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Using pseudo-symmetrization to overcome dendrimer surface steric crowding: a birth of L-lysine-β-alanine architecture

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A synthetic approach to overcoming the surface crowding of polylysine dendrimers is reported. The introduction of a β-alanine unit on the α-amine of L-lysine creates a pseudo-symmetry between the two amino groups, which is found to reduce the steric bias when used as a dendrimer building block, compared with the parent L-lysine. Our findings show that this approach allows the unhindered growth of the L-lysine-β-alanine dendrimers until generation 8, thus significantly increasing the generation at which de Gennes' critical dense state of surface functional groups is reached, compared with traditional polylysine dendrimers. Highly uniform high molecular weight nanostructures have been isolated, purified, and characterized by NMR spectroscopy, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectroscopy, and gel-permeation chromatography (GPC).

Introduction

Polyamide dendrimers[1–5] are soft monodisperse nanostructures synthesized by iterative stepwise methods where the final three-dimensional globular structure emerges from the ellipsoidal or disc-like core. As a result, the functional groups are concentrated at the periphery.[6] This feature distinguishes dendrimers from linear polymers, inspiring their widespread adoption in the biomedical field.[7,8] The number of terminal functional groups grows in accordance with the dendrimer generation number and the core and branch multiplicities.[9,10] It is predicted that at a certain generation (depending on core and branching unit nature and multivalency), the density of functional groups at the periphery would be so high that a reduction in the reaction rate would be observed.[11] Even with the revised theory that clarifies that the terminal groups are to be distributed not only on the surface but throughout the molecule, the geometric rise in end group number will reach the point where the growth is hindered. Beyond this point, further growth is possible, but incomplete structures would be formed, as some functional groups will remain unreacted.[12] For example, in the case of aliphatic polyamide, polyamidoamine (PAMAM) dendrimers, a reduction in the reaction rate is first seen at generations 4–6, and a significant decrease is observed at generations 7–8, albeit even larger generations of defect-containing structures are still possible.[12] Such behavior is generally seen to negatively affect their utility in biomedical applications since incomplete functional group transformations will, in turn, produce heterogeneous biologically active conjugated products. The presence of ionizable unreacted functional groups, such as amines, can also cause increased cytotoxicity.[13] Apart from the crowding of surface functional groups, the back-folding of peripheral groups[14] and self-interruption due to imperfect conformation[15] have also been observed as possible growth-limiting factors.

Such growth limitations due to steric crowding thwart efforts by scientists to access well-defined high molecular weight monodisperse structures in innovative applications that could revolutionize nanomedicine, nanoscience, and nanotechnology. Although the existence of surface steric crowding was recognized almost 4 decades ago,[11] the solution that would allow overcoming it in high generations largely remains absent and is limited to either starting synthesis with highly elaborate long branching units[16] or indiscriminately adding spacers to functional groups of branching units.[17] Also, even though the recently proposed proportionate branching may have the potential to succeed, it has only been tested on low-generation dendrimers.[18]

Of all reported polyamide dendrimers, polylysines possess several unique qualities. They are entirely made from a single amino acid L-lysine. Thanks to its multivalency (having one carboxylic acid and two amine groups (Fig. 1)), it can act as a branching unit.[4] Just like other dendrimers, polylysines also experience surface functional group crowding during synthesis, with generation 5 being the largest reported defect-free dendrimer,[19] although higher generations of defective molecules are possible.[4] In the case of L-lysine, the unequal steric environment of two amines (at α and ε positions) is seen as the potential reason for the growth limitation. At certain generations (4–5), it is speculated that some of the α amines of the terminal lysine units may be disproportionately sterically

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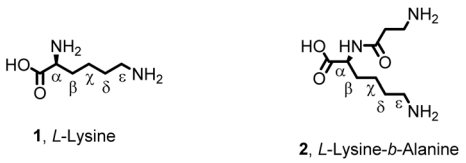


Fig. 1 Structures of L-lysine and L-lysine-β-alanine.

hindered, ultimately limiting the defect-free growth.[20] The growth of defect-free polyamide dendrimers beyond G4–5 is extremely important, as most biological applications seem to benefit from the size and end-group polyvalency of PAMAM G5–G6 dendrimers.[7,21] The G5 PAMAM dendrimer (built from the divalent core) has 128 terminal groups, and achieving the equivalent number of terminal groups from polylysine dendrimers would require a G6 polylysine dendrimer, which is beyond the point at which defect-free polylysines can currently be synthesized. Herein, we introduce the novel branching unit L-lysine-β-alanine to reduce the above-mentioned disproportional steric difference between the two amines (at α and ε positions) of each L-lysine unit. The introduction of the single β-alanine unit on the α-amine of L-lysine creates a "pseudo-symmetry" between the two amino groups present in the molecule and reduces the steric bias found in L-lysine. Indeed, we find that highly uniform polyamide dendrimers made from L-lysine-β-alanine can be synthesized up to generation 8, demonstrating the successful increase in surface functional group accessibility well beyond the current state of the art.

Pseudo-symmetrization of L-lysine to reduce the steric crowding of the surface amines on polylysine dendrimers was achieved by combining two amino acids, specifically L-lysine and β-alanine. This approach is advantageous for several reasons. Firstly, the resulting branching unit **2** (Fig. 1) would have a pseudo-symmetric arrangement of two amines where each of them is now distant from α carbon by the same number of chemical bonds. Although the spatial distance is still anticipated to be different due to differences in bond lengths, angles, and conformations, both amines are expected to be much more accessible than the α amine was in the parent L-lysine. Secondly, the resulting structures would still be entirely amino acid-based, strengthening their potential utility in nano-biomedicine. Lastly, the presence of two amino acid combinations where one of them (β-alanine) can potentially be substituted by another amino acid opens the door for other combinations as well. This creates an opportunity where thousands of unique amino acid-based dendritic structures can be generated, which is especially relevant to research where structure–activity relationship studies are desired.[22,23]

Results and discussion

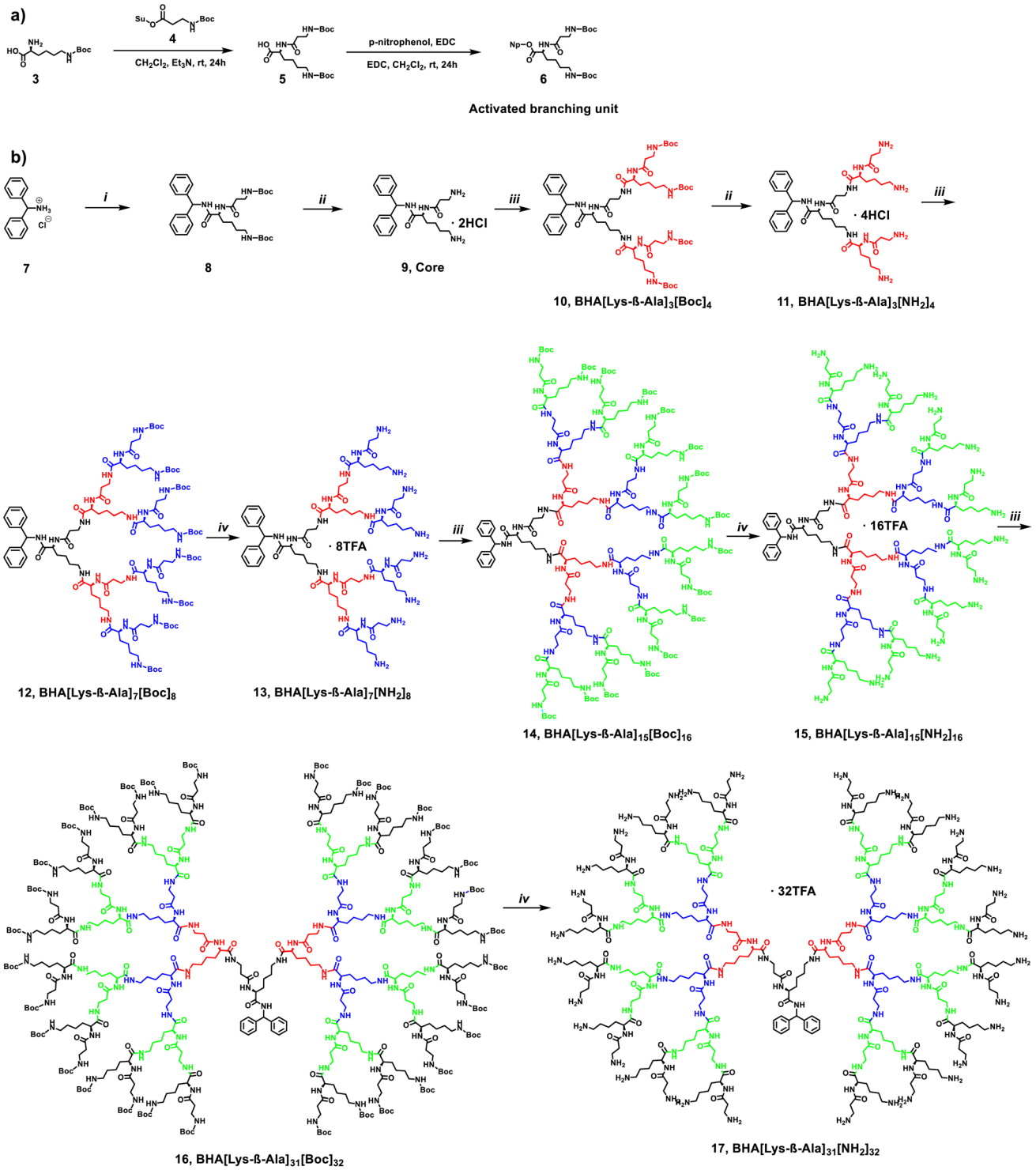
Synthesis

The synthesis of the reactive L-lysine-β-alanine branching unit **6** was achieved in two high-yielding steps starting from commercially available mono-protected L-lysine **3**. Firstly, the pseudo-symmetrization of amino groups was achieved by reacting **3** with commercially available activated β-alanine **4** (Scheme 1). The carboxylic acid of the resulting intermediate **5** was then activated using *p*-nitrophenol under coupling conditions to yield amino-reactive branching unit **6**. This two-step process was scaled up to afford a large quantity of pure **6** that was needed for dendrimer growth.

The synthesis of L-lysine-β-alanine dendrimers was achieved *via* stepwise growth from the core unit. Each successful generation (new layer of L-lysine-β-alanine) was built through a two-step process where, during the first step, a terminal amine group of each generation was reacted with activated branching unit 6, and the protected terminal amino groups of the resulting higher generation molecule were deprotected under acidic conditions during the second step. The synthesis was started from commercially available diphenylmethylamine **7**, which upon reaction with activated branching unit **6** gave intermediate **8**. Boc protecting groups were then removed under acidic conditions to afford core molecule **9** as HCl salt. From **9**, the above-mentioned two-step process was repeated to access higher-generation molecules (Schemes 1, 2 and Fig. S1, S2). Interestingly, similar to **9**, the first-generation dendrimer **11** was also isolated as HCl salt, but due to solubility limitations, the higher-generation dendrimers **13**, **15**, **17**, **19**, **21**, **23**, and **25** were formed and isolated as TFA salts.

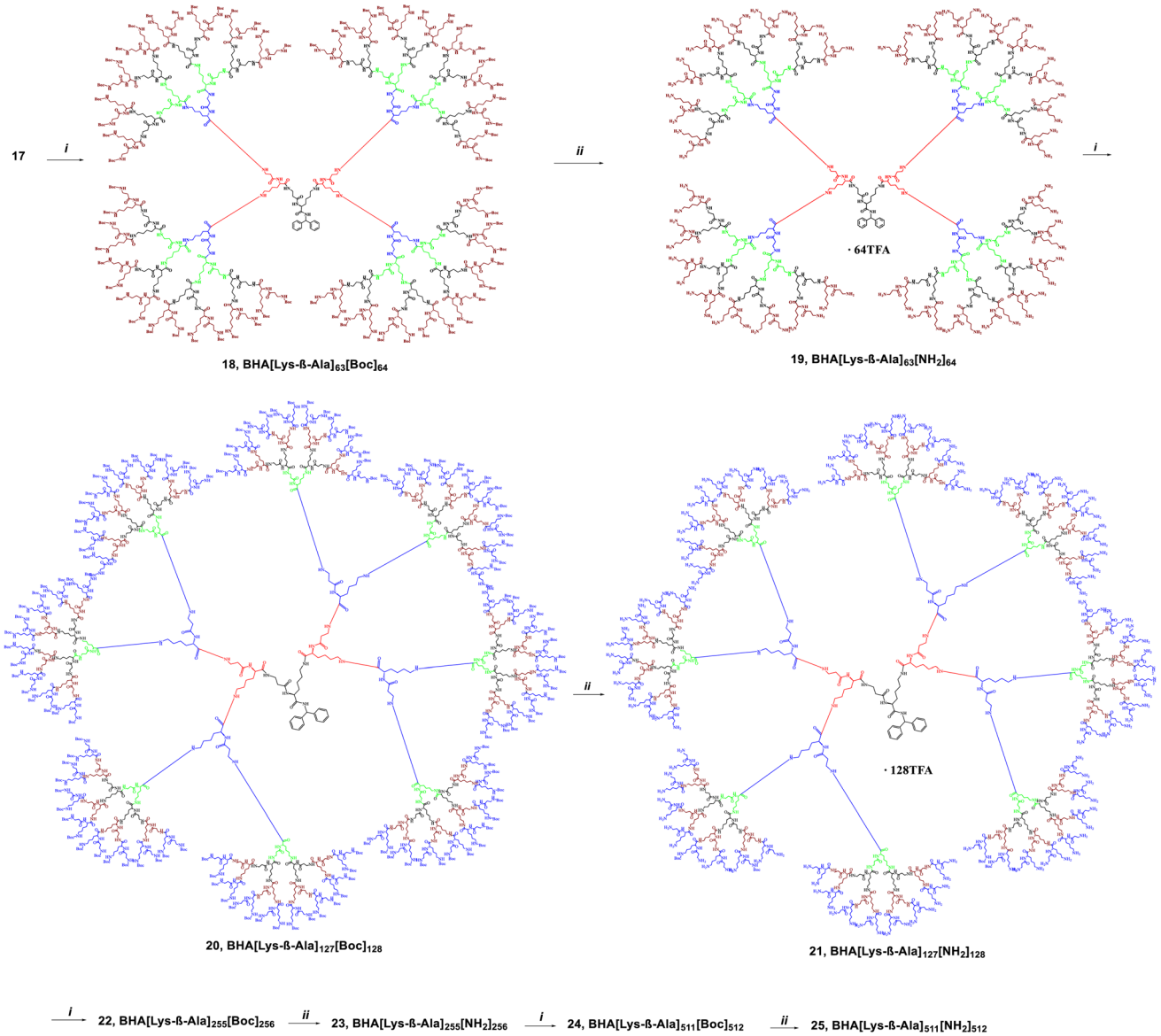
Characterization

The progress of dendrimer growth and the purity and identity of each molecule was monitored by a number of analytical techniques such as ^{1}H, ^{13}C, and 2D NMR methods, high-performance liquid chromatography-mass spectroscopy (HPLC-MS), matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectroscopy, and gel-permeation chromatography (GPC). The combination of ^{1}H and ^{13}C NMR, GPC, and MALDI-TOF was used for each growth step to confirm the structure and the purity of each product, while a more complex 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) experiment was used for structure confirmation and peak assignment (Fig. S3). Interestingly, even beyond integration and peak positioning data, ^{1}H NMR provided an important trend about dendrimer size and globular nature as well. Firstly, the progressive disappearance/dilution of core diphenylmethylamine signals located at 7.4–7.2 ppm and 6.2 ppm with the generation increase was observed with the dendrimer size increase. This can be seen in NMR overlays of both, Boc protected dendrimers **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, and **24** and their deprotected counterparts **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, and **25** (Fig. 2 and S4) as well. Secondly, the progressive signal broadening observed in both aliphatic and aromatic regions indicated the growth of molecules into the three-dimensional, globular structures where sharper signals gradually become broad multiplets due to all different conformations of each signal of larger, slower-rotating molecules being averaged out. We must note that some of the peak broadenings must also be a result of a progressively larger number of magnetically different protons arising from the chiral, nonsymmetric nature of the L-lysine unit.



Scheme 1 The synthesis of L-lysine-β-alanine dendrimers (G0–G4). Reagents and conditions: (i) **6**, CH_2Cl_2, Et_3N, rt, 24 h; (ii) HCl, MeOH, rt, 30 min; (iii) **6**, DMF, Et_3N, rt, 24 h; (iv) TFA, MeOH, rt, 24 h.

The direct proof of the molecular weight was obtained using MALDI-TOF mass spectroscopy. Namely, MALDI-TOF provided clear experimental evidence that large, highly uniform structures were formed. In generations 1–4, the single peak corresponding to $[M + H]^+$ was detected, while generations 5–8 showed the broad signals corresponding to either $[M - (Boc)_n + H]^+$ or $[M - (Boc)_n + 2H]^{2+}$. This is due to the fact that much higher laser intensities are required to ionize such large molecules, and the decomposition is taking place where the loss of terminal Boc protecting groups has become unavoidable.[24,25] Still, employing the fit covering the range between the theoretical MW and all Boc groups being lost (Fig. 3), matches very well



Scheme 2 The synthesis of L-lysine-β-alanine dendrimers G5–G8 (structures of G7 and G8 are not drawn). Reagents and conditions: (i) **6**, DMF, Et_3N, rt, 24 h; (ii) TFA, MeOH, rt, 24 h.

to the onset (right side of the spectra, closest to the theoretical MW) of each peak and provides good confirmation of the observed molecular weight for each molecule (Fig. 3). The broadness of the peak in G6–G8 beyond the fit towards the lower MW region likely indicates the further decomposition (beyond the loss of all Boc groups) of ions. Generation 5 is a very interesting example and holds multiple clues about the behavior of such molecules. In this case, the $[M + H]^+$ signal is a broad peak showing a distribution similar to larger generations, yet the $[M + 2H]^{2+}$ is a sharper peak from which the molecular weight can be confirmed (Fig. 3). Overall, in every example between generations 1 and 7, we have observed no evidence of structural defects. The last generation explored (generation 8), however, showed a minor, yet noticeable deviation from the theoretical molecular weight (data obtained from the fit were lower than the theoretical), indicating the absence of a few branching units, *i.e.*, the formation of incomplete dendrimers (Table S1). This finding was further confirmed by ^1H NMR analysis. Specifically, the integration values of distinct signals present in the terminal layer *vs.* those from the internal layer helped us gain an understanding of the degree of functionalization in each growth step. For example, signals *p* (3.2–2.9 ppm) and *q* (2.6–2.3 ppm), each arising from single methylene units of L-lysine (signal *p*) and β-alanine (signal *q*) (Fig. 2) of the terminal layer, respectively, was utilized. Signal *p* is well resolved in each generation, while beyond generation 0, signal *q* overlaps with similar β-alanine methylene protons of internal layers. Therefore, in any given generation, a complete functionalization of terminal amines (uninterrupted growth) should give rise to the signal at (3.2–2.9 ppm) with integral value of $2n$, while the signal

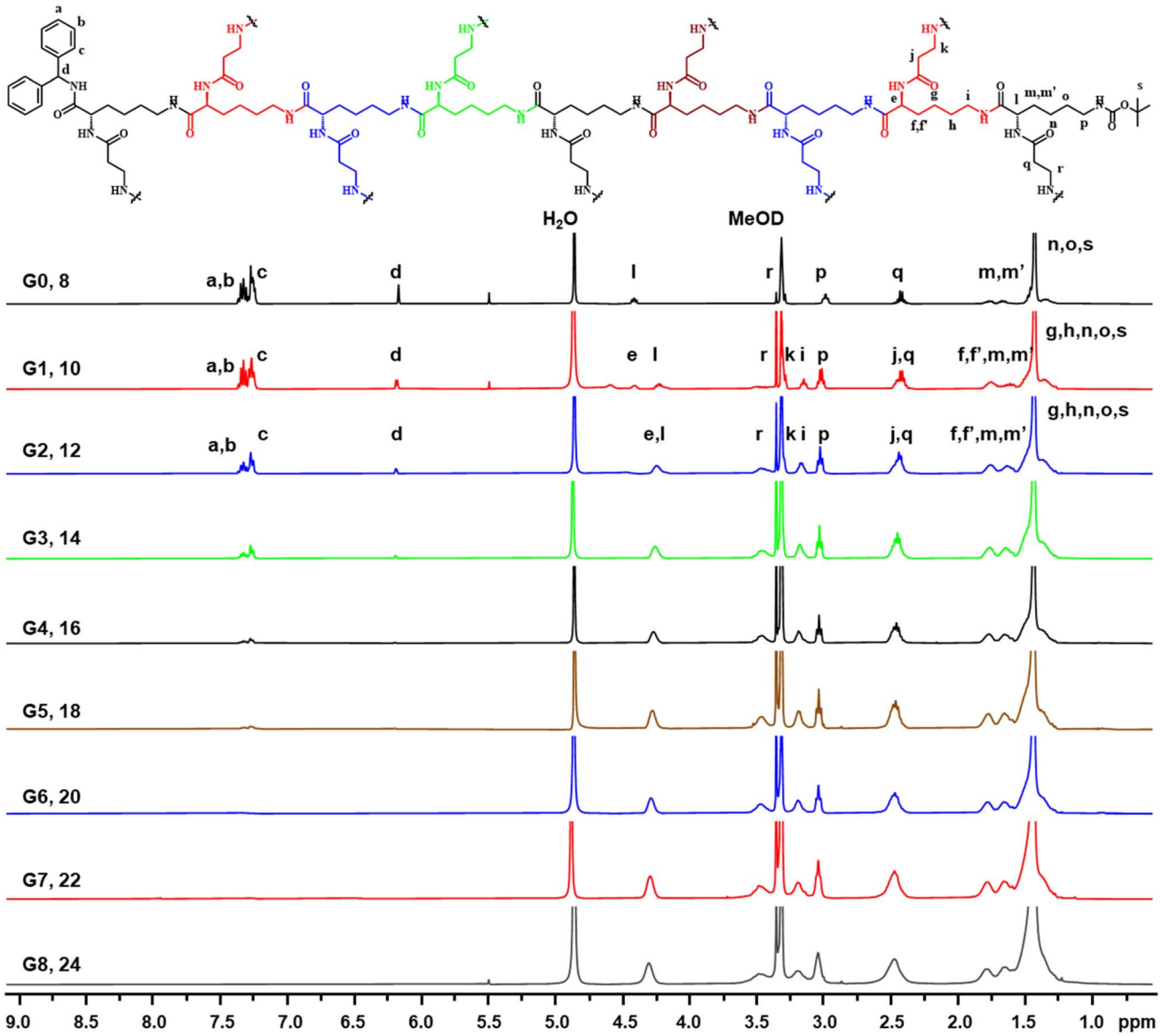


Fig. 2 ^{1}H-NMR spectra of Boc-protected dendrimers G0–G8. For clarity, only the terminal, first internal layer, and diphenylmethylamine moiety are labeled. Peak assignments are provided only on G0–G2, where some change in chemical shift from the previous generation can be seen. Higher generation data (G3–G8) mirror well the signals seen in generation 2.

at (2.6–2.3 ppm) should have a value of $2n + 2(n - 1)$. Where $2(n - 1)$ refers to methylene units of L-alanine groups present in internal layers, and n refers to the number of terminal L-lysine-β-alanine branching units. As such, the ratio of integral values of signals p and q was used to determine whether the functionalization of all terminal amine groups was successful or not. We employed this methodology to supplement the MW data coming from MALDI-TOF (Table S1). As shown in Table S1, based on the above-mentioned method, we estimate that every generation until 8 shows the right ratio of integral values as expected from fully functionalized theoretical structures, indicating an uninterrupted growth. At generation 8, however, we see a clear deviation from the theoretically expected value. Integral values indicate the absence of about 26 terminal branching units (Table S1). This observation, along with direct MW measurements from MALDI-TOF, clearly indicates reduced reactivity on the surface after generation 7 and identifies generation 8 to be the critical point where the reaction rate reduction reappears. While it would still be possible to continue building even higher generation dendrimers, it is likely that each successive generation will have an increasingly larger number of defects, further deviating from the monodisperse nature of dendrimers.

Finally, gel permeation chromatography (GPC) was used to monitor the purity of the dendrimers in each generation. Specifically, we looked for both a higher and lower molecular weight species. Due to solubility limitations, only Boc-protected molecules could be analyzed, but it showed remarkable purity and absence of both lower and higher molecular weight species, which indicated that during this synthesis, there is no

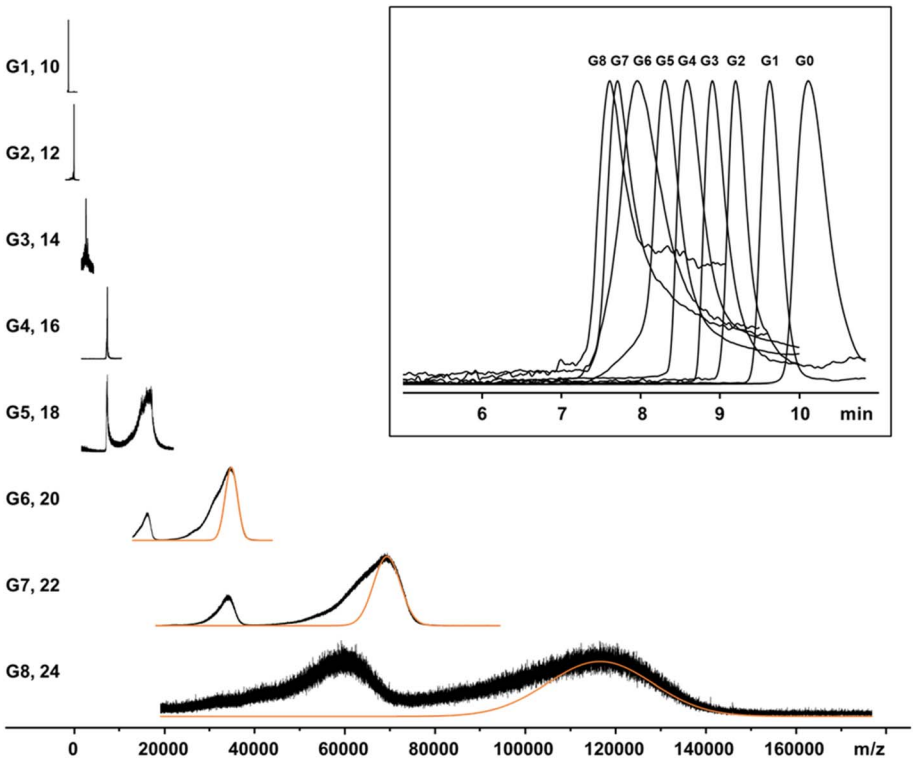


Fig. 3 MALDI-TOF spectra and GPC traces (inset) of Boc-protected dendrimers G0–G8.

detectable amount of either higher or lower molecular weight species (Fig. 3, inset).

Conclusions

In conclusion, the described pseudo-symmetrization approach demonstrates that it can relieve the steric interference found in the early generation of polylysine dendrimers and postpone the formation of a critically dense surface state until a much higher generation G8 molecule. The synthesis is achieved *via* high-yielding, scalable reactions where neither step growth nor deprotection steps require extensive purification. The high-purity products are achieved using simple precipitation procedures, indicating the potential scalability of the project well beyond tested amounts. Indeed, in our experiments, many of the high-generation dendrimers were prepared at more than the gram scale, and the starting branching unit and smaller generation dendrimers on a multigram (>10 g) scale. We have no evidence that further scaling up using appropriate techniques/precautions should present any significant issues. The potential interest of thus formed molecules in biomedical applications is expected to be high, considering that each of these molecules is highly uniform and entirely made from amino acids and can be used as scaffolds for attaching drugs or imaging agents.[26–29] The use of two amino acid combinations opens the door for the generation of thousands of new dendritic structures with potentially unique functional properties suitable for research where structure–activity relationship studies are desired.[22,23] Moreover, the interest of such structures in nanoscience is expected to be high as well. Especially, due to the high stability of polyamide linkages, such macromolecules can be used to coat biorelevant nanoparticles,[30] improving their stability and/or biocompatibility compared to polyester[31,32] and polycatenar[33] type ligands.

Author contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare competing financial interests. Parts of this work have been included in a provisional patent disclosure.

Data availability

Additional figures, synthetic procedures, and compound characterization details. See DOI: **https://doi.org/10.1039/d5ra04817f**.

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