$ ($c = 0.82$). SEC retention time: 18.03 min. ^{1}H NMR: $\delta = 0.89$ (d, $J = 6.5$ Hz, 12H), 1,32 (t, $J = 7.1$ Hz, 3H), 1.38 (s, 18H), 1.90–2.05 (m, 2H), 3.90 (t, $J = 7.8$ Hz, 2H), 4.31 (q, $J = 7.0$ Hz, 2H), 6.94 (d, $J = 8.3$ Hz, 2H), 7.95 (s, 2H), 8.26 (s, 1H), 10.22 ppm (s, 2H); ^{13}C NMR: $\delta = 15.2$, 19.5, 20.2, 29.2, 31.2, 61.7, 61.9, 79.0, 115.1, 115.7, 131.6, 140.4, 156.6, 166.4, 172.1 ppm; MS (FAB): m/z (%): 578 (M^+, 16); HRMS (L-SIMS): calcd for M^+: 578.3308; found: 578.3302; elemental analysis calcd (%) for $C_{29}H_{46}N_4O_8 \cdot H_2O$: C 58.37, H 8.11, N 9.39; found: C 58.21, H 8.05, N 9.39.[12]

General procedure for the synthesis of (Cl$^-$ H$_3$N$^+$-aa^1)$_2$-CO_2Et: G1-(aa^1)$_2$-CO_2Et was stirred in a HCl solution in ethanol (2.1 M) at 25 °C. The reaction was monitored by TLC until completion. The solvent was then evaporated in vacuo and the residue poured into a large amount of diethyl ether. The precipitate formed was collected by filtration under dry nitrogen, and washed with diethyl ether to give the desired product.

(Cl$^-$ H$_3$N$^+$-A)$_2$-CO_2Et: Starting from G1-A$_2$-CO_2Et (5.22 g, 10.0 mmol) and a HCl solution in ethanol (60 mL, 2.1 M), the title compound was obtained as a white solid (3.86 g, 98%). T_m 259 °C. $[\alpha]_D^{20} = -3.7$ ($c = 0.37$, MeOH); ^{1}H NMR: $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H), 1.48 (d, $J = 6.9$ Hz, 6H), 4.11 (q, $J = 6.8$ Hz, 2H), 4.31 (q, $J = 7.0$ Hz, 2H), 8.07 (d, $J = 1.9$ Hz, 2H), 8.23 (t, $J = 1.7$ Hz, 1H), 8.45 (br. s, 6H), 11.15 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.1, 49.9, 62.0, 115.5, 116.4, 131.8, 140.0, 166.1, 169.6 ppm; MS (FAB): m/z (%): 323 ([M−2HCl+H]$^+$, 37); HRMS (FAB): calcd for [M−2HCl+H]$^+$: 323.1713; found: 323.1692.

(Cl$^-$ H$_3$N$^+$-F)$_2$-CO_2Et: Starting from G1-F$_2$-CO_2Et (6.74 g, 10.0 mmol) and a HCl solution in ethanol (80 mL, 2.1 M), the target compound was obtained as a white solid (5.42 g, 99%). T_m 280 °C. $[\alpha]_D^{20} = +111.9$ ($c = 0.34$, MeOH). ^{1}H NMR: $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H), 3.11–3.27 (m, 4H), 4.26–4.40 (m, 4H), 7.19–7.38 (m, 10H), 8.00 (d, $J = 1.8$ Hz, 2H), 8.09 (t, $J = 1.7$ Hz, 1H), 8.56 (br. s, 6H) 11.20 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 37.8, 55.1, 62.0, 115.8, 116.7, 128.1, 129.5, 130.5, 131.7, 135.8, 139.7, 166.1, 168.0 ppm; MS (FAB): m/z (%): 475 ([M−2HCl+H]$^+$, 100); HRMS (L-SIMS): calcd for [M−2HCl+H]$^+$: 475.2338; found: 475.2332.

(Cl$^-$ H$_3$N$^+$-V)$_2$-CO_2Et: Starting from G1 V$_2$-CO_2Et (5.78 g, 10.0 mmol) and a HCl solution in ethanol (50 mL, 2.1 M), the title compound was obtained as a white solid (4.34 g, 98%). T_m 268 °C. $[\alpha]_D^{20} = +47.2$ ($c = 0.60$, MeOH). ^{1}H NMR: $\delta = 0.99$ (d, $J = 2.5$ Hz, 6H), 1.01 (d, $J = 2.5$ Hz, 6H), 1.32 (t, $J = 7.1$ Hz, 3H), 2.14–2.29 (m, 2H), 3.89 (d, $J = 5.9$ Hz, 2H), 4.32 (q, $J = 7.0$ Hz, 2H), 8.08 (d, $J = 1.8$ Hz, 2H), 8.27 (t, $J = 1.8$ Hz, 1H), 8.40 (br. s, 6H), 11.14 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.9, 19.4, 30.9, 58.9, 62.0, 115.6, 116.5, 131.8, 139.8, 166.1, 168.3 ppm; MS (FAB): m/z (%): 379 ([M−2HCl+H]$^+$, 34); HRMS (L-SIMS): calcd for [M−2HCl+H]$^+$: 379.2338; found: 379.2337.

General procedure for the synthesis of G1-(aa^1)$_2$-CO_2H: An aqueous solution of KOH (2.0 M) was added to a stirred solution of G1-(aa^1)$_2$-CO_2Et

in MeOH at 25 °C. The reaction mixture was monitored by TLC until completion. The solvent was evaporated in vacuo and the residue poured into a large amount of water. The precipitate formed was collected by filtration and washed with water to give the target product.

G1-A_2-CO_2H: Starting from G1-A_2-CO_2Et (10.44 g, 20.0 mmol) in MeOH (150 mL) and aqueous KOH solution (40.0 mL, 2.0 M), the title compound was obtained as a white solid (7.51 g, 76 %). T_m 150 °C. $[\alpha]_D^{20} = -60.7$ ($c = 0.14$). SEC retention time: 17.31 min. ^{1}H NMR (CO_2H not observed): $\delta = 1.25$ (d, $J = 6.9$ Hz, 6H), 1.38 (s, 18H), 3.95–4.18 (m, 2H), 7.11 (d, $J = 6.9$ Hz, 2H), 7.91 (s, 2H), 8.18 (s, 1H), 10.12 ppm (s, 2H); ^{13}C NMR: $\delta = 18.8$, 29.2, 51.4, 79.0, 114.8, 115.9, 132.4, 140.5, 156.1, 168.0, 173.1 ppm; MS (FAB): m/z (%): 494 ([M]$^+$, 32); HRMS (L-SIMS): calcd for M^+: 494.2369; found: 494.2406; elemental analysis calcd (%) for $C_{23}H_{34}N_4O_8 \cdot H_2O$: C 53.90, H 7.08, N 10.93; found: C 53.21, H 6.79, N 10.82.

G1-F_2-CO_2H: Starting from G1-F_2-CO_2Et (13.48 g, 20.0 mmol) in MeOH (240 mL) and aqueous KOH solution (40.0 mL, 2.0 M), the title compound was obtained as a white solid (12.8 g, 99 %). T_m 160 °C. $[\alpha]_D^{20} = +8.8$ ($c = 0.19$). SEC retention time: 17.37 min. ^{1}H NMR (CO_2H not observed): $\delta = 1.32$ (s, 18H), 2.73–2.91 (m, 2H), 2.91–3.05 (m, 2H), 4.15–4.35 (m, 2H), 7.08–7.39 (m, 12H), 7.90 (s, 2H), 8.19 (s, 1H), 10.23 ppm (s, 2H); ^{13}C NMR: $\delta = 29.2$, 38.4, 57.8, 79.2, 114.6, 116.2, 127.4, 129.1, 130.3, 139.0, 140.3, 156.5, 168.2, 172.1 ppm; MS (FAB): m/z (%): 646 ([M]$^+$, 100); HRMS (L-SIMS): calcd for [M+H]$^+$: 647.3073; found: 647.3083; elemental analysis calcd (%) for $C_{35}H_{42}N_4O_8 \cdot 3H_2O$: C 59.99, H 6.90, N 7.99; found: C 60.38, H 6.50, N 7.81.

G1-V_2-CO_2H: Starting from G1-V_2-CO_2Et (11.56 g, 20.0 mmol) in MeOH (150 mL) and aqueous KOH solution (40.0 mL, 2.0 M), the title compound was obtained as a white solid (10.20 g, 93 %). T_m 152 °C. $[\alpha]_D^{20} = -56.9$ ($c = 0.063$). SEC retention time: 17.61 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.89$ (d, $J = 6.5$ Hz, 12H), 1.38 (s, 18H), 1.81–2.08 (m, 2H), 3.90 (t, $J = 7.9$ Hz, 2H), 6.92 (d, $J = 8.3$ Hz, 2H), 7.93 (s, 2H), 8.19 (s, 1H), 10.17 ppm (s, 2H); ^{13}C NMR: $\delta = 19.5$, 20.2, 29.2, 31.2, 61.7, 79.0, 114.9, 116.0, 132.5, 140.3, 156.6, 168.0, 172.0 ppm; MS (FAB): m/z (%): 589 ([M+K]$^+$, 3); HRMS (L-SIMS): calcd for M^+: 550.2995; found: 550.3022.

General procedure for the synthesis of G2-(aa^1)$_4$(aa^2)$_2$-CO_2Et: DCC (2.2 equiv) was added to a stirred mixture of G1-(aa^1)$_2$-CO_2H (2.2 equiv), (Cl^- H_3N^+-aa^2)$_2$-CO_2Et (1 equiv), 4-methylmorpholine (2 equiv),and HOBt (2.2 equiv) in DMF under a nitrogen atmosphere at −10 °C. The mixture was kept at −10 °C for 2 h and then at 25 °C for 48 h. The insoluble DCU produced was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in $CHCl_3$, and washed successively with saturated $NaHCO_3$ solution, 10 % citric acid solution, saturated $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give the target compound that was purified by flash chromatography on silica gel.

G2-A_4F_2-CO_2Et: Starting from G1-A_2-CO_2H (5.26 g, 10.7 mmol), (Cl^- H_3N^+-F)$_2$-CO_2Et (2.65 g, 4.8 mmol), 4-methylmorpholine (0.98 g, 9.7 mmol), HOBt (1.44 g, 10.7 mmol), and DCC (2.19 g, 10.7 mmol) in DMF (50 mL), the title compound was obtained as a white solid (6.37 g, 92 %) after flash chromatography (eluent: $CHCl_3$/MeOH 60/1 gradient to 30/1). T_m 182 °C. $[\alpha]_D^{20} = -52.6$ ($c = 0.33$). SEC retention time: 15.88 min. ^{1}H NMR: $\delta = 1.26$ (d, $J = 7.0$ Hz, 12H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.38 (s, 36H), 3.07–3.21 (m, 4H), 4.05–4.22 (m, 4H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.78–4.88 (m, 2H), 7.08 (d, $J = 7.0$ Hz, 4H), 7.15–7.49 (m, 10H), 7.66 (s, 4H), 7.97 (s, 2H), 8.11 (s, 2H), 8.29 (s, 1H), 8.67 (d, $J = 7.3$ Hz, 2H), 10.05 (s, 4H), 10.43 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.9, 29.1, 38.0, 51.3, 56.7, 61.8, 79.0, 113.9, 114.4, 115.4, 115.9, 127.3, 129.1, 130.1, 131.5, 136.4, 138.8, 140.1, 140.4, 156.1, 166.3, 167.7, 171.4, 173.0 ppm; MS (FAB): m/z (%): 1449.6 ([M+Na]$^+$, 9); HRMS (FAB): calcd for [M+Na]$^+$: 1449.6701; found: 1449.6664; elemental analysis calcd (%) for $C_{73}H_{94}N_{12}O_{18} \cdot 2H_2O$: C 59.91, H 6.75, N 11.48; found: C 59.67, H 6.69, N 11.18.

G2-A_4V_2-CO_2Et: Starting from G1-A_2-CO_2H (6.52 g, 13.2 mmol), (Cl^- H_3N^+-V)$_2$-CO_2Et (2.71 g, 6.0 mmol), 4-methylmorpholine (1.21 g, 12.0 mmol), HOBt (1.78 g, 13.2 mmol), and DCC (2.72 g, 13.2 mmol) in DMF (50 mL), the target product was obtained as a white solid (7.18 g, 90 %) after flash chromatography (eluent: $CHCl_3$/MeOH 35/1). T_m 181 °C. $[\alpha]_D^{20} = -74.8$ (c 0.88). SEC retention time: 16.04 min. ^{1}H NMR: $\delta = 0.97$ (d, $J = 6.5$ Hz, 6H), 0.99 (d, $J = 6.4$ Hz, 6H), 1.25 (d, $J = 7.1$ Hz, 12H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.37 (s, 36H), 2.12–2.24 (m, 2H), 4.07–4.16 (m, 4H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.40 (t, $J = 8.2$ Hz, 2H), 7.08 (d, $J = 7.2$ Hz, 4H), 7.68 (s, 4H), 8.00 (s, 2H), 8.18 (s, 2H), 8.31 (s, 1H), 8.36 (d, $J = 7.5$ Hz, 2H), 10.07 (s, 4H), 10.40 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.9, 19.8, 20.2, 29.1, 31.1, 51.4, 60.9, 61.8, 79.0, 113.7, 114.3, 115.2, 115.8, 131.6, 136.6, 140.2, 140.3, 156.1, 166.3, 168.0, 171.5, 173.0 ppm; MS (FAB): m/z (%): 1353.4 ([M+Na]$^+$, 16); HRMS (FAB): calcd for [M+Na]$^+$: 1353.6701; found: 1353.6671; elemental analysis calcd (%) for $C_{65}H_{94}N_{12}O_{18}$: C 58.63, H 7.12, N 12.62; found: C 58.43, H 7.11, N 12.42.

G2-F_4A_2-CO_2Et: Starting from G1-F_2-CO_2H (10.44 g, 16.2 mmol), ($Cl^-H_3N^+$-A)$_2$-CO_2Et (2.90 g, 7.4 mmol), 4-methylmorpholine (1.48 g, 14.7 mmol), HOBt (2.18 g, 16.2 mmol), and DCC (3.33 g, 16.2 mmol) in DMF (65 mL), the target compound was obtained as a white solid (10.8 g, 93 %) after flash chromatography (eluent: $CHCl_3$/MeOH 50/1). T_m 173 °C. $[\alpha]_D^{20} = +26.1$ ($c = 0.61$). SEC retention time: 16.00 min. ^{1}H NMR: $\delta = 1.29$–1.39 (m, 3H), 1.32 (s, 36H), 1.43 (d, $J = 6.9$ Hz, 6H), 2.68–2.90 (m, 4H), 2.90–3.08 (m, 4H), 4.16–4.39 (m, 6H), 4.51–4.65 (m, 2H), 7.10–7.38 (m, 24H), 7.73 (s, 4H), 8.00 (s, 2H), 8.19 (s, 2H), 8.33 (s, 1H), 8.64 (d, $J = 6.0$ Hz, 2H), 10.25 (s, 4H), 10.34 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.6, 29.1, 38.3, 50.9, 57.6, 61.8, 79.0, 113.9, 114.6, 115.2, 115.7, 127.2, 129.0, 130.2, 131.5, 136.5, 138.9, 140.1, 140.6, 156.3, 166.4, 167.6, 172.0, 172.6 ppm; MS (FAB): m/z (%): 1601.9 ([M+Na]$^+$, 13); HRMS (FAB): calcd for [M+Na]$^+$: 1601.7327; found: 1601.7351; elemental analysis calcd (%) for $C_{85}H_{102}N_{12}O_{18} \cdot H_2O$: C 63.90, H 6.56, N 10.52; found: C 63.56, H 6.47, N 10.41.

G2-F_4V_2-CO_2Et: Starting from G1-F_2-CO_2H (4.64 g, 7.2 mmol), ($Cl^-H_3N^+$-V)$_2$-CO_2Et (1.47 g, 3.3 mmol), 4-methylmorpholine (0.66 g, 6.5 mmol), HOBt (0.97 g, 7.2 mmol), and DCC (1.48 g, 7.2 mmol) in DMF (35 mL), the title compound was obtained as a white solid (5.29 g, 84 %) after flash chromatography (eluent: $CHCl_3$/MeOH 80/1 gradient to 60/1). T_m 182 °C. $[\alpha]_D^{20} = -0.6$ ($c = 0.49$). SEC retention time: 16.05 min. ^{1}H NMR: $\delta = 0.99$ (d, $J = 6.7$ Hz, 6H), 1.01 (d, $J = 6.6$ Hz, 6H), 1.26–1.38 (m, 3H), 1.32 (s, 36H), 2.10–2.28 (m, 2H), 2.72–2.91 (m, 4H), 2.91–3.07 (m, 4H), 4.21–4.47 (m, 8H), 7.12–7.37 (m, 24H), 7.71 (s, 4H), 8.02 (s, 2H), 8.20 (s, 2H), 8.34 (s, 1H), 8.41 (d, $J = 7.7$ Hz, 2H), 10.24 (s, 4H), 10.43 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 19.9, 20.2, 29.1, 31.2, 38.3, 57.6, 60.9, 61.9, 79.0, 113.8, 114.5, 115.2, 115.8, 127.2, 129.0, 130.2, 131.6, 136.7, 138.9, 140.1, 140.4, 156.3, 166.4, 168.0, 171.5, 172.0 ppm; MS (FAB): m/z (%): 1657.8 ([M+Na]$^+$, 7); HRMS (FAB): calcd for [M+Na]$^+$: 1657.7953; found: 1657.8028.

G2-V_4A_2-CO_2Et: Starting from G1-V_2-CO_2H (3.63 g, 6.6 mmol), ($Cl^-H_3N^+$-A)$_2$-CO_2Et (1.19 g, 3.0 mmol), 4-methylmorpholine (0.61 g, 6.0 mmol), HOBt (0.89 g, 6.6 mmol), and DCC (1.36 g, 6.6 mmol) in DMF (40 mL), the target compound was obtained as a white solid (3.63 g, 87 %) after flash chromatography (eluent: $CHCl_3$/MeOH 45/1). T_m 185 °C. $[\alpha]_D^{20} = -19.6$ ($c = 0.44$). SEC retention time: 16.28 min. ^{1}H NMR: $\delta = 0.90$ (d, $J = 6.4$ Hz, 24H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.38 (s, 36H), 1.42 (d, $J = 7.3$ Hz, 6H), 1.88–2.11 (m, 4H), 3.93 (t, $J = 7.9$ Hz, 4H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.52–4.61 (m, 2H), 6.88 (d, $J = 8.4$ Hz, 4H), 7.72 (s, 4H), 7.97 (s, 2H), 8.17 (s, 2H), 8.31 (s, 1H), 8.61 (d, $J = 6.3$ Hz, 2H), 10.11 (s, 4H), 10.32 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.6, 19.4, 20.2, 29.1, 31.2, 50.9, 61.6, 61.8, 79.0, 113.9, 114.6, 115.3, 115.7, 131.5, 136.5, 139.9, 140.6, 156.5, 166.4, 167.6, 171.9, 172.6 ppm; MS (FAB): m/z (%): 1409.4 ([M+Na]$^+$, 25); HRMS (FAB): calcd for [M+Na]$^+$: 1409.7327; found: 1409.7407; elemental analysis calcd (%) for $C_{69}H_{102}N_{12}O_{18} \cdot 2H_2O$: C 58.21, H 7.50, N 11.81; found: C 58.36, H 7.33, N 11.77.

G2-V_4F_2-CO_2Et: Starting from G1-V_2-CO_2H (3.63 g, 6.6 mmol), ($Cl^-H_3N^+$-F)$_2$-CO_2Et (1.64 g, 3.0 mmol), 4-methylmorpholine (0.61 g, 6.6 mmol), HOBt (0.89 g, 6.6 mmol), and DCC (1.36 g, 6.6 mmol) in DMF (35 mL), the title compound was obtained as a white solid (3.18 g, 69 %) after flash chromatography (eluent: $CHCl_3$/MeOH 80/1 gradient to 60/1). T_m 191 °C. $[\alpha]_D^{20} = +13.3$ ($c = 0.40$). SEC retention time: 16.19 min. ^{1}H NMR: $\delta = 0.90$ (d, $J = 6.1$ Hz, 24H), 1.38 (s, 36H), 1.38 (m, 3H), 1.90–2.08 (m, 4H), 3.05–3.21 (m, 4H), 3.93 (t, $J = 7.4$ Hz, 4H), 4.32 (q, $J =$

6.7 Hz, 2H), 4.77–4.88 (m, 2H), 6.90 (d, J=8.2 Hz, 4H), 7.14–7.42 (m, 10H), 7.68 (s, 4H), 7.97 (s, 2H), 8.12 (s, 2H), 8.31 (s, 1H), 8.69 (d, J= 7.0 Hz, 2H), 10.10 (s, 4H), 10.44 ppm (s, 2H); ^{13}C NMR: δ=15.1, 19.4, 20.2, 29.1, 31.3, 38.1, 56.7, 61.5, 61.8, 79.0, 114.0, 114.6, 115.4, 115.9, 127.3, 129.1, 130.2, 131.5, 136.5, 138.8, 139.9, 140.4, 156.5, 166.4, 167.7, 171.4, 171.9 ppm; MS (FAB): m/z (%): 1561.8 ([M+Na]$^+$, 10); HRMS (FAB): calcd for [M+Na]$^+$: 1561.7953; found: 1561.7960; elemental analysis calcd (%) for $C_{81}H_{110}N_{12}O_{18}\cdot 2H_2O$: C 61.74, H 7.29, N 10.67; found: C 61.98, H 7.25, N 10.60.

General procedure for the synthesis of G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$H: An aqueous KOH solution (2.0 M) was added to a solution of G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$Et in MeOH or in a 1/1 mixture of MeOH and THF. The reaction mixture was stirred at 25 °C until completion of reaction as monitored by TLC. The solvent was evaporated in vacuo and the residue poured into water. The precipitate formed was collected by filtration and washed with water.

G2-A$_4$F$_2$-CO$_2$H: Starting from G2-A$_4$F$_2$-CO$_2$Et (2.85 g, 2.0 mmol) in MeOH (40 mL) and aqueous KOH solution (6.0 mL, 2.0 M), the title compound was obtained as a white solid (2.57 g, 92 %). T_m 176 °C. $[\alpha]_D^{20}$= −73.5 (c=0.41). SEC retention time: 15.85 min. ^{1}H NMR (CO$_2$H not observed): δ=1.26 (d, J=7.0 Hz, 12H), 1.38 (s, 36H), 3.06–3.16 (m, 4H), 4.05–4.16 (m, 4H), 4.76–4.88 (m, 2H), 7.09 (d, J=7.1 Hz, 4H), 7.15–7.41 (m, 10H), 7.66 (s, 4H), 7.95 (s, 2H), 8.12 (s, 2H), 8.23 (s, 1H), 8.40 (d, J=7.7 Hz, 2H), 10.05 (s, 4H), 10.38 ppm (s, 2H); ^{13}C NMR: δ=18.9, 29.1, 38.1, 51.3, 56.7, 78.9, 113.9, 114.4, 115.0, 116.2, 127.3, 129.1, 130.1, 136.4, 138.8, 140.1, 140.2, 156.1, 167.7, 171.3, 173.0 ppm; MS (FAB): m/z (%): 1421.3 ([M+Na]$^+$, 8); HRMS (FAB): calcd for [M+Na]$^+$: 1421.6388; found: 1421.6438.

G2-A$_4$V$_2$-CO$_2$H: Starting from G2-A$_4$V$_2$-CO$_2$Et (4.00 g, 3.0 mmol) in MeOH (55 mL) and aqueous KOH solution (9.0 mL, 2.0 M), the target compound was obtained as a white solid (3.47 g, 89 %). T_m 180 °C. $[\alpha]_D^{20}$= −58.9 (c=0.42). SEC retention time: 15.83 min. ^{1}H NMR (CO$_2$H not observed): δ=0.97 (d, J=6.2 Hz, 6H), 0.99 (t, J=6.1 Hz, 6H), 1.25 (d, J= 7.0 Hz, 12H), 1.37 (s, 36H), 2.13–2.24 (m, 2H), 3.95–4.19 (m, 4H), 4.40 (t, J=8.1 Hz, 2H), 7.08 (d, J=7.1 Hz, 4H), 7.68 (s, 4H), 7.97 (s, 2H), 8.18 (s, 2H), 8.25 (s, 1H), 8.36 (d, J=7.5 Hz, 2H), 10.08 (s, 4H), 10.35 ppm (s, 2H); ^{13}C NMR: δ=18.9, 19.9, 20.2, 29.2, 31.2, 51.4, 60.9, 79.0, 113.7, 114.4, 115.0, 116.2, 132.8, 136.6, 140.2, 156.1, 168.0, 171.4, 173.0 ppm; MS (FAB): m/z (%): 1325.5 ([M+Na]$^+$, 7); HRMS (FAB): calcd for [M+Na]$^+$: 1325.6388; found: 1325.6381.

G2-F$_4$A$_2$-CO$_2$H: Starting from G2-F$_4$A$_2$-CO$_2$Et (4.00 g, 2.5 mmol) in a 1/1 mixture of THF/MeOH (40 mL) and aqueous KOH solution (5.1 mL, 2.0 M), the target compound was obtained as a white solid (3.29 g, 84 %). T_m 173 °C. $[\alpha]_D^{20}$= +141.7 (c=0.34). SEC retention time: 15.89 min. ^{1}H NMR (CO$_2$H not observed): δ=1.31 (s, 36H), 1.43 (d, J=6.7 Hz, 6H), 2.71–2.93 (m, 4H), 2.93–3.08 (m, 4H), 4.16–4.39 (m, 4H), 4.58–4.67 (m, 2H), 7.12–7.37 (m, 24H), 7.74 (s, 4H), 7.91 (s, 2H), 8.20 (s, 2H), 8.23 (s, 1H), 8.60 (d, J=5.6 Hz, 2H), 10.21 (s, 2H), 10.26 ppm (s, 4H); ^{13}C NMR: δ=18.8, 29.1, 38.3, 50.9, 57.6, 79.0, 113.8, 114.1, 114.6, 116.4, 127.2, 129.0, 130.2, 136.5, 138.9, 140.0, 140.1, 156.3, 167.5, 172.0, 172.3 ppm; MS (FAB): m/z (%): 1574.1 ([M+Na]$^+$, 2); HRMS (FAB): calcd for [M+Na]$^+$: 1573.7014; found: 1573.6979; elemental analysis calcd (%) for $C_{83}H_{98}N_{12}O_{18}\cdot 3H_2O$: C 62.08, H 6.53, N 10.47; found: C 62.24, H 6.27, N 10.38.

G2-F$_4$V$_2$-CO$_2$H: Starting from G2-F$_4$V$_2$-CO$_2$Et (3.78 g, 2.3 mmol) in a 1/1 mixture of THF/MeOH (70 mL) and aqueous KOH solution (4.6 mL, 2.0 M), the target compound was obtained as a white solid (3.39 g, 91 %). T_m 165 °C. $[\alpha]_D^{20}$= −48.4 (c=0.56). SEC retention time: 15.88 min. ^{1}H NMR (CO$_2$H not observed): δ=0.99 (d, J=6.1 Hz, 6H), 1.01 (d, J= 5.9 Hz, 6H), 1.31 (s, 36H), 2.15–2.26 (m, 2H), 2.74–2.91 (m, 4H), 2.91–3.05 (m, 4H), 4.19–4.48 (m, 6H), 7.12–7.38 (24H, m), 7.72 (s, 4H), 7.99 (s, 2H), 8.22 (s, 2H), 8.26 (s, 1H), 8.40 (d, J=6.9 Hz, 2H), 10.26 (s, 4H), 10.35 ppm (s, 2H); ^{13}C NMR: δ=19.5, 19.8, 28.7, 30.8, 37.9, 57.2, 60.5, 78.6, 113.3, 114.1, 115.9, 126.8, 128.6, 129.7, 136.2, 138.5, 139.5, 139.6, 155.9, 167.5, 170.9, 171.6 ppm; MS (FAB): m/z (%): 1629.9 ([M+Na]$^+$, 5); HRMS (FAB): calcd for [M+Na]$^+$: 1629.7640; found: 1629.7673.

G2-V$_4$A$_2$-CO$_2$H: Starting from G2-V$_4$A$_2$-CO$_2$Et (2.07 g, 1.5 mmol) in MeOH (20 mL) and aqueous KOH solution (3.0 mL, 2.0 M), the target compound was obtained as a white solid (1.84 g, 91 %). T_m 186 °C. $[\alpha]_D^{20}$= −1.8 (c=0.39). SEC retention time: 15.99 min. ^{1}H NMR (CO$_2$H not observed): δ=0.89 (d, J=6.5 Hz, 24H), 1.38 (s, 36H) 1.42 (m, 6H), 1.92–2.05 (m, 4H), 3.93 (t, J=7.9 Hz, 4H), 4.53–4.62 (m, 2H), 6.88 (d, J= 8.5 Hz, 4H), 7.73 (s, 4H), 7.90 (s, 2H), 8.19 (s, 3H), 8.57 (d, J=6.1 Hz, 2H), 10.13 (s, 4H), 10.16 ppm (s, 2H); ^{13}C NMR: δ=18.8, 19.4, 20.1, 29.1, 31.2, 50.8, 61.5, 79.0, 113.8, 114.5, 116.5, 136.5, 139.7, 139.9, 156.4, 167.5, 171.8, 172.2 ppm; MS (FAB): m/z (%): 1381.5 ([M+Na]$^+$, 5); HRMS (FAB): calcd for [M+Na]$^+$: 1381.7014; found: 1381.7062.

G2-V$_4$F$_2$-CO$_2$H: Starting from G2-V$_4$F$_2$-CO$_2$Et (4.64 g, 3.02 mmol) in a 1/1 mixture of THF/MeOH (40 mL) and aqueous KOH solution (8.0 mL, 2.0 M), the title compound was obtained as a white solid (4.01 g, 88 %). T_m 174 °C. $[\alpha]_D^{20}$= +45.1 (c=0.41). SEC retention time: 16.08 min. ^{1}H NMR (CO$_2$H not observed): δ=0.90 (d, J=6.6 Hz, 24H), 1.38 (s, 36H), 1.90–2.08 (m, 4H), 3.06–3.23 (m, 4H), 3.93 (t, J=8.0 Hz, 4H), 4.83 (q, J=8.3 Hz, 2H), 6.90 (d, J=8.4 Hz, 4H), 7.15–7.41 (m, 10H), 7.68 (s, 4H), 7.95 (s, 2H), 8.12 (s, 2H), 8.24 (s, 1H), 8.70 (d, J=7.4 Hz, 2H), 10.10 (s, 4H), 10.39 ppm (s, 2H); ^{13}C NMR: δ=19.5, 20.3, 29.2, 31.3, 38.2, 56.8, 61.6, 79.1, 114.1, 114.7, 115.2, 116.3, 127.4, 129.2, 130.3, 136.6, 139.0, 140.0, 140.3, 156.6, 167.8, 171.4, 172.0 ppm; MS (FAB): m/z (%): 1533.7 ([M+Na]$^+$, 7); HRMS (FAB): calcd for [M+Na]$^+$: 1533.7640; found: 1533.7603.

General procedure for the synthesis of G3-(aa^1)$_8$(aa^2)$_4$(aa^3)$_2$-CO$_2$Et: EDCI (2.2 equiv) was added to a stirred mixture of G2-(aa^1)$_4$(aa^2)$_2$-CO$_2$H (2.2 equivalent), (Cl$^-$ H$_3$N$^+$-aa^3)$_2$-CO$_2$Et (1 equiv), 4-methylmorpholine (2 equiv), and HOBt (2.2 equiv) in DMF under nitrogen at −10 °C. The mixture was kept at −10 °C for 2 h and then at 25 °C for 60 h. The insoluble precipitate produced was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in $CHCl_3$, and washed successively with saturated $NaHCO_3$ solution, 10 % citric acid solution, saturated $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give the target compound that was purified by flash chromatography on silica gel.

G3-A$_8$F$_4$V$_2$-CO$_2$Et: Starting from G2-A$_4$F$_2$-CO$_2$H (1.25 g, 0.89 mmol), (Cl$^-$ H$_3$N$^+$-V)$_2$-CO$_2$Et (0.17 g, 0.37 mmol), 4-methylmorpholine (0.075 g, 0.75 mmol), HOBt (0.12 g, 0.89 mmol), and EDCI (0.27 g, 0.89 mmol) in DMF (10 mL), the product was obtained as a white solid (0.71 g, 61 %) after flash chromatography (eluent: CHCl$_3$/MeOH = 60/1 gradient to 40/1). T_m 186 °C. $[\alpha]_D^{20}$= −121.4 (c=0.36). SEC retention time: 14.61 min. ^{1}H NMR: δ=0.98 (d, J=7.6 Hz, 6H), 1.00 (d, J=7.2 Hz, 6H), 1.25 (d, J=6.8 HZ, 24H), 1.29–1.38 (m, 3H), 1.37 (s, 72H), 2.11–2.30 (m, 2H), 3.02–3.22 (m, 8H), 3.95–4.18 (m, 8H), 4.28 (q, J=7.0 Hz, 2H), 4.38 (t, J=7.4 Hz, 2H), 4.78–4.92 (m, 4H), 7.08 (d, J=6.8 Hz, 8H), 7.39–7.18 (m, 20H), 7.66 (s, 8H), 7.76 (s, 4H), 8.04 (s, 2H), 8.16 (s, 4H), 8.24 (s, 3H), 8.41 (br. s, 2H), 8.67 (br. s, 4H), 10.05 (s, 8H), 10.39 ppm (s, 6H); ^{13}C NMR: δ=15.1, 18.9, 20.0, 20.2, 29.2, 31.2, 38.1, 51.4, 56.7, 61.0, 61.8, 79.0, 113.9, 114.4, 114.7, 115.2, 115.9, 127.3, 129.1, 130.2, 131.6, 136.5, 136.7, 138.9, 140.1, 140.4, 156.1, 166.4, 167.7, 168.0, 171.4, 171.5, 173.0 ppm.

G3-A$_8$V$_4$F$_2$-CO$_2$Et: Starting from G2-A$_4$V$_2$-CO$_2$H (2.50 g, 1.92 mmol), (Cl$^-$ H$_3$N$^+$-F)$_2$-CO$_2$Et (0.48 g, 1.15 mmol), 4-methylmorpholine (0.18 g, 1.15 mmol), HOBt (0.26 g, 1.92 mmol), and EDCI (0.57 g, 1.92 mmol) in DMF (24 mL), the target compound was obtained as a white solid (1.25 g, 47 %) after flash chromatography (eluent: CHCl$_3$/MeOH 60/1). T_m 183 °C. $[\alpha]_D^{20}$= −35.3 (c=0.48). SEC retention time: 14.68 min. ^{1}H NMR: δ=0.97 (d, J=5.6 Hz, 12H), 0.99 (d, J=5.6 Hz, 12H), 1.25 (d, J=6.9 Hz, 24H), 1.27–1.31 (m, 3H), 1.36 (s, 72H), 2.13–2.25 (m, 4H), 3.05–3.21 (m, 4H), 3.92–4.18 (m, 8H), 4.33 (q, J=7.0 Hz, 2H), 4.43 (t, J=7.7 Hz, 4H), 4.78–4.95 (m, 2H), 7.07 (d, J=6.9 Hz, 8H), 7.14–7.38 (m, 10H), 7.69 (s, 8H), 7.73 (s, 4H), 7.99 (s, 2H), 8.18 (s, 7H), 8.34 (br. s, 4H), 8.71 (d, J=6.2 Hz, 2H), 10.07 (s, 8H), 10.30 (s, 4H), 10.41 ppm (s, 2H); ^{13}C NMR: δ=15.1, 18.9, 19.9, 20.2, 29.2, 31.2, 38.1, 51.4, 56.7, 61.0, 61.8, 79.0, 113.7, 114.35, 114.79, 115.3, 115.9, 127.3, 129.1, 130.1, 131.5, 136.5, 136.6, 138.8, 139.9, 140.2, 140.4, 156.1, 166.4, 167.7, 168.0, 171.4, 173.0 ppm; elemental analysis calcd (%) for $C_{153}H_{206}N_{28}O_{38}\cdot 6H_2O$: C 58.27, H 6.97, N 12.44; found: C 58.35, H 6.73, N 12.19.

G3-F$_8$A$_4$V$_2$-CO$_2$Et: Starting form G2-F$_4$A$_2$-CO$_2$H (2.50 g, 1.61 mmol), (Cl$^-$ H$_3$N$^+$-V)$_2$-CO$_2$Et (0.30 g, 0.67 mmol), 4-methylmorpholine (0.14 g,

1.34 mmol), HOBt (0.22 g, 1.61 mmol), and EDCI (0.48 g, 1.61 mmol) in DMF (25 mL), the title compound was obtained as a white solid (0.93 g, 40%) after flash chromatography (eluent: $CHCl_3$/MeOH 60/1 gradient to 50/1). T_m 190°C. $[\alpha]_D^{20} = -81.9$ ($c = 0.37$). SEC retention time: 14.63 min. ^{1}H NMR: $\delta = 0.96$ (d, $J = 6.9$ Hz, 6H), 0.99 (d, $J = 6.8$ Hz, 6H), 1.22–1.30 (m, 3H), 1.30 (s, 72H), 1.43 (d, $J = 6.8$ Hz, 12H), 2.10–2.25 (m, 2H), 2.72–2.88 (m, 8H), 2.88–3.05 (m, 8H), 4.18–4.49 (m, 12H), 4.58–4.69 (m, 4H), 7.10–7.36 (m, 48H), 7.72 (s, 8H), 7.75 (s, 4H), 8.04 (s, 2H), 8.19 (s, 4H), 8.22 (s, 1H), 8.27 (s, 2H), 8.41 (d, $J = 7.3$ Hz, 2H), 8.62 (br. s, 4H), 10.23 (s, 8H), 10.26 (s, 4H), 10.40 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.7, 20.0, 20.2, 29.1, 31.2, 38.3, 50.8, 57.6, 61.0, 61.8, 79.0, 113.8, 114.6, 115.1, 115.8, 127.2, 129.0, 130.2, 131.6, 136.5, 136.6, 138.9, 140.0, 140.2, 140.3, 156.3, 166.3, 167.6, 168.0, 171.5, 172.0, 172.5 ppm; elemental analysis calcd (%) for $C_{185}H_{222}N_{28}O_{38}\cdot 5H_2O$: C 62.84, H 6.61, N 11.09; found: C 62.58, H 6.40, N 10.89.

G3-$F_8V_4A_2$-CO_2Et: Starting form G2-F_4V_2-CO_2H (2.09 g, 1.30 mmol), (Cl^- H_3N^+-A)$_2$-CO_2Et (0.20 g, 0.50 mmol), 4-methylmorpholine (0.10 g, 1.00 mmol), HOBt (0.18 g, 1.30 mmol), and EDCI (0.39 g, 1.30 mmol) in DMF (20 mL), the target compound was obtained as a white solid (0.67 g, 38%) after flash chromatography (eluent: $CHCl_3$/MeOH 80/1 gradient to 60/1). T_m 186°C. $[\alpha]_D^{20} = +23.4$ ($c = 0.51$). SEC retention time: 14.68 min. ^{1}H NMR: $\delta = 0.95$–1.08 (m, 24H), 1.22–1.32 (m, 3H), 1.30 (s, 72H), 1.41 (d, $J = 6.6$ Hz, 6H), 2.14–2.27 (m, 4H), 2.76–2.90 (m, 8H), 2.90–3.04 (m, 8H), 4.18–4.40 (10H, m), 4.40–4.49 (m, 4H), 4.49–4.68 (m, 2H), 7.12–7.37 (48H, m), 7.71 (s, 8H), 7.79 (s, 4H), 8.02 (s, 2H), 8.20 (s, 4H), 8.24 (s, 3H), 8.39 (4H, br. s), 8.64 (2H, br. s), 10.25 (s, 8H), 10.32 (s, 2H), 10.34 ppm (s, 4H); ^{13}C NMR: $\delta = 15.1$, 18.7, 19.9, 20.2, 29.1, 31.2, 38.3, 50.9, 57.6, 60.9, 61.8, 79.0, 113.7, 114.1, 114.5, 114.8, 115.7, 127.2, 129.0, 130.2, 131.5, 136.6, 136.7, 138.9, 139.9, 140.1, 140.6, 156.3, 166.4, 167.6, 167.9, 171.4, 172.0, 172.6 ppm; elemental analysis calcd (%) for $C_{189}H_{230}N_{28}O_{38}\cdot 7H_2O$: C 62.57, H 6.78, N 10.81; found: C 62.33, H 6.52, N 10.52.

G3-$V_8A_4F_2$-CO_2Et: Starting from G2-V_4A_2-CO_2H (2.50 g, 1.84 mmol), (Cl^- H_3N^+-F)$_2$-CO_2Et (0.42 g, 0.77 mmol), 4-methylmorpholine (0.15 g, 1.53 mmol), HOBt (0.25 g, 1.84 mmol), and EDCI (0.55 g, 1.84 mmol) in DMF (20 mL), the product was obtained as a white solid (1.50 g, 62%) after flash chromatography (eluent: $CHCl_3$/MeOH 100/1 gradient to 40/1). T_m 196°C. $[\alpha]_D^{20} = -104.5$ ($c = 0.36$). SEC retention time: 14.93 min. ^{1}H NMR: $\delta = 0.89$ (d, $J = 6.2$ Hz, 48H), 1.29–1.38 (m, 3H), 1.37 (s, 72H), 1.42 (m, 12H), 1.89–2.08 (m, 8H), 3.03–3.22 (m, 4H), 3.92 (t, $J = 7.6$ Hz, 8H), 4.31 (q, $J = 7.0$ Hz, 2H), 4.54–4.70 (m, 4H), 4.78–4.88 (m, 2H), 6.88 (d, $J = 8.3$ Hz, 8H), 7.16–7.38 (m, 10H), 7.70 (s, 4H), 7.72 (s, 8H), 8.00 (s, 2H), 8.17 (s, 4H), 8.21 (s, 3H), 8.60 (d, $J = 5.3$ Hz, 4H), 8.69 (d, $J = 6.2$ Hz, 2H), 10.11 (s, 8H), 10.22 (s, 4H), 10.42 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.7, 19.4, 20.2, 29.1, 31.3, 38.1, 50.8, 56.7, 61.6, 61.8, 79.0, 113.8, 114.2, 114.6, 115.3, 115.9, 127.3, 129.1, 130.1, 131.5, 136.4, 136.6, 138.8, 139.9, 140.1, 140.4, 156.5, 166.4, 167.6, 167.7, 171.4, 171.9, 172.5 ppm.

G3-$V_8F_4A_2$-CO_2Et: Starting from G2-V_4F_2-CO_2H (4.01 g, 2.66 mmol), ($Cl^-H_3N^+$-A)$_2$-CO_2Et (0.44 g, 1.11 mmol), 4-methylmorpholine (0.22 g, 2.22 mmol), HOBt (0.36 g, 2.66 mmol), and EDCI (0.79 g, 2.66 mmol) in DMF (80 mL), the product was obtained as a white solid (1.95 g, 53%) after flash chromatography (eluent: $CHCl_3$/MeOH 80/1 gradient to 40/1). T_m 193°C. $[\alpha]_D^{20} = -17.5$ ($c = 0.32$). SEC retention time: 14.91 min. ^{1}H NMR: $\delta = 0.89$ (d, $J = 6.5$ Hz, 48H), 1.27–1.39 (m, 3H), 1.37 (s, 72H), 1.42 (d, $J = 6.6$ Hz, 6H), 1.87–2.08 (m, 8H), 3.04–3.20 (m, 8H), 3.92 (t, $J = 7.7$ Hz, 8H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.51–4.66 (m, 2H), 4.80–4.88 (m, 4H), 6.89 (d, $J = 8.4$ Hz, 8H), 7.13–7.42 (m, 20H), 7.67 (s, 8H), 7.76 (s, 4H), 8.02 (s, 2H), 8.11 (s, 4H), 8.22 (s, 3H), 8.65–8.68 (m, 6H), 10.10 (s, 8H), 10.31 (s, 4H), 10.38 ppm (s, 2H); ^{13}C NMR: $\delta = 15.1$, 18.7, 19.4, 20.2, 29.1, 31.2, 38.1, 50.9, 56.7, 61.6, 61.8, 79.0, 114.0, 114.6, 114.8, 115.7, 127.3, 129.1, 130.2, 131.5, 136.5, 138.9, 139.9, 140.6, 156.5, 166.4, 167.6, 167.7, 171.3, 171.9, 172.6 ppm.

General procedure for the synthesis of G3-(aa^1)$_8$(aa^2)$_4$(aa^3)$_2$-CO_2H: An aqueous KOH solution (2.0 M) was added to a solution of G3-(aa^1)$_8$(aa^2)$_4$-(aa^3)$_2$-CO_2Et in a mixture of MeOH and THF. The reaction mixture was stirred at 25°C until the reaction went to completion as monitored by TLC. The solvent was evaporated in vacuo and the residue poured into water. The precipitate formed was collected by filtration and washed with water.

G3-$A_8F_4V_2$-CO_2H: Starting from G3-$A_8F_4V_2$-CO_2Et (0.47 g, 0.15 mmol) in a 2/1 mixture of THF/MeOH (20 mL) and aqueous KOH solution (2.0 mL, 2.0 M), the product was obtained as a white solid (0.34 g, 72%). T_m 182°C. $[\alpha]_D^{20} = -89.6$ ($c = 0.21$). SEC retention time: 14.70 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.98$ (d, $J = 6.5$ Hz, 6H), 1.00 (d, $J = 6.3$ Hz, 6H), 1.25 (d, $J = 6.7$ Hz, 24H), 1.37 (s, 72H), 2.08–2.25 (m, 2H), 3.00–3.20 (m, 8H), 3.91–4.21 (m, 8H), 4.33–4.48 (m, 2H), 4.78–4.95 (m, 4H), 7.08 (d, $J = 6.4$ Hz, 8H), 7.38–7.17 (m, 20H), 7.66 (s, 8H), 7.75 (s, 4H), 8.00 (s, 2H), 8.12 (s, 4H), 8.18 (s, 1H), 8.24 (s, 2H), 8.42 (br. s, 2H), 8.68 (br. s, 4H), 10.06 (s, 8H), 10.33 (s, 2H), 10.39 ppm (s, 4H); ^{13}C NMR: $\delta = 18.9$, 20.0, 20.2, 29.2, 31.2, 38.1, 51.4, 56.7, 61.0, 79.0, 113.9, 114.5, 114.7, 116.4, 127.3, 129.1, 130.2, 136.5, 136.7, 138.9, 140.1, 156.1, 167.7, 168.0, 171.4, 173.0 ppm.

G3-$A_8V_4F_2$-CO_2H: Starting from G3-$A_8V_4F_2$-CO_2Et (1.00 g, 0.38 mmol) in a 1/1 mixture of THF/MeOH (30 mL) and aqueous KOH solution (4.0 mL, 2.0 M), the target compound was obtained as a white solid (0.78 g, 79%). T_m 178°C. $[\alpha]_D^{20} = -39.5$ ($c = 0.68$). SEC retention time: 14.67 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.98$ (d, $J = 5.7$ Hz, 12H), 1.00 (d, $J = 3.9$ Hz, 12H), 1.25 (d, $J = 6.9$ Hz, 24H), 1.36 (s, 72H), 2.09–2.28 (m, 4H), 3.02–3.20 (m, 4H), 3.90–4.19 (m, 8H), 4.43 (t, $J = 7.5$ Hz, 4H), 4.78–4.88 (m, 2H), 7.08 (d, $J = 6.9$ Hz, 8H), 7.12–7.41 (m, 10H), 7.69 (s, 8H), 7.72 (s, 4H), 7.98 (s, 2H), 8.19 (s, 7H), 8.35 (d, $J = 5.9$ Hz, 4H), 8.72 (d, $J = 6.0$ Hz, 2H), 10.08 (s, 8H), 10.30 (s, 4H), 10.37 ppm (s, 2H); ^{13}C NMR: $\delta = 18.9$, 19.9, 20.2, 29.2, 31.2, 38.1, 51.4, 56.8, 60.9, 79.0, 113.7, 114.4, 114.8, 116.3, 127.3, 129.1, 130.1, 136.55, 136.64, 138.8, 139.8, 140.2, 156.1, 167.7, 168.0, 171.4, 173.0 ppm; elemental analysis calcd (%) for $C_{151}H_{202}N_{28}O_{38}\cdot 5H_2O$: C 58.36, H 6.88, N 12.62; found: C 58.61, H 6.76, N 12.55.

G3-$F_8A_4V_2$-CO_2H: Starting from G3-$F_8A_4V_2$-CO_2Et (0.64 g, 0.19 mmol) in a 1/1 mixture of THF/MeOH (20 mL) and aqueous KOH solution (2.0 mL, 2.0 M), the target product was obtained as a white solid (0.55 g, 87%). T_m 185°C. $[\alpha]_D^{20} = -69.1$ ($c = 0.35$). SEC retention time: 14.74 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.98$ (d, $J = 5.9$ Hz, 12H) 1.31 (s, 72H), 1.44 (d, $J = 6.5$ Hz, 12H), 2.13–2.22 (m, 2H), 2.75–2.91 (m, 8H), 2.91–3.09 (m, 8H), 4.19–4.40 (m, 8H), 4.40–4.48 (m, 2H), 4.58–4.71 (m, 4H), 7.16–7.37 (m, 48H), 7.78 (s, 8H), 7.79 (s, 4H), 7.89 (s, 2H), 8.23 (s, 7H), 8.36 (br. s, 2H), 8.65 (br. s, 4H), 10.05 (s, 2H), 10.29 (s, 4H), 10.36 ppm (s, 8H); ^{13}C NMR: $\delta = 18.9$, 19.9, 20.3, 29.1, 31.4, 38.3, 50.7, 57.7, 61.1, 79.0, 113.9, 114.7, 117.2, 127.2, 129.0, 130.2, 136.4, 136.7, 138.9, 140.1, 140.2, 156.3, 167.5, 167.8, 170.9, 172.0, 172.4 ppm.

G3-$F_8V_4A_2$-CO_2H: Starting from G3-$F_8V_4A_2$-CO_2Et (1.00 g, 0.29 mmol) in a 3/1 mixture of THF/MeOH (20 mL) and aqueous KOH solution (3.0 mL, 2.0 M), the title compound was obtained as a white solid (0.78 g, 79%). T_m 187°C. $[\alpha]_D^{20} = +34.0$ ($c = 0.47$). SEC retention time: 14.73 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.89$–0.99 (m, 24H), 1.30 (s, 72H), 1.41 (d, $J = 6.8$ Hz, 6H), 2.13–2.28 (m, 4H), 2.75–2.92 (m, 8H), 2.92–3.09 (m, 8H), 4.18–4.36 (m, 8H), 4.36–4.49 (m, 4H), 4.49–4.59 (m, 2H), 7.11–7.36 (m, 48H), 7.71 (s, 8H), 7.78 (s, 4H), 8.00 (s, 2H), 8.20 (s, 4H), 8.25 (s, 3H), 8.37 (br. s, 4H), 8.63 (d, $J = 5.5$ Hz, 2H), 10.30 (s, 10H), 10.34 ppm (s, 4H); ^{13}C NMR: $\delta = 18.7$, 19.9, 20.2, 29.1, 31.2, 38.3, 50.9, 57.6, 60.9, 79.1, 113.8, 114.1, 114.5, 114.8, 116.1, 127.3, 129.0, 130.2, 136.7, 138.9, 139.9, 140.1, 140.4, 156.4, 167.7, 167.9, 171.4, 172.0, 172.6 ppm; elemental analysis calcd (%) for $C_{187}H_{226}N_{28}O_{38}\cdot 7H_2O$: C 62.39, H 6.72, N 10.89; found: C 62.23, H 6.43, N 10.85.

G3-$V_8A_4F_2$-CO_2H: Starting from G3-$V_8A_4F_2$-CO_2Et (1.21 g, 0.38 mmol) in a 1/1 mixture of THF/MeOH (15 mL) and aqueous KOH solution (0.6 mL, 2.0 M), the title compound was obtained as a white solid (1.01 g, 84%). T_m 186°C. $[\alpha]_D^{20} = -66.1$ ($c = 0.42$). SEC retention time: 14.83 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.89$ (d, $J = 6.4$ Hz, 48H), 1.37 (s, 72H), 1.42 (d, $J = 7.0$ Hz, 12H), 1.83–2.05 (m, 8H), 2.98–3.19 (m, 4H), 3.92 (t, $J = 7.9$ Hz, 8H), 4.51–4.68 (m, 4H), 4.78–4.89 (m, 2H), 6.90 (d, $J = 8.4$ Hz, 8H), 7.10–7.38 (m, 10H), 7.71 (s, 4H), 7.74 (s, 8H), 7.93 (s, 2H), 8.19 (s, 7H), 8.50- 8.75 (m, 6H), 10.12 (s, 2H), 10.16 (s, 8H), 10.23 ppm (s, 4H); ^{13}C NMR: $\delta = 18.8$, 19.4, 20.2, 29.1, 31.2, 38.2, 50.8, 56.8, 61.6, 79.0, 113.9, 114.6, 127.3, 129.1, 130.1, 136.5, 138.9, 139.9, 140.1, 156.5, 167.5, 171.1, 171.9, 172.4 ppm.

G3-$V_8F_4A_2$-CO_2H: Starting from G3-$V_8F_4A_2$-CO_2Et (0.30 g, 0.091 mmol) in a 1/1 mixture of THF/MeOH (10 mL) and aqueous KOH solution (1.0 mL, 2.0 M), the title product was obtained as a white solid (0.21 g, 71 %). T_m 186 °C. $[\alpha]_D^{20} = -13.1$ ($c = 0.35$). SEC retention time: 14.84 min. ^{1}H NMR (CO_2H not observed): $\delta = 0.89$ (d, $J = 6.4$ Hz, 48H) 1.20–1.45 (m, 6H), 1.37 (s, 72H), 1.85–2.02 (m, 8H), 3.01–3.19 (m, 8H), 3.92 (t, $J =$ 7.5 Hz, 8H), 4.48–4.63 (m, 2H), 4.81–4.96 (m, 4H), 6.89 (d, $J = 8.2$ Hz, 8H), 7.13–7.42 (m, 20H), 7.68 (s, 8H), 7.76 (s, 4H), 7.99 (s, 2H), 8.11 (s, 4H), 8.18 (s, 1H), 8.24 (s, 2H), 8.55–8.76 (m, 6H), 10.09 (s, 8H), 10.27 (s, 2H), 10.38 ppm (s, 4H); ^{13}C NMR: $\delta = 18.7$, 19.4, 20.1, 29.1, 31.2, 38.1, 50.9, 56.7, 61.5, 79.0, 114.0, 114.6, 114.8, 116.1, 127.3, 129.1, 130.2, 136.5, 138.9, 139.9, 140.0, 140.4, 156.5, 167.6, 167.7, 168.0, 171.3, 171.9, 172.5 ppm; elemental analysis calcd (%) for $C_{171}H_{226}N_{28}O_{38}\cdot 4H_2O$: C 61.24, H 7.03, N 11.69; found: C 61.19, H 7.00, N 11.53.

Gelation test: A weighed sample of gelator was mixed with a solvent (1 mL) in a septum-capped vial and heated. If the compound was unable to dissolve, it was noted as insoluble (I). If a clear solution was obtained, it was then cooled down to room temperature and left for 12 h. The aggregation state was then assessed. If no flow was observed when inverting the vial, a stable gel was formed and classified as transparent gel (CG), translucent gel (TG) or opaque gel (OG) according to its transparency. If part of the mixture formed a gel but flow was still observed, the phenomenon was recorded as partial gelation (PG). If crystallization or precipitation occurred, C and P were noted respectively, and if the clear solution was retained, it was marked as soluble (S). The mgc of the organogelator was determined by measuring the minimum amount of gelator required for the formation of a stable gel.

^{1}H NMR dilution studies: ^{1}H NMR spectra were recorded at 293 K on a Brüker DPX spectrometer at 300 MHz using freshly prepared solutions. $CDCl_3$ was distilled from CaH_2 and kept over 4 Å molecular sieves prior to use. The molecular sieves employed were freshly activated. Relatively concentrated NMR samples of G1-V_2-CO_2Et ($c \geq 100$ mM) in $CDCl_3$ were prepared in volumetric flasks. Moderately concentrated samples (10 mM $= c <$ 100 mM) were obtained by serial dilution of a 100 mM stock solution with $CDCl_3$. Very diluted samples ($c <$ 10 mM) were prepared from serial dilution of a 10 mM stock solution.

X-ray diffraction study of G1-V_2-CO_2Et: A crystal suitable for X-ray diffraction was obtained by recrystallization from ethyl acetate solution. The diffraction experiment was carried out on a Bruker SMART 1 K CCD diffractometer with a graphite-monochromated $Mo_{K\alpha}$ radiation at 293(2) K, ω scan mode with increment of 0.3°. Preliminary unit cell parameters were obtained from 45 frames. Final unit cell parameters were obtained by global refinements of reflections obtained from integration of all the frame data. The collected frames were integrated using the preliminary cell-orientation matrix. The SMART software was used for collecting frames of data, indexing reflections, and determination of lattice constants; SAINT-PLUS was used for integration of intensity of reflections and scaling;[13a] SADABS for absorption correction;[13b] and all the structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software.[13c] Non-hydrogen atoms were refined in anisotropic, and hydrogen atoms in isotropic approximation. The CO_2Et group in one of the monomers exhibits orientational disorder. The site occupancy factors for these two orientations were found to be 0.5228 and 0.4772 respectively. The disordered atoms O1′, O2′, C8′, O1″, O2″ and C8″ are refined isotropically. The site occupancy factor for the poorly resolved ethyl acetate solvent molecule was suitably assigned as 1/2. Hydrogen atoms are omitted for the disordered CO_2Et group and the poorly resolved ethyl acetate solvent molecule.

Crystallographic data for 2 G1-V_2-CO_2Et·1/2($CH_3CO_2C_2H_5$): $C_{60}H_{96}N_8O_{17}$ ($M_w = 1201.45$ g mol^{-1}), monoclinic, space group $P2_1$, $a = 10.836(1)$, $b =$ 23.831(2), $c = 15.154(1)$ Å, $\beta = 107.764(2)°$, $V = 3726.7(5)$ Å^3, $Z = 2$, $\rho_{calcd} =$ 1.071 g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.078$ mm^{-1}, $T = 293$ K, $2\theta_{max} = 56.58°$, $wR2 =$ 0.2523 (21364 reflections collected, 12470 unique), $R1 = 0.0976$ [$I > 2\sigma(I)$], GOF = 0.951. CCDC-263412 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

FT-IR experiments: A hot solution of the organogelator G1-F_2-CO_2H (1 % w/v) was prepared in the solvent or solvent mixture of interest and then transferred into a cell. The infrared spectrum was recorded on a Nicolet 420 FT-IR spectrophotometer after the sample was cooled to room temperature and equilibrated for 5 minutes. The spectrum of solid G1-F_2-CO_2H was recorded as KBr pellet.

CD spectroscopy: CD spectra were recorded on a JASCO J-715 spectropolarimeter connected to a NESLAB RTE-211 temperature controller. A weighed, hot solution of the gelator G1-F_2-CO_2H (1 %, w/v) was prepared in *p*-xylene and then transferred into a quartz cell (0.1 cm path length) to allow gel formation. The temperature of the cell was detected by a thermometer attached to the chamber supporting the quartz cell. At each temperature, the sample was equilibrated for 30 minutes before scanning. As the sol–gel transition temperature of G1-F_2-CO_2H in *p*-xylene is beyond the highest temperature obtainable (~62 °C) by the temperature controller, scanning was started immediately after the hot solution in *p*-xylene was put into the chamber in order to measure the CD spectrum of the solution state. After the spectrum was recorded, the sample was checked again to make sure it was still in the solution state.

Electron microscopy: A gel was prepared as described above and frozen in liquid nitrogen. The freezed sample was dried in a Labconco Freeze Dryer under vacuum at −50 °C for 24 h. The xerogel thus obtained was subjected to electron microscopic examination. A Leo 1450 VP scanning electron microscope was used for taking the SEM micrographs. A small slice of the xerogel was transferred on to a stub and was then sputtered coated with gold. The sample was examined with an accelerating voltage of 20 kV.

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[6] The term "layer-block sequence" here refers to the order of disposition of the amino acid layers from the surface toward the interior of the dendron.

[7] The notation Gn-$(aa^1)_{(2^n)}\cdot\cdot(aa^n)_2$-$CO_2R$ is used to represent the structure of the dendrons, where n denotes the dendron generation, aa^1, ···, aa^n refer to the nature of the amino acid layers from the surface toward the focal point of the dendrons, respectively. The protective groups on the N-termini are *tert*-butyloxycarbonyl (Boc) groups.

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