Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3975–3988

TETRAHEDRON

Synthesis and properties of polyaromatic dendrimers possessing a repetitive amide–ester coupling sequence

Barbara Romagnoli,[a] Peter R. Ashton,[b] Laurence M. Harwood,[a] Douglas Philp,[c] David W. Price,[a,†] Melanja H. Smith[c] and Wayne Hayes[a,*]

[a]*School of Chemistry, The University of Reading, Whiteknights, Reading, Berkshire RG6 6AD, UK*
[b]*School of Chemical Sciences, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*
[c]*Centre for Biomolecular Sciences, School of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife KY16 9ST, UK*

Received 30 October 2002; revised 13 December 2002; accepted 10 January 2003

Abstract—A series of novel polyaromatic dendrimers that feature *tris*-(2-ethylamino)amine as the central core unit has been synthesized up to the third generation by employing a convergent growth strategy. The building blocks 1,3-diamino-2-hydroxypropane and 4-carboxybenzaldehyde were used for dendron construction, a process that involved the cyclic repetition of esterification, oxidation and selective amidation steps. Molecular modelling of this class of dendrimers has been used to predict potential solution state conformations employing molecular mechanics and molecular dynamic simulations. In addition, the results of preliminary metal binding studies using the first generation dendritic system are also outlined. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The synthesis and physical studies of dendrimers has received extensive interest[1] as a result of the possibility to tailor effectively the properties of dendritic molecules by the introduction of reactive functional groups at either the core,[2] the peripheral surface,[3] the branching unit[4] or at multiple sites within the dendrimer,[5] ultimately to lead to a variety of applications such as drug delivery,[6] catalysis[7] or energy transfer.[8] Numerous branched structures have been used in dendrimer construction and, in particular, the incorporation of chemically and thermally stable amide bonds within the hyperbranched architectures has been shown to be desirable.[9] In addition, it has been shown that dendrimers or hyperbranched polymers possessing polyaromatic amide branched repeat units exhibit a high degree of rigidity, yet also suffer from low solubility characteristics in common organic solvents.[9]

Within the framework of our studies upon the chiroptical properties of chiral dendrimers derived from a combination of chiral core and achiral dendrons, a synthetic programme toward the synthesis of rigid polyaromatic amide dendrons was initiated in order to maintain the optical activity of the defined chiral core.[10] A new polyaromatic amide branched system has been designed with the specific aim of introducing a high degree of rigidity, but in turn retaining acceptable solubility characteristics in common organic solvents.[9] In this article, the synthesis of a series of polyaromatic amide dendrons derived from the branched AB_2 type monomer 1,3-diamino-2-hydroxypropane and 4-carboxybenzaldehyde (that acts as a rigid 'linker' between two branching units) is presented. Coupling of the resultant [G-1], [G-2] and [G-3] dendrons to *tris*-(2-ethylamino)-amine as the central core led to achiral [G-1], [G-2] and [G-3] dendrimers, respectively, and these were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, MALDI-TOF mass spectrometric and GPC analyses.

2. Results and discussion

2.1. Molecular modelling studies on first and second generation dendrons

The first and second generation dendrons, **[G-1]-OH 1**, and **[G-2]-OH 2**, respectively, were analysed using molecular mechanics techniques (employing the Universal Force-Field v1.02 and QEq charges in each case) in order to identify possible stable conformations of this type of hyperbranched structure. From the gas phase studies undertaken, both dendrons **2** and **5** were found to adopt low energy conformations in which the two dendritic arms extended away from the focal point in a parallel fashion rather than adopting conformations in which the bulky arms extended away from the focal point and each other in an anti-parallel fashion (see Fig. 1). This

Keywords: dendrimer; polyamide; polyester; convergent synthesis.
* Corresponding author. Tel.: +44-118-931-6491; fax: +44-118-931-6331; e-mail: w.c.hayes@reading.ac.uk
† Current address: AWE, Aldermaston, Reading, Berkshire RG7 4PR, UK.

0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00466-6

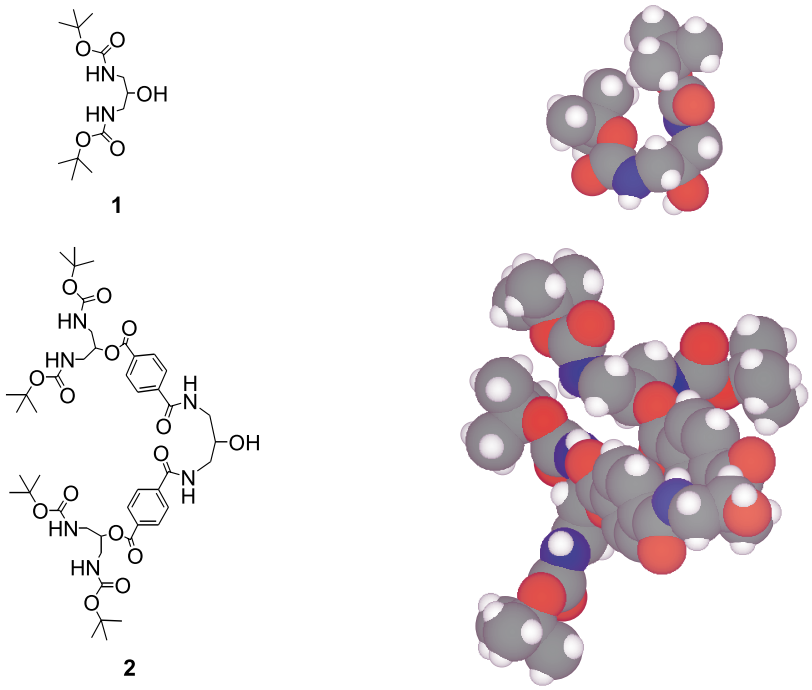
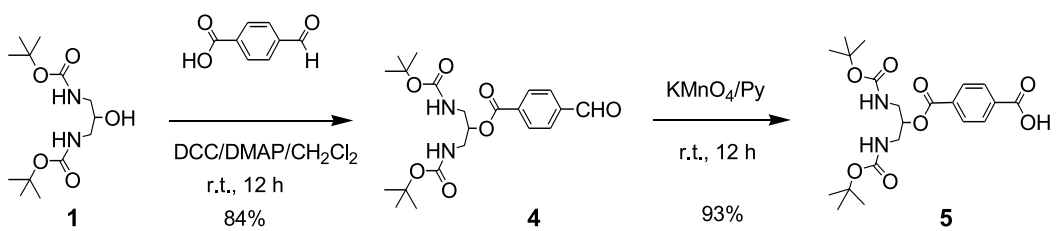


Figure 1. Molecular models of the first and second generation dendrons **1** and **2**, respectively.

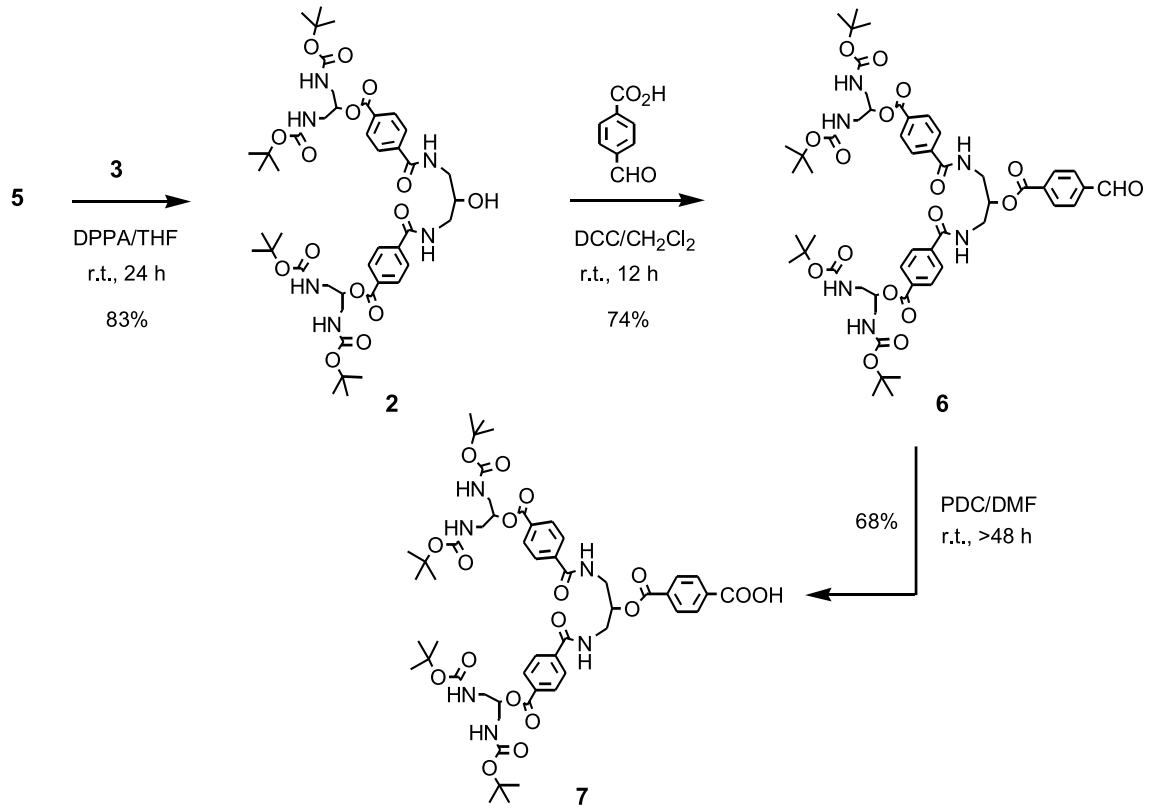
behaviour is favourable for dendrimer formation, since the branched 'arms' of the dendrons already adopt a divergent conformation that is found within the dendrimers. In the case of **[G-1]-OH 1**, conformations in which the dendritic arms are anti-parallel were calculated to be +11.3 kJ mol^{-1} higher in energy relative to the ground state conformation. Detailed conformational analysis of **[G-2]-OH**, **2** proved extremely difficult since numerous local minima were observed, however, it is clear that highly extended conformations were approximately +41.8 kcal mol^{-1} above the ground state conformation, in which the dendritic arms extend from the focal point parallel to each other. There is also a clear potential for aromatic $\pi-\pi$ stacking interactions between the phenyl rings of the two dendritic arms, which is not totally fulfilled since one of the aromatic rings is twisted by approximately 30° along the axis of the dendritic arm with respect to the second ring in the other dendritic arm. This twisting still allows close contacts between the two rings (as short as 3.56 Å and 3.82 Å).[11] This association phenomenon may be one of the driving forces towards the parallel disposition of the two arms, but the dipolar attraction between an amide-proton of one dendritic arm and a carbamate oxygen in the other arm (separated by only 2.760 Å) may also contribute. It is clear from these preliminary molecular mechanics and dynamic simulations that the gross structural conformation of dendritic systems of this type that the hyperbranched arms emanate from the focal point in a divergent fashion.

2.2. Synthesis of first, second and third generation dendrons

The proposed polyaromatic amide dendrons were synthesized using a convergent approach[12] in order to avoid the formation of structural defects during dendrimer construction.[1b] Commercially available 1,3-diamino-2-hydroxypropane **3** was selected as the AB_2 type monomer, and 4-carboxybenzaldehyde has been used as the rigid 'linker' between the branched points (Scheme 1). Protection of the two primary amino groups of 1,3-diamino-2-hydroxypropane **3** was considered necessary in order to avoid detrimental amide formation with 4-carboxybenzaldehyde. The *tert*-butyloxycarbonyl (*t*-Boc) group was employed to protect the peripheral primary amine residue of 1,3-diamino-2-hydroxypropane[13] using water/dioxane (1:2) as the solvent system[14] and the desired product was isolated in 95% yield. The first generation aldehyde [G-1]-CHO **4** was obtained in 84% yield by esterification[15] of **1** with 4-carboxybenzaldehyde using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP).[16]



Scheme 1. Synthesis of the first generation dendron [G-1]-CO_2H **5**.



Scheme 2. Synthesis of the second generation dendron [G-2]-CO_2H **7**.

Oxidation of **4** to afford the first generation carboxylic acid [G-1]-CO_2H **5** was carried out using either pyridinium dichromate (PDC)[17] (54% yield) or $KMnO_4$ (Yield=93%).[18]

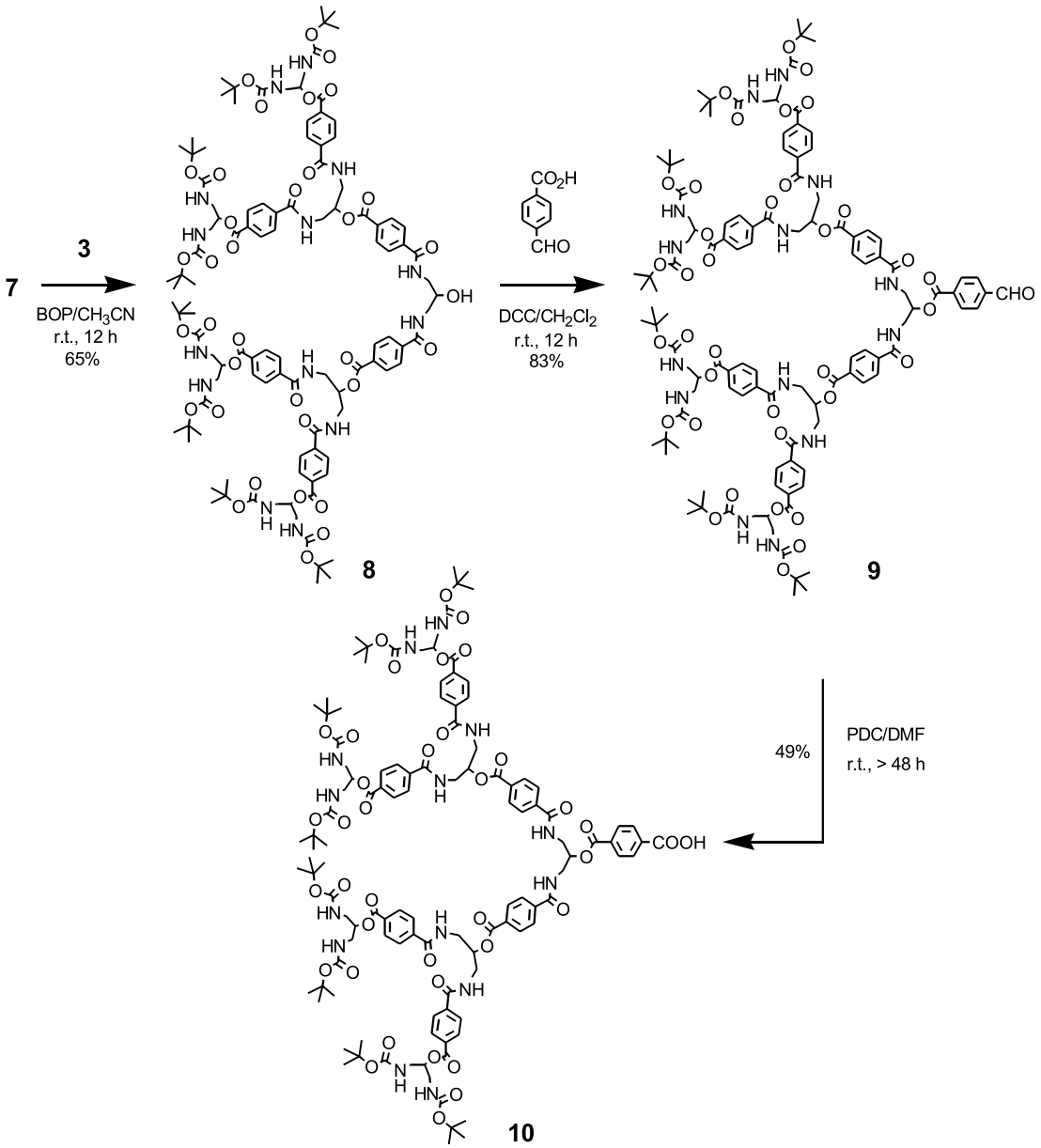
The [G-1]-CO_2H dendron **5** was then coupled selectivity with the AB_2 monomer **3** to produce the desired [G-2]-OH dendron **2** (Scheme 2). A range of coupling reagents were screened to determine the most selective conditions for the coupling of [G-1]-CO_2H **5** and the AB_2 monomer **3** including 1,1-carbonyldiimidazole[19] (CDI), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)[20] and diphenylphosphorylazide[21] (DPPA). The use of DPPA in dry THF enabled the selective amidation of **3** to afford [G-2]-OH 2 as a white solid in a yield of 83%. The [G-2]-OH dendron **2** thus obtained was subsequently coupled with 4-carboxybenzaldehyde, employing the same conditions as described previously for the synthesis of [G-1]-CHO **4** to afford the resultant [G-2]-CHO dendron **6** in 74% yield. In contrast to the synthesis of [G-1]-CO_2H dendron **5** oxidation of [G-2]-CHO **6** using $KMnO_4$ proved problematic (the MnO_2 by-product proved to be inseparable from the [G-2]-CO_2H dendron **7**) and thus an optimisation process was required. Several oxidation procedures were examined[22–24] and the optimum yield (55%) of the desired [G-2]-CO_2H **7** was obtained using PDC.[17]

Optimal synthesis of [G-3]-OH dendron **8** (Scheme 3) also necessitated the screening of a range of coupling agents (including CDI, EDCI, 1-hydroxy-7-azabenzotriazole (HOAt),1-hydroxybenzotriazole (HOBt)[25] and benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP)[26]). As observed previously in the synthesis of [G-2]-OH dendron **2**, DPPA proved to be the optimal coupling agent and afforded the desired [G-3]-OH dendron **8** in an acceptable yield of 65%. The [G-3]-CHO and [G-3]-CO_2H dendrons **9** and **10** were then synthesised with yields of 73 and 49%, respectively, following the same procedures as described previously for [G-2]-CHO dendron **6** and [G-2]-CO_2H dendron **7**.

2.3. Synthesis of first, second and third generation dendrimers

The commercially available tris-(2-ethylamino)amine **11** was chosen as the central core for the proposed polyaromatic amide dendrimers. As a consequence of the synthetic studies towards the polyaromatic dendrons, amide formation of the first, second and third generation carboxylic acids, **5**, **7** and **10**, respectively, with tris-(2-ethylamino)-amine was carried out initially using DPPA as the coupling reagent to afford the desired dendrimers **12**, **13** and **14** (Scheme 4). The first and the second generation dendrimers were isolated in yields of 65 and 48%, respectively, whereas the synthesis of the third generation dendrimer **14** did not proceed efficiently with this coupling agent. Improved results were obtained when BOP was employed as the coupling agent in the presence of triethylamine in CH_3CN.[26] The first and second generation dendrimers were isolated in yields of 83 and 55%, respectively, and reverse phase HPLC analysis revealed purity values >97% for both of these dendritic products (Fig. 2).

In contrast, the synthesis of the third generation dendrimer **14** proved to be more problematic, as product formation was

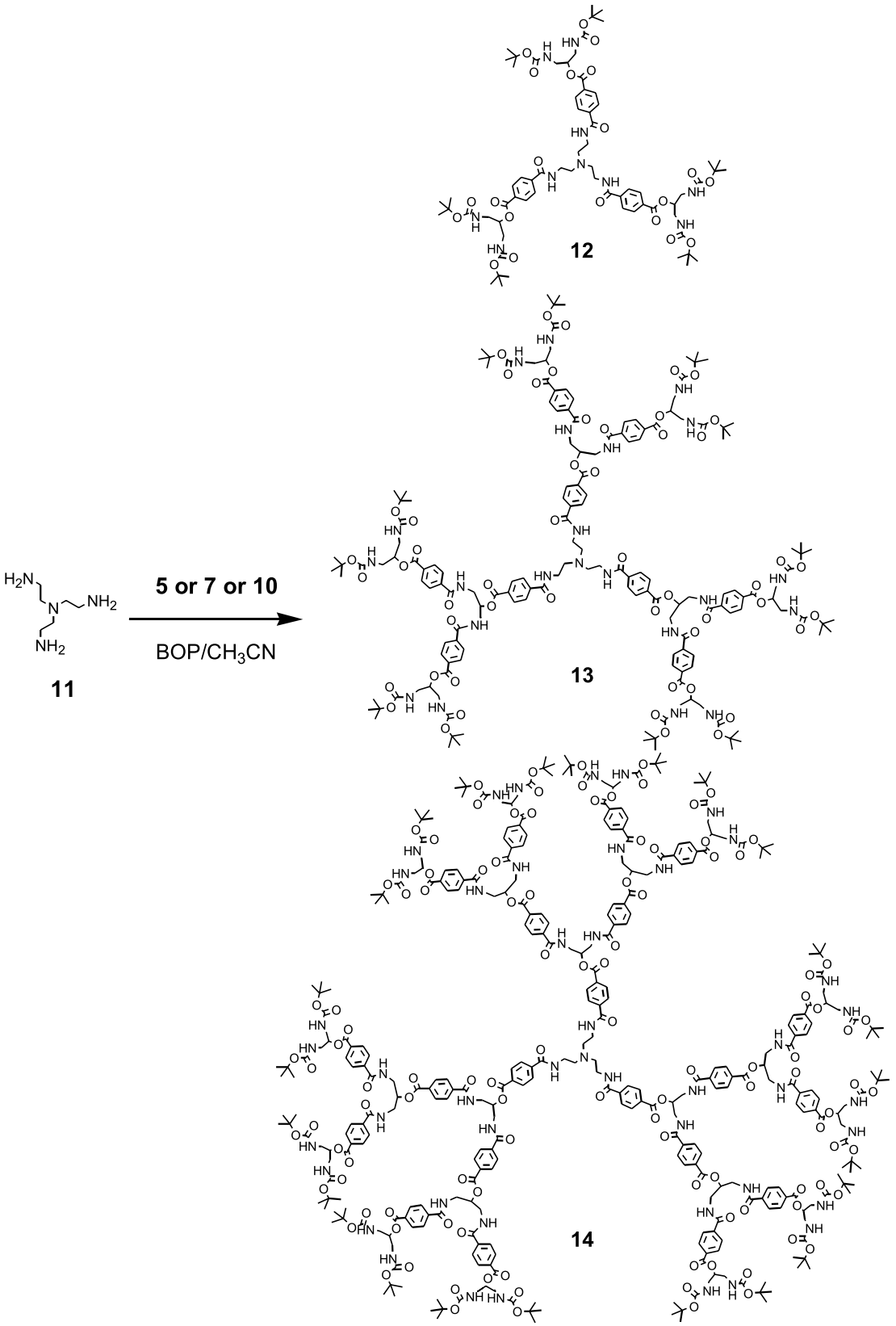


Scheme 3. Synthesis of the third generation dendron [G-2]-CO_2H **10**.

observed when BOP was employed as the coupling agent and a three-fold excess of the acid was used. The desired product could not be isolated in a pure form even after extensive column chromatography (see Fig. 3 for the MALDI-TOF mass spectrum of the isolated material). In common with other convergent dendrimer syntheses,[12] the yields of the final amidation to produce the desired dendrons and dendrimers decreased as the generation number of the dendron increased, indicating a significant increase in steric hindrance around the reactive core. Several studies have described[27] the successful synthesis of poly(aromatic amide) dendrimers up to the second generation, but also detail problems associated with the purification of the corresponding third generation dendritic species.[27–29] Therefore, it is not unreasonable to assume that the core system **11** becomes sterically hindered after the coupling of two dendritic [G-3]-CO_2H **10** subunits and exhaustive coupling of the third dendritic branch proved very difficult. However, this detrimental effect was not completely unexpected upon consideration of the high congestion that would originate from geometrical restrictions imposed by the amide bonds.[30]

2.4. Synthesis of the deprotected first and second generation dendrimers

Deprotection of the first and second generation dendrimers **12** and **13** (Scheme 5) was carried out in order to obtain dendritic systems bearing amino functionalities at the surface to use as 'scaffolds' for successive functionalisation such as anchoring of saccharide units.[31] In the light of the different deprotection strategies[26] available, it was decided to adopt the deprotection method described[32] by Liskamp and co-workers which enabled the desired product $(NH_2)_6$-[G-1]$_3$-N **15** (as the triflate salt) to be isolated as a white solid in >99% yield. ^{1}H NMR spectroscopic analysis



Scheme 4. Synthesis of the first, second and third generation dendrimers **12**–**14**, respectively.

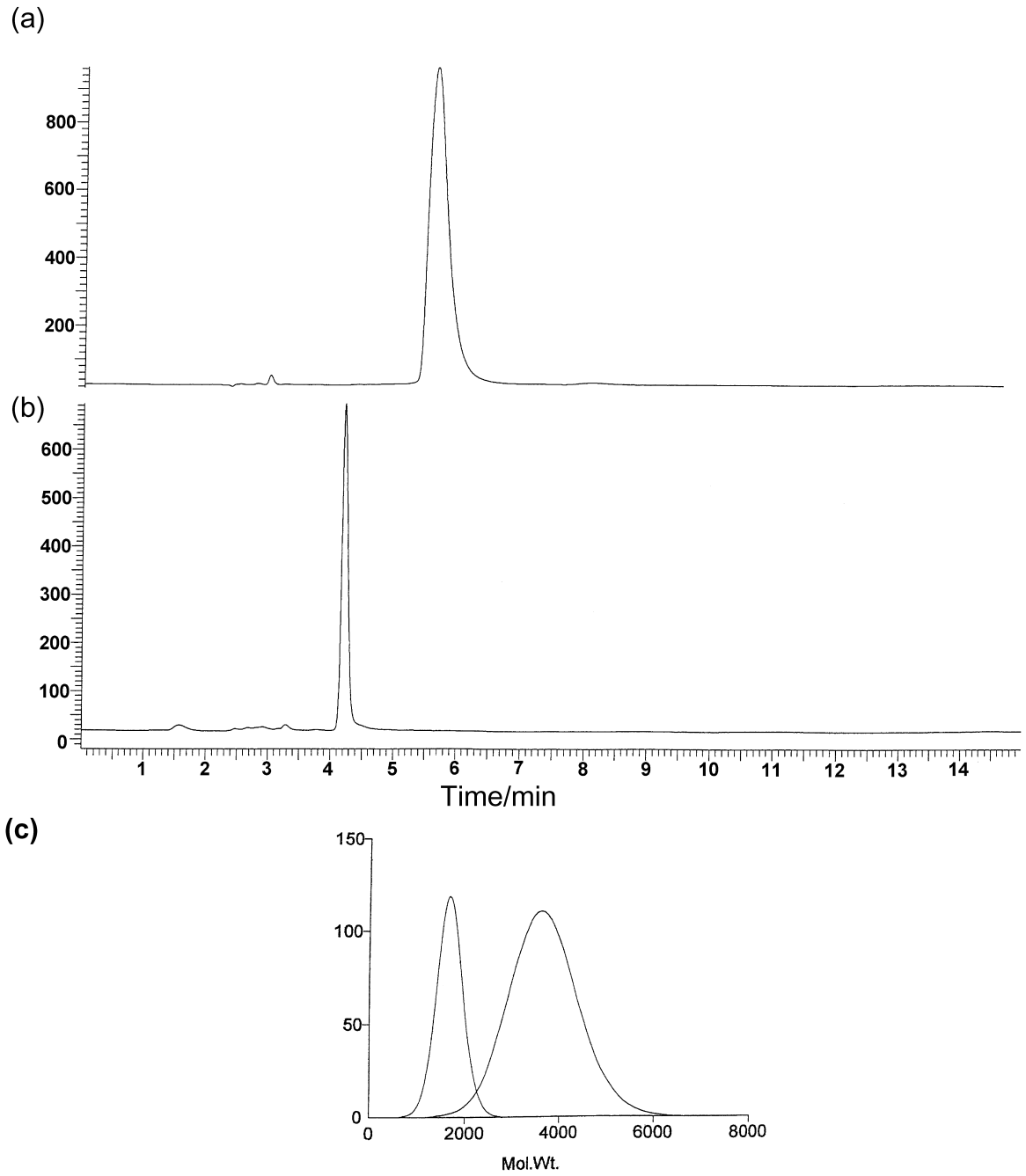


Figure 2. Chromatographic analysis of the dendritic systems: (a) and (b) reverse phase HPLC analysis and (c) GPC analysis of the first and second generation dendrimers **12** and **13**, respectively.

confirmed that total deprotection of the Boc groups had occurred. A similar procedure was employed for the Boc deprotection of the second generation dendrimer **13** and the desired product $(NH_2)_{12}$-[G-2]$_3$-N **16** (as the triflate salt) was isolated as a white solid in >99% yield.

2.5. Characterization

These novel polyaromatic amide dendritic systems exhibited high solubilities in the majority of the organic solvent systems used in this study ($CHCl_3$, THF, DMF, DMSO). In particular, the presence of the peripheral *tert*-butoxycarbonyl protecting groups ensured that the hyperbranched building blocks were soluble in relatively apolar solvents such as $CHCl_3$. However, whereas the first generation dendrimer **12** dissolved almost immediately in $CHCl_3$, in comparison the second and the third generation dendrimers (**13** and **14**) took longer to dissolve at comparable concentrations (ca. 20 mg/mL). Interesting gelation properties were found in the case of the second generation dendrimer [G-2]$_3$-N **13**, but not for [G-1]$_3$-N **12** when left in solution. Gel formation was observed[33] after allowing the solution to stand for 12 h at room temperature. However, the resultant gel was not robust and could be easily broken up eventually to regenerate a clear solution by either the action of gentle heat or mechanical shaking of the sample. This behaviour was attributed to the formation of intermolecular hydrogen bonds leading to self-association/aggregation of

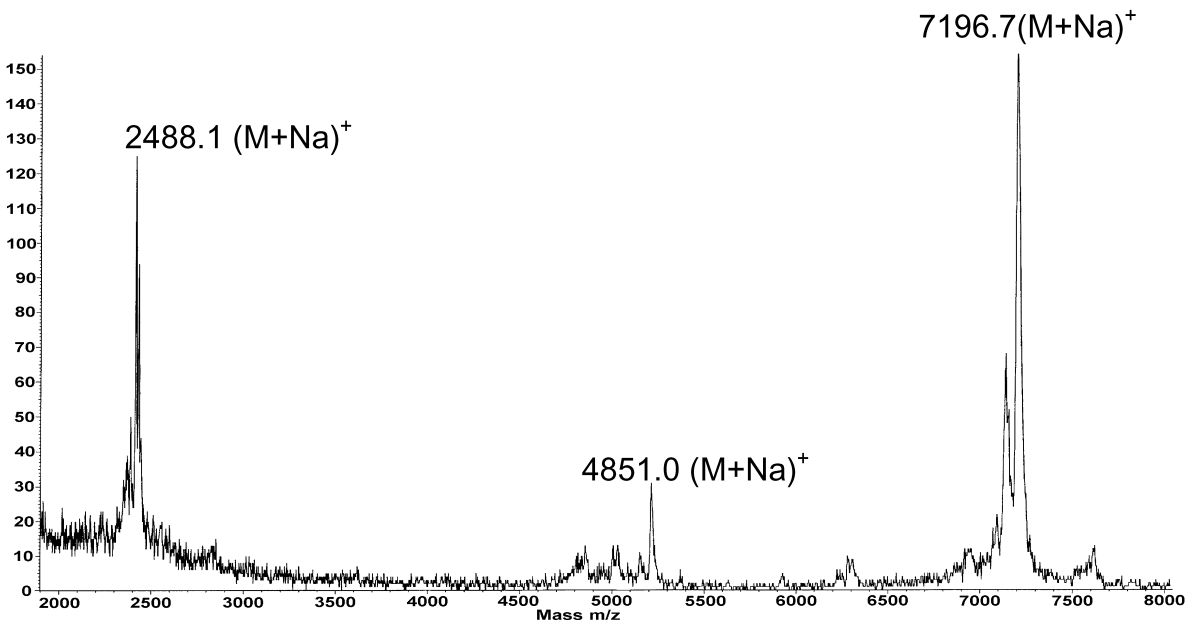
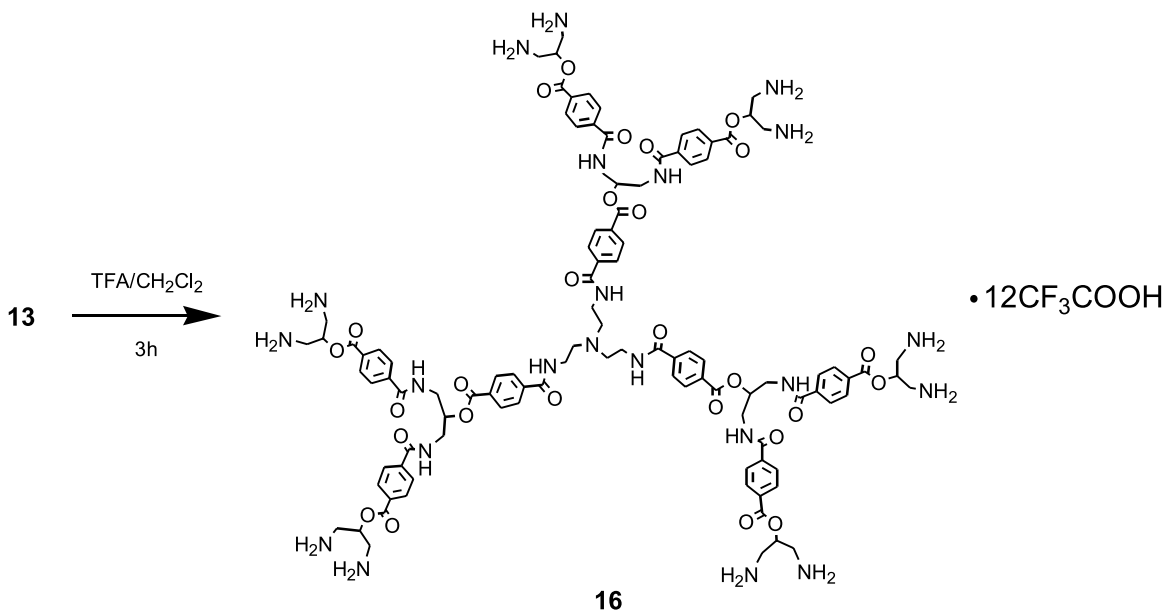


Figure 3. MALDI TOF mass spectrometric analysis of the third generation dendrimer **14** after purification via size exclusion chromatography. (*trans*-Indoleacrylic acid was used as the matrix and the analysis was performed in linear mode.)



Scheme 5. Synthesis of the deprotected second generation dendrimers **16**.

the dendritic macromolecules in solution especially at higher generation dendrimers (with higher number of amide and carbamate groups). The fact that these gelation properties are observed only in relatively apolar solvents such as $CHCl_3$ and not in more polar solvents such as DMF or DMSO reinforces this hypothesis. The self-association properties of these structures via hydrogen bonding phenomena was also evident from ^{1}H NMR spectroscopic investigations.[34] The ^{1}H NMR spectrum of the second generation dendrimer **13** in $CDCl_3$ revealed numerous broad resonances that were assigned to the dendritic structure proposed. However, when the same compound was reanalysed in deuterated DMSO, the resolution of the resonances in the ^{1}H NMR spectrum obtained had increased. Furthermore, as the temperature of the deuterated DMSO solution was increased (up to 90°C), the line-width was reduced significantly (especially in the aliphatic region); an observation consistent with the disruption of intra- and intermolecular hydrogen bonding and an increased rate of rotation of the amide bonds (see Fig. 4). In addition, the aromatic protons signals revealed only a small chemical shift variation ($\Delta\delta$ ca. 0.02 ppm) as the temperature of the solution was increased, whereas a significant variation ($\Delta\delta$ ca. 0.5 ppm) could be observed for the amide and carbamate protons, confirming the predominance of hydrogen bonding (in comparison to other type of interaction such as $\pi-\pi$ stacking interactions). The temperature coefficient $|\Delta\delta/\Delta T|$ has been used to obtain

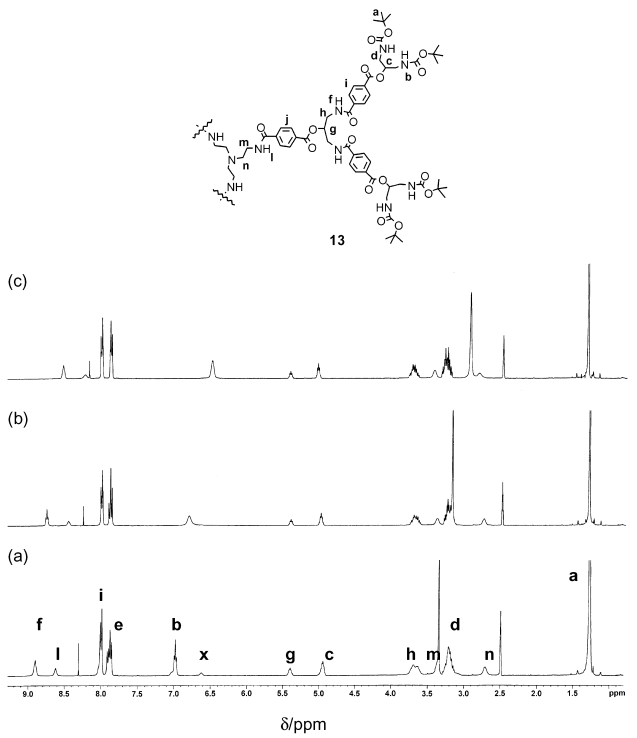


Figure 4. ^{1}H NMR spectra of the second generation dendrimer **13** recorded at 400 MHz in d_6-DMSO at (a) 20°C, (b) 50°C and (c) 90°C.

an indication of the presence of intra- or intermolecular hydrogen bonding.[35] When the value of this coefficient is less then 2.0×10^{-3} ppm K^{-1} in deuterated DMSO, the presence of intramolecular hydrogen bonding is indicated; whereas values greater then 4.0×10^{-3} ppm K^{-1} are attributed to intermolecular hydrogen bonding. Relatively high temperature coefficients were observed for the carbamate protons as well as for the outer and inner amide protons in this system (7.0×10^{-3} and 5.7×10^{-3} ppm K^{-1}, respectively), suggesting that not only the peripheral carbamate groups are involved in intermolecular hydrogen bonding but also the amide protons of the 'internal' layers. In general, despite the large size of these systems, their symmetrical architecture simplified the peak assignment. In fact, the ^{1}H NMR spectrum of the second generation dendrimer **13** clearly reveals the presence of the different generation layers of branched building blocks within the dendritic structure. The resonance observed at 8.96 ppm was attributed to the amide bonds of the outer shell (**f** in Fig. 4); whereas the signal of the amide bonds in the inner layer (**I**) was observed at higher field (ca. 8.68 ppm). The aromatic protons (**j** and **i**) resonate between 7.93 and 8.03 ppm, and the resonance of the protons of the peripheral carbamate groups (**b**) was observed at 7.04 ppm. Both the amide and carbamate proton resonances were evident as a partially resolved multiplet at room temperature that broadens significantly as the temperature of the solution was increased in conjunction with a concomitant upfield shift ($\Delta\delta$ ca. 0.55 ppm). An interesting feature related with the carbamate proton resonances is the presence of a small signal (**x**) (~6.65 ppm) that is present in the ^{1}H NMR spectra of all the dendritic system formed from the Boc protected branching unit. Interestingly, the integration of the proton resonance of the carbamate group was slightly lower then the expected value (by approximately one-tenth) but, when the integral of this 'satellite' peak was added to the integral of the proton resonance of the carbamic group, a perfect correspondence to the predicted value was found. Similar results were reported[36] by Schlüter and co-workers when preparing Boc terminated poly(aromatic amide) dendrimers and the presence of this satellite peak was attributed to intermolecular hydrogen-bonding within the dendritic aggregates. This hypothesis was supported with the disappearance of these peaks when d_4-MeOH was added in order to suppress the formation of the aggregates. However, the addition of d_4-MeOH (50%) to the solution of **13** in deuterated DMSO before recording the ^{1}H NMR spectrum did not lead to a considerable variation of the intensity of this peak. Chow et al. obtained[37] a similar result and attributed the two proton resonances to the *anti* and *syn* rotamers of the carbamic groups. In the case of secondary amides or carbamates, the *anti*-rotamer is more stable by *ca*. 1 kcal mol^{-1} at room temperature with respect to the corresponding *syn*-rotamer, thus leading to two peaks of different intensities in the ^{1}H NMR spectrum. The presence of these two rotamers associated with Boc-carbamate groups has been described[38] by Nudelman and co-workers when α-amino acid derivatives of this type have been studied. Consequently, the main proton resonance at 7.04 ppm was attributed to the energetically favoured *anti*-rotamer of the carbamate group and the peak at 6.65 ppm to the corresponding *syn*-rotamer, thereby the exact number of carbamate protons was the product of the sum of the integrals of both signals. The temperature increase leads, as expected, to the disappearance of the signal related to the less favoured rotamer with the formation of a single averaged peak as a consequence of the faster rotation around the amide bond.

The methine protons of the outer and inner layers of the poly(aromatic amide) dendritic systems can be distinguished clearly in their ^{1}H NMR spectra, resonating as complex multiplets at 4.95 and 5.40 ppm, respectively (**c** and **g**). The methylenic protons of the outer and inner layer of the dendritic branches resonate as complex multiplets at 3.20 and 3.70 ppm, respectively (**d** and **h**); whereas in the case of the methylenic protons associated with the core systems only the proton resonance of those closer to the central amine (**n**) can be observed, as the other methylene signal (**m**) is overlapped by the resonance of the residual water present in DMSO. However, on increasing the temperature, the resonance of the water protons shifts to higher field and it was possible to observe the resonance of the methylene protons (**m**). All the dendritic systems from the second generation onwards revealed the tendency to encapsulate solvents as also observed in the ^{1}H NMR spectrum of the dendrimer **13** from the peak of $CHCl_3$ at 7.30 ppm that could not be eliminated even after prolonged placement of the sample under high vacuum.

The molecular weights of the dendrons and the corresponding dendrimers were investigated using a combination of MALDI-TOF mass spectrometric analysis and gel permeation chromatography (see Figs. 2c and 3). Optimum results were obtained when *trans*-2-indoleacrylic acid was used as the matrix. The mass spectra of the first (MW 1430.8 $(M+Na)^+$ and 1446.9 $(M+K)^+$) and second (MW 3352.6

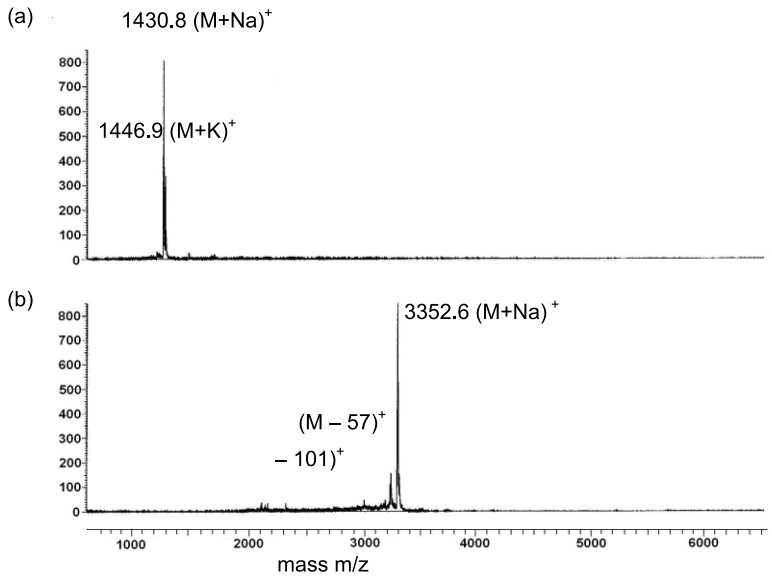


Figure 5. MALDI-TOF mass spectra of the first (a) and second (b) generation dendrimers **12** and **13**, respectively.

$(M+Na)^+$) generation dendrimers are shown in Figure 5 ((a) and (b), respectively). An interesting feature that was observed in the spectra of the different generation dendrons and dendrimers was the presence of smaller peaks of lower mass differing by ca. 55–57 and 101 amu from the mass ions corresponding to the desired dendritic products. These peaks correspond approximately to the loss of *tert*-butyl $(CH_3)_3C-$ and a *tert*-butylcarbonate $(CH_3)_3COOC-$ groups, respectively, indicating clearly the involvement of a peripheral Boc group of the dendritic system. This observed fragmentation pattern was very similar to that revealed by CI MS when compounds bearing Boc protecting groups are analysed. Furthermore, if a Boc group had been cleaved from the dendritic system in one of the steps of the convergent dendrimer synthesis, only the peak corresponding to the mass loss of all the Boc group (i.e. 101 amu) should have been present. In addition, the ^{1}H NMR spectra did not reveal the presence of impurity or structural defects in the dendritic systems because the integration of all the protons resonances corresponded to the exact number of protons of the 'perfect' dendritic structure. To date, MALDI-TOF mass spectrometric has been considered a 'mild' technique for the determination of the mass of macromolecules that are susceptible to extensive decomposition during other types of mass spectrometric techniques (i.e. CI or EI MS). However, fragmentation occurring during the MALDI-TOF mass spectrometric analysis induced by the exposure to the acidic matrix and to intense laser light has been described for both dendrimers and hyperbranched polymers.[39] Since Boc groups are removed under acidic conditions, the use of *trans*-2-indoleacrylic acid as the matrix could have caused this fragmentation especially under irradiation by the MALDI-TOF mass spectrometry nitrogen laser source.

The thermal stability of the poly(aromatic amide) dendrons and corresponding dendrimers was revealed by differential scanning calorimetry (DSC) analysis. Glass transition temperatures (T_g) were not observed (even after several heating/cooling cycles) for these type of structures. However, melting endotherms were observed for all the dendritic systems within a range of ca. 200–250°C indicating the presence of a partial crystallinity that is related to the formation of a relatively organised hydrogen bonding network-findings consistent with related studies.[27,40] A higher melting endotherm was also observed for all the dendron and dendrimer systems at ca. 350°C that was probably related to decomposition of the aliphatic backbone, although thermo-gravimetric analyses have not been carried out to confirm this hypothesis.

2.6. Metal binding assays

A preliminary study of the metal affinity of the poly(aromatic amide) dendrimers was carried out using NMR spectroscopic analysis. The frequencies and linewidths of the resonances of a series of Group I metal nuclei (^{7}Li, ^{23}Na, ^{39}K and ^{133}Cs) were studied in deuterated acetonitrile in the presence of the $[G\text{-}1]_3$-N **12**. In all cases, minimal changes in the chemical shift value of the metal nuclei resonances were observed (the maximum was $\Delta\delta \sim 0.2$ ppm in the case of ^{7}Li)—however, significant differences in the linewidths of the resonance of the lithium and sodium nuclei were evident (see Fig. 6). The spin-lattice relaxation constants (T_1) were thus calculated for these nuclei in the presence of the dendritic ligand species and compared to the free metal nuclei in solution. In the case of ^{23}Na, the spin-lattice relaxation constant decreased from 22 ms in the original sample to 9 ms when the dendrimer was added. An even more dramatic change was observed for ^{7}Li—in this case the spin-lattice relaxation constant decreased from 2.3 s in the original sample to 1.1 s when the dendrimer was added. It is worth noting that although a substantial increase in linewidth was observed in the ^{39}K NMR spectra of the dendrimer/K^+ mixture, the extreme insensitivity of the ^{39}K nucleus prevented accurate determination of the metal

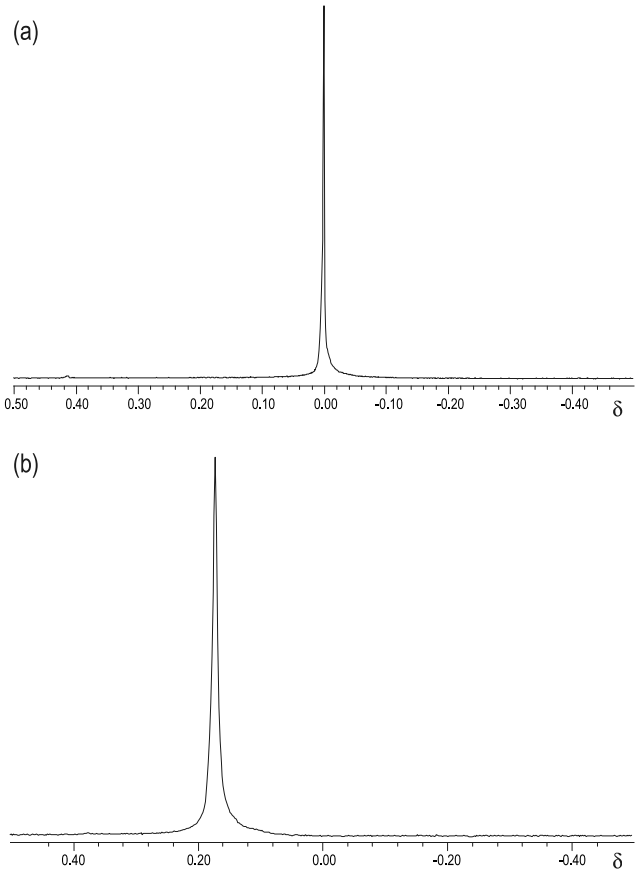


Figure 6. 116.6 MHz ^{7}Li NMR spectra recorded in CD_3CN at room temperature of (a) a 15 mM solution of $LiBF_4$ and (b) a mixture $LiBF_4$ and **12** each at a concentration of 15 mM.

cation T_1. These results are consistent with the hypothesis that the metal ions in solution are bound inside the dendrimer system[41] or within dendritic aggregates.[42]

3. Conclusion

Molecular modelling studies of this class of dendrimers were used to predict potential solution state conformations and the results of these studies proved consistent with related theoretical treatments of hyperbranched polymers. A convergent growth strategy has been employed to construct a series of novel polyaromatic dendrimers that feature *tris*-(2-ethylamino)amine as the central core unit and a branched building block comprised of 1,3-diamino-2-hydroxypropane and 4-carboxybenzaldehyde. The dendritic growth involved the cyclic repetition of esterification, oxidation and selective amidation steps and a wide range of coupling agents were studied in order to optimize the amidation and esterification reactions. The novel hyperbranched systems have been characterized by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry. Interesting gelation behaviour was observed for the higher generation dendrimers in relatively apolar solvents such as $CHCl_3$. Furthermore, preliminary spectroscopic investigations have revealed interesting binding characteristics for a range of metals. This class of novel dendrimers has also been utilized[43] as a suitable scaffold upon which to develop chiral macromolecules, which in turn, may find applications in homogeneous catalysis.

4. Experimental

4.1. Molecular modelling studies

The minimum energy conformations of the [G-1]-OH **1**, and [G-2]-OH **2** dendrons were generated by combining molecular mechanics and molecular dynamics techniques using the Cerius2 v4.2.[44] The Universal Force-Field v1.02[45] and QEq charges were used in each case. Initially, structures were constructed using a graphical user interface and the energies of these structures minimised initially by the steepest descent method followed by a truncated Newton-Raphson method. In order to obtain the low energy conformations of the dendrons, two molecular dynamics simulations for each dendron were carried out on the structures using an NVT ensemble; one simulation starting with the dendrons possessing a folded-back conformation and the other simulation beginning in an extended linear form. These simulations were performed with single molecules in the gas phase at 1000 K for a period of 50 ps using a time-step of 1 fs and trajectory files containing the atomic co-ordinates were saved after every 50 iterations. Ten structures that had a low potential energy were then extracted from each trajectory file and these were then energy minimised as described above. The resulting set of 20 conformers for each molecule was then ranked according to their minimised energy level and the conformer with the lowest energy was selected for each dendron.

4.2. General methods

Triethylamine was dried over 4 Å molecular sieves and distilled before use. All other reagents were purchased from Aldrich Chemical Company or Acros Chimica, and were used as received without purification. Solvents were used as supplied, with the exception of the following: dimethylformamide (DMF), dichloromethane and pyridine were distilled from calcium hydride under reduced pressure; tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl, and methanol (MeOH) was distilled from anhydrous calcium sulfate under reduced pressure.

Thin-layer chromatography (TLC) was performed on aluminium sheets coated with Merck 5735 Kieselgel 60F. Developed TLC plates were air-dried and scrutinized under a UV lamp. Sorbsil 60 (0.040–0.063 mm mesh, Merck 9385) was used to perform column chromatography. Melting points were determined on an Electrothermal digital melting points apparatus and are uncorrected. Differential scanning calorimetry (DSC) was performed using a Mettler DSC 20 System. Mass spectra (MS) of lower molecular weight materials were obtained using a VG Autospec mass spectrometer operating in the chemical ionisation mode employing ammonia as the impact gas or fast atom bombardment mode using nitrobenzyl alcohol as the matrix. ESI mass spectra were recorded on a Micromass LCI Mass Spectrometer using CH_3CN/H_2O 50:50 as the mobile phase. MALDI-TOF mass spectra were obtained

using either a SAI LT3 LaserTof or a Bruker Biflex IV mass spectrometers with *trans*-3-indoleacrylic acid as the matrix. A typical sample preparation is described as follows: 3 μL of a solution of the analyte in THF (1–10 mg/mL) was combined with 10–20 μL of the freshly prepared matrix (0.1 or 0.2 M in THF) in a minivial, and from the mixture was taken a 2 μL aliquot which was transferred onto a sample plate and left to air dry prior to analysis. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC250 (250 MHz) or Bruker AMX400 (400 MHz) spectrometers (using the solvent proton signal as internal reference). ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC250 (62.5 MHz) or Bruker AMX400 (100.1 MHz) spectrometers. The metal binding assays were performed using a Bruker AM300 equipped with a 10 mm broadband probe. The deuterated solvent employed in all cases was CD_3CN. The binding assays were carried out as follows: the metal salts—tetrafluoroborate salts of Li, Na and K, respectively, and the tetraphenylborate salt of Cs—were dissolved in CD_3CN at an approximate concentration of 15 mM. Approximately 2.3 mL was transferred into a clean, dry 10 mm NMR tube and the spectra recorded. Subsequently, an equimolar amount of the first generation dendrimer [G-1]$_3$-N **12** was added this solution and the spectrum of this mixture was then recorded after a short equilibration period (approximately 2 min). The two spectra were then compared in order to determine the change in the chemical shift value ($\Delta\delta$) of the metal nucleus resonance. Infrared (IR) spectroscopic analyses were performed on a Perkin Elmer 1720-X Infrared Fourier Transform spectrometer using Nujol mulls for sample preparation. Preparative gel permeation chromatography (GPC) was performed on Bio-Beads® S-X1 beads (BIO-RAD), 200–400 mesh, with THF as the mobile phase. Analytical GPC was performed on a PL-GPC 220 coupled with a refractive index detector, with THF as the eluent at a flow rate of 1.0 mL min^{-1} and temperature of 40°C. HPLC analysis of the dendrimers was carried out using a Perkin Elmer Series 200 LC pump in conjunction with either an Applied Biosystems 785A programmable absorbance detector (operating at a single wavelength of 254 nm) or a Polymer Laboratories PL-RI 800 refractive index detector. The sample concentration employed in analytical scale separations was 0.05 mg/mL with an injection volume (20 μL) introduced onto a LiChrosorb RP18 column (15 cm×4.6 mm i.d.). The flow rate of the mobile phase (90:10 CH_3CN/H_2O) was 1 mL/min.

4.2.1. *tert*-Butoxy-3-(*tert*-butoxycarbonylamino)-2-hydroxypropylaminomethane [G-1]-OH (1).[13] To a solution of 1,3-diamino-2-hydroxypropane **3** (1.00 g, 11.0 mmol) in THF/H_2O (1:1, 18 mL) was added, a solution of di-*tert*-butyldicarbonate (6.55 g, 30.0 mmol) dissolved in THF (15 mL) dropwise over 30 min. The mixture was stirred for 24 h and then the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (20 mL), washed with 10% citric acid (aq.) (2×20 mL) and then with water (20 mL). The organic phase was dried over $MgSO_4$, filtered under reduced pressure and then the solution was concentrated in vacuo to obtain a pale oil that was precipitated by adding petroleum ether (60–80°C) to afford **1** as a white solid (2.81 g, 95%). Mp: 98–100°C. TLC R_f 0.6 (CH_2Cl_2/EtOH, 6:4). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (18 H, s, $(CH_3)_3C$), 3.14 (4H, m, $-NHCH_2$), 3.66 (1H, m, $-CH-$), 5.18 (2H, bs, $-NH$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.7, 43.9, 71.1, 80.1, 156.6; IR ν 3488, 3312, 1688 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{26}N_2O_5$: 290.1842 (M^+); obsd: 291.1928 (M+H).

4.2.2. 2-(*tert*-Butoxycarbonylamino)-1-(*tert*-butoxycarbonylaminomethyl)ethyl-4-formyl benzoate [G-1]-ArCHO (4). A solution of **1** (0.39 g, 1.33 mmol), 4-carboxybenzaldehyde (0.20 g, 1.33 mmol) and catalytic amount of dimethylaminopyridine (DMAP) in dry CH_2Cl_2 (5 mL) was cooled to 0°C under nitrogen. Dicyclohexylcarbodiimide (DCC) (0.23 g, 1.33 mmol) in dry CH_2Cl_2 (5 mL) was then added dropwise to the stirred solution. The mixture was stirred for 12 h and then filtered. The organic solution was concentrated in vacuo and the residue dissolved in EtOAc (10 mL) and then washed with 5% $NaHCO_3$ (aq.) (10 mL) and water (10 mL). The organic phase was dried over $MgSO_4$, filtered and then concentrated in vacuo to afford the crude product that was purified by crystallization from hexane-EtOAc to yield the pure product **4** as a white powder (0.47 g, 68%). Mp 88–90°C. TLC R_f 0.4 (CH_2Cl_2/EtOH, 95:5). ^{1}H NMR (250 MHz, d_6-DMSO) δ 1.31 (18H, s, $(CH_3)_3C$), 3.22 (4H, m, $-OCONHCH_2-$), 4.99 (1H, m, $-CHOCO-$), 7.04 (2H, bm, $-NHCOO-$), 8.02 (2H, AA′XX′, Ar-H), 8.16 (2H, AA′XX′, Ar-H), 10.11 (1H, s, CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.7, 40.6, 73.8, 80.1, 129.8, 130.8, 135.3, 139.6, 156.7, 165.4, 192.1; IR ν 3348, 1722, 1708, 1686 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{30}N_2O_7$:422.2053, (M^+); obsd: 423.2116 (M+H).

4.2.3. 4-[2-(*tert*-Butoxycarbonylamino)-1-(*tert*-butoxycarbonylaminomethyl)ethyloxy carbonyl]benzoic acid [G-1]-ArCO$_2$H (5). A solution of **4** (0.20 g, 0.47 mmol) in dry pyridine (5 mL) was cooled down to 0°C and then $KMnO_4$ (0.07 g, 0.47 mmol) was added portionwise. The reaction mixture was allowed to warm to room temperature and then stirred for a further 12 h. The solution was concentrated in vacuo and the resultant dark residue dissolved in CH_2Cl_2 (10 mL). The dark coloured organic solution was washed with 0.5% HCl (aq.) and then filtered. Evaporation of the solvent under reduced pressure afforded the **5** as a white solid (0.19 g, 93%). Mp 98–100°C. TLC R_f 0.7 (CH_2Cl_2/EtOH, 8:2). ^{1}H NMR (250 MHz, d_6-DMSO) δ 1.32 (18H, s, $(CH_3)_3C$), 3.20 (4H, bm, $-OCONHCH_2-$), 4.98 (1H, bm, $-CHOCO-$), 7.03 (2H, bm, $-OCONH-$), 8.05 (4H, bm, Ar-H); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 28.5, 40.5, 73.7, 78.2, 129.5, 130.0, 133.3, 135.6, 156.1, 165.6, 167.0; IR ν 3323, 1702, 1680 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{30}N_2O_8$: 438.2002, (M^+); obsd: 439.2084 (M+H).

4.2.4. Second generation dendron [G-2]-OH (2). Diphenylphosphorylazide (DPPA) (0.98 mL, 4.58 mmol) was added under nitrogen to a solution of **5** (2.00 g, 4.56 mmol), 1,3-diamino-2-hydroxypropane (0.21 g, 2.28 mmol), and freshly distilled triethylamine (4 mL, 28.70 mmol) in dry THF (20 mL). The mixture was stirred for 24 h at room temperature and then the solvent was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (40 mL), washed with water (2×30 mL) and then dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded **2** as a white solid (1.76 g, 83%). Mp 235–237°C. TLC R_f 0.5 (CH_2Cl_2/EtOH, 9:1). ^{1}H

NMR (250 MHz, d_6-DMSO) δ 1.32 (36H, s, $(CH_3)_3C$), 3.25 (12H, bm, $-OCONHCH_2-$), 4.98 (2H, bm, $-CHOCO$), 5.25 (1H, bm, $-CHOH$), 7.03 (4H, bm, $-OCONH-$), 7.98 (8H, AA′XX′, H-Ar), 8.70 (H, bm, $-CONH-$); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 28.7, 40.5, 43.5, 69.9, 73.6, 80.1, 127.6, 130.3, 132.9, 138.2, 156.9, 165.6, 168.3; IR ν 3339, 1716, 1686 cm^{-1}; MALDI-TOF MS calcd for $C_{45}H_{66}O_{15}N_6$: 930.65, (M^+); obsd: 953.97 $(M+Na)^+$, 969.95 $(M+K)^+$.

4.2.5. Second generation dendron [G-2]-ArCHO (6). Employing an identical procedure used to produce **[G-1]-ArCHO 6**, the second generation dendron [G-2]-ArCHO **6** was obtained as a white solid (0.108 g, 74%) from [G-2]-OH **2** (0.12 g, 0.13 mmol), 4-carboxybenzaldehyde (0.02 g, 0.13 mmol), dry THF (2 mL), DCC (0.03 g, 0.13 mmol) and DMAP (catalytic amount). Mp 233–235°C. TLC R_f 0.6 (CH_2Cl_2/EtOH, 9:1). ^1H NMR (250 MHz, d_6-DMSO) δ 1.35 (36H, s, $(CH_3)_3C-$), 3.27 (8H, bm, $-OCONHCH_2-$), 3.74 (4H, bm, $-CONHCH_2-$), 5.01 (2H, bm, $-CHOCO-$), 5.50 (1H, bm, $-CHOCO-$), 7.07 (4H, bm, $-OCONH-$), 7.93 (2H, AA′XX′, H-Ar), 8.07 (8H, AA′XX′, H-Ar), 8.21 (2H, AA′XX′, H-Ar), 8.98 (2H, bm, $-CONH-$); 10.16 (1H, s, CHO); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 28.1, 40.7, 43.5, 72.9, 73.3, 77.8, 127.1, 129.4, 129.5, 130.0, 132.4, 134.8, 138.1, 139.0, 156.8, 164.9, 165.1, 166.0, 192.1; IR ν 3340, 1720, 1708, 1626 cm^{-1}; MALDI-TOF MS: calcd for $C_{53}H_{70}O_{17}N_6$: 1062.78 (M^+); obsd: 1086.52 $(M+Na)^+$, 1102.43 $(M+K)^+$.

4.2.6. Second generation dendron [G-2]-ArCO$_2$H (7). A solution of **6** (0.50 g, 0.47 mmol) and pyridinium dichromate (PDC) (0.47 g, 1.25 mmol) in dry DMF (5 mL) was stirred at room temperature for 48 h. Water (10 mL) was added to the mixture and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phases were washed with 1M HCl (10 mL) and brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and then concentrated in vacuo to afford a cream solid that was purified by column chromatography (CH_2Cl_2/EtOH, 95:5). The pure product **7** was isolated as a white solid (0.28 g, 55%). Mp 236–238°C. TLC R_f 0.5 (CH_2Cl_2/EtOH, 85:15). ^1H NMR (250 MHz, d_6-DMSO) δ 1.23 (36H, s, $(CH_3)_3C$), 3.16 (8H, bm, $-OCONHCH_2-$), 3.59 (4H, bm, $-CONHCH_2-$), 4.90 (2H, bm, $-CHOCO$), 5.35 (1H, bm, $-CHOCO-$), 6.95 (4H, bm, $-OCONH-$), 7.86 (12H, AA′XX′, H-Ar), 8.92 (2H, bm, $-CONH-$); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 27.3, 39.2, 39.9, 71.0, 72.1, 78.7, 126.5, 128.4, 128.6, 129.3, 131.5, 131.9, 132.0, 136.5, 156.3, 164.1, 164.7, 166.5, 167.1; IR ν 3323, 1704, 1680 cm^{-1}; MALDI-TOF MS: calcd for $C_{53}H_{70}O_{18}N_6$: 1078.78 (M^+); obsd: 1102.23 $(M+Na)^+$.

4.2.7. Third generation dendron [G-3]-OH (8). 1-Benzotriazolyloxy-*tris*-(dimethylamino)-phosphonium hexafluorophosphane (BOP) (0.161 g, 0.36 mmol) was added under nitrogen to a solution of **7** (0.39 g, 0.36 mmol), 1,3-diamino-2-hydroxypropane (0.16 g, 0.18 mmol), and freshly distilled triethylamine (0.1 mL, 0.72 mmol) in dry CH_3CN (3 mL). The mixture was stirred for 12 h at room temperature and brine (10 mL) was added. The aqueous phase was extracted with EtOAc (2×30 mL) and the combined organic phase wee dried over Na_2SO_4, and evaporated in vacuo. Column chromatography ($CHCl_3$/EtOH, 88:12) afforded **8** as a white solid (0.39 g, 65%. Mp 245–247 °C. TLC R_f 0.6 ($CHCl_3$/EtOH, 88:12). ^1H NMR (250 MHz, d_6-DMSO) δ 1.35 (72H, s, $(CH_3)_3C$), 3.25 (16H, bm, $-OCONHCH_2-$), 3.68 (12H, bm, $-CONHCH_2-$), 5.01 (4H, bm, $-CHOCO$), 5.20 (1H, bm, $-CHOH$), 5.46 (2H, bm, $-CHOCO-$), 7.05 (8H, bm, $-OCONH-$), 8.01 (28H, AA′XX′, H-Ar), 8.73 (2H, bm, $-CONH-$), 8.97 (4H, bm, $-CONH-$); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 28.5, 40.8, 43.5, 72.6, 72.9, 73.5, 78.2, 127.5, 127.7, 129.7, 129.8, 132.6, 132.8, 138.5, 138.7, 156.1, 165.2, 165.4, 166.0, 166.3; IR ν 3323, 1704, 1680 cm^{-1}; MALDI-TOF MS: calcd for $C_{109}H_{146}O_{35}N_{14}$: 2211.01 ($M^+$); obsd; 2234.03 $(M+Na)^+$.

4.2.8. Third generation dendron [G-3]-ArCHO (9). Employing an identical procedure used to produce [G-1]-ArCHO **4**, the third generation dendron [G-3]-ArCHO **9** was obtained as a white solid (0.24 g, 73%) from [G-3]-OH **8** (0.30 g, 0.14 mmol), 4-carboxybenzaldehyde (0.02 g, 0.14 m mol) dry THF (3 mL), DCC (0.03 g, 0.14 mmol) and DMAP (catalytic amount). Mp 236–265°C. TLC R_f 0.7 ($CHCl_3$/EtOH, 9:1). ^1H NMR (250 MHz, d_6-DMSO) δ 1.35 (72H, s, $(CH_3)_3C$), 3.27 (16H, bm, $-OCONHCH_2-$), 3.75 (12H, bm, $-CONHCH_2-$), 5.01 (4H, bm, $-CHOCO$), 5.50 (3H, bm, $-CHOCO$), 7.06 (8H, bm, $-OCONH-$), 7.93 (12H, AA′XX′, H-Ar), 8.08 (14H, AA′XX′, H-Ar), 8.09 (2H, AA′XX′, H-Ar), 8.97 (2H, bm, $-CONH-$), 10.16 (1H, s, CHO); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 28.4, 40.70, 42.3, 43.5, 72.9, 73.4, 73.9, 79.5, 127.0, 127.4, 127.6, 129.5, 129.8, 130.4, 132.6, 132.8, 135.0, 138.4, 138.6, 139.4, 156.1, 165.2, 165.4, 165.8, 166.3, 193.3, IR ν 3338, 1718, 1708, 1655 cm^{-1}; MALDI-TOF MS: calcd for $C_{117}H_{150}O_{37}N_{14}$: 2343.03 ($M^+$); obsd; 2366.13 $(M+Na)^+$, 2382.02 $(M+K)^+$.

4.2.9. Third generation dendron [G-3]-ArCO$_2$H (10). Employing an identical procedure used to produce [G-2]-ArCO$_2$H **7**, the third generation dendron [G-3]-ArCO$_2$H **10** was obtained as a white solid (0.060 g, 49%) from [G-3]-ArCHO **9** (0.13 g, 0.06 mmol), PDC (0.80 g, 0.21 mmol) and DMF (1 mL). Mp 230–232 °C. TLC R_f 0.5 ($CHCl_3$/EtOH, 85:15). ^1H NMR (250 MHz, d_6-DMSO) δ 1.28 (72H, s, $(CH_3)_3C$), 3.21 (16H, bm, $-OCONHCH_2-$), 3.67 (12H, bm, $-CONHCH_2-$), 4.95 (4H, bm, $-CH-$), 5.40 (3H, bm, $-CH-$), 7.00 (8H, bm, $-OCONH-$), 7.87 (28H, AA′XX′, H-Ar), 8.91 (6H, bm, $-CONH-$); ^{13}C NMR (100.1 MHz, d_6-DMSO) δ 28.1, 40.6, 41.2, 43.5, 72.5, 73.2, 73.5, 77.8, 127.1, 127.3, 127.5, 129.1, 129.4, 129.5, 132.3, 132.4, 132.5, 138.1, 138.3, 138.4, 155.8, 164.8, 164.9, 165.0, 165.1, 166.0, 167.5; IR ν 3343, 1725, 1720, 1650 cm^{-1}; MALDI-TOF MS: calcd for $C_{117}H_{150}O_{38}N_{14}$: 2359.02 ($M^+$); obsd; 2382.13 $(M+Na)^+$, 2398.02 $(M+K)^+$.

4.2.10. First generation dendrimer [G-1]$_3$-N (12). BOP (0.300 g, 0.56 mmol) was added to a solution of **5** (0.30 g, 0.68 mmol), tris-(2-ethylamino)amine (0.03 mL), 0.22 mmol) and triethylamine (0.2 mL, 1.44 mmol) in dry CH_3CN (5 mL) under nitrogen. The mixture was stirred for 2 days at room temperature and then water (20 mL) was added. The aqueous phase was extracted with $CHCl_3$ (3×20 mL) and the combined organic phase were dried over Na_2SO_4. The solution was filtered and then concentrated in vacuo to yield the crude product. Column

chromatography ($CHCl_3$/EtOH, 98:2) afforded **12** as a white solid (0.31 g, 83%). Mp 250–252°C. R_f 0.6 ($CHCl_3$/EtOH, 90:10). ^{1}H NMR (250 MHz, d_6-DMSO) δ, ppm 1.30 (54H, s, $(CH_3)_3C$), 2.27 (6H, bm, -$(CH_2)_2N$–); 2.99 (12H, bm, –$OCONHCH_2$–); 3.17 (6H, bm, –$CONHCH_2$–); 4.72 (3H, bm, –CHOCO–); 6.76 (6H, bm, –OCONH–); 7.66 (6H, AA′XX′, H-Ar); 7.70 (6H, AA′XX′, H-Ar); 8.39 (3H, bm, –NH–); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ, ppm 28.5; 38.5; 40.5; 53.7; 73.5; 78.2; 127.6; 129.8; 132.6; 138.6; 156.1; 165.3; 165.7; IR ν 3350, 1699, 1645 cm^{-1}; MALDI-TOF MS: calcd for $C_{69}H_{102}O_{21}N_{10}$ (M^+) 1407.02, found: 1429.60 $(M+Na)^+$; HPLC (CH_3CN/MeOH, 95:5), (retention time 5.7 min), 99.40%; GPC (THF) PDI 1.032; $C_{69}H_{102}O_{10}N_{21}.1H_2O$ calcd C 58.13, H 7.35, N 9.82, found C 58.05, H 7.33, N 9.81.

4.2.11. Second generation dendrimer [G-2]$_3$-N (13). Employing an identical procedure used to produce **[G-1]$_3$-N 12**, the second generation dendrimer [G-2]$_3$-N **13** was obtained as a white solid (0.33 g, 55%) from [G-2]-$ArCO_2H$ **7** (0.60 g, 0.55 mmol), BOP (0.25 g, 0.55 mmol), tris-(2-aminoethylamino) amine (0.026 mL, 0.18 mmol), dry triethylamine (0.16 mL, 1.14 mmol) and dry CH_3CN (6 mL). Mp 241–243°C. TLC R_f 0.5 ($CHCl_3$/EtOH, 88:12). ^{1}H NMR (250 MHz, d_6-DMSO) δ 1.34 (108H, s, $(CH_3)_3C$), 2.77 (6H, bm, –$(CH_2)_3N$–), 3.27 (24H, bm, –$OCONHCH_2$–), 3.74 (18H, bm, –$OCONHCH_2$–), 5.03 (6H, bm, –CHOCO–), 5.46 (3H, bm, –CHOCO), 7.04 (12H, bm, –NH–), 7.93 (18H, AA′XX′, H-Ar), 8.03 (18H, AA′XX′, H-Ar), 8.68 (3H, bm, –CONH–), 8.96 (6H, m, –CONH–); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ, ppm 28.4, 38.0, 41.0, 54.0, 72.9, 73.5, 78.1, 127.3, 127.5, 129.7, 129.8, 132.4, 132.7, 138.4, 138.7, 156.1, 165.1, 165.4, 165.6, 165.8, 166.3; IR ν 3340, 1720, 1650, 1531 cm^{-1}; MALDI-TOF MS: calcd for $C_{165}H_{222}O_{51}N_{22}$: 3327.55 ($M^+$); obsd: 3350.6 $(M+Na)^+$, 3361.5 $(M+K)^+$; HPLC (CH_3CN/MeOH, 95:5), (retention time 4.3 min.), 97.54%; GPC (THF) PDI 1.047; $C_{165}H_{222}N_{22}O_{51}$ calcd C 59.52, H 6.72, N 9.25, found C 60.04, H 6.91, N 9.25.

4.2.12. Third generation dendrimer [G-3]$_3$-N (14). Employing an identical procedure used to produce [G-1]$_3$-N **12**, the third generation dendrimer [G-3]$_3$-N **14** was obtained as a white solid (0.033 g) from [G-3]-$ArCO_2H$ **10** (0.300 g, 0.127 mmol), BOP (0.057 g, 0.127 mmol), tris-(2-aminoethylamino) amine (0.002 mL, 0.014 mmol), dry triethylamine (0.053 mL, 0.38 mmol) and dry CH_3CN (4 mL).

Purification by preparative GPC using THF as the mobile phase was carried out and provided a mixture of products identified by MALDI-TOF mass spectrometric analysis: *m/z* 2488.1 (mono-coupled product+Na)$^+$, 4851.0 (Di-coupled product+Na)$^+$, 7196.7 $(M+Na)^+$.

4.2.13. Deprotected first generation dendrimer (H_2N)$_6$-[G-1]$_3$-N (15). A solution of **12** (0.20 g, 0.14 mmol) in TFA/CH_2Cl_2 (4 mL, 50:50) was stirred at room temperature for 3 h. After evaporation of the solvent, an oily residue was obtained that was triturated with Et_2O to afford the product **15** as a white solid (0.21 g, >99%). ^{1}H NMR (250 MHz, D_2O) δ 3.32 (12H, bm, 6×–CH_2NH_2); 3.44 (6H, bm, 3×–CH_2CH_2N–); 3.70 (6H, bm, 3×–CH_2CH_2N–); 5.42 (3H, bm, 3×–CHOCO–); 7.98 (6H, appt. d, J=8.3 Hz, 6×*H*-ArCONH–); 7.76 (6H, appt. d, J=8.3 Hz, 6×*H*-ArCOO–); 8.31 (12H, bm, 6×–CH_2NH_2); 9.07 (3H, bm, 3×–CH_2CONH–); ^{13}C NMR (62.5 MHz, D_2O) δ 35.6, 40.7, 54.6, 69.1, 114.3, 127.9, 130.4, 131.5, 137.8, 163.5, 167.1, 170.7; IR ν 3286, 1679, 1524, 1203, 1018, 840 cm^{-1}; ESI MS calcd for $C_{39}H_{54}O_9N_{10}$: 806.9, $(M)^+$; obsd: 806.8 $(M)^+$.

4.2.14. Deprotected second generation dendrimer (H_2N)$_{12}$-[G-2]$_3$-N (16). Employing an identical procedure used to produce $(NH_2)_6$-[G-1]$_3$-N **15**, the second generation dendrimer $(NH_2)_{12}$-[G-2]$_3$-N **16** was obtained as a white solid (0.17 g, >99%) from Boc_{12}-[G-2]$_3$-N **13** (0.15 g, 0.05 mmol). ^{1}H NMR (250 MHz, D_2O) δ 3.44 (24H, bm, 12×–CH_2NH_2); 3.69 (18H, bm, 3×–CH_2CH_2N- and 6×–CH_2NHCO–); 3.80 (6H, bm, 3×–CH_2CH_2N–); 5.40 (3H, bm, 3×–CHOCO–); 5.62 (6H, bm, 6×–CHOCO–); 7.20 (6H, appt. d, J=8.5 Hz, 6×*H*-ArCONH–); 7.57 (6H, appt. d, J=8.5 Hz, 6×*H*-ArCOO–); 7.76 (12H, appt. d, J=8.5 Hz, 12×*H*-ArCONH–); 7.97 (12H, appt. d, J=8.5 Hz, 12×*H*-ArCOO–); ^{13}C NMR (62.5 MHz, D_2O) δ 35.6, 40.7, 40.8, 55.0, 69.0, 72.3, 114.3, 127.6, 127.8, 129.6, 130.5, 131.3, 132.8, 137.5, 138.6, 163.5, 166.8, 169.8, 170.7; IR ν 3300, 1680, 1500, 1203, 870 cm^{-1}; MALDI TOF MS: calcd for $C_{105}H_{126}O_{27}N_{22}$: $(M+Na)^+$ 2149.20; obsd: 2149.80 $(M+Na)^+$.

Acknowledgements

B. R. would like to thank the University of Reading Research Endowment Trust Fund for a postgraduate studentship. The authors would like to acknowledge EPSRC (GR/M91884) and SAI Ltd for the funding provided for the MALDI-TOF MS facilities at the University of Reading. The authors would also like to thank EPSRC (GR/R06441) and Polymer Laboratories Ltd for the funding provided for the gel permeation facilities at the University of Reading. W. H. would like to thank EPSRC (GR/M42824) for providing funds for the HPLC equipment used in this study. D. W. P. would like to thank Professor M. G. B. Drew for access to the molecular modelling computing facilities used in this study.

References

1. (a) Tomalia, D. A.; Baker, H.; Dewold, J. R.; Hall, M.; Kallas, G.; Martin, S.; Roack, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117. (b) Fréchet, J. M. J. *Comprehensive Polymer Science*; Russo, A., Ed.; Pergammon: New York, 1996; p 71 Chapter 3; suppl. 2. (c) Vögtle, F.; Gestermann, S.; Hesse, R.; Schwierz, H.; Windisch, B. *Prog. Polym. Sci.* **2000**, *25*, 987.
2. (a) Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J.; Maskus, M.; Abruña, H. D. *Chem. Mater.* **1998**, *10*, 3078. (b) Malenfant, P. R. L.; Groenendaal, L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1998**, *120*, 1647. (c) Brewis, M.; Clarkson, G. J.; Holder, A. M.; McKeown, N. B. *J. Chem. Soc. Chem. Commun.* **1998**, 969.
3. (a) Albrecht, M.; Gossage, R. A.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1998**, 1003. (b) Reetz, M. T.;

Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl* **1997**, *36*, 1526.
4. McElhanon, J. R.; McGrath, D. V. *J. Am. Chem. Soc.* **1998**, *120*, 1526.
5. (a) Wang, P.-W.; Liu, Y.-J.; Devadoss, C.; Bharati, P.; Moore, J. S. *Adv. Mater.* **1996**, *8*, 237. (b) Balzani, V.; Capagna, S.; Denti, G.; Juris, A.; Serroni, S.; Venturi, M. *Acc. Chem. Res.* **1998**, *31*, 26.
6. (a) Kono, K.; Liu, M. J.; Fréchet, J. M. J. *Bioconjugate Chem.* **1999**, *10*, 1115. (b) Liu, M. J.; Fréchet, J. M. J. *Pharmaceut. Sci. Technol. Today* **1999**, *2*, 393. (c) Liu, M. J.; Kono, K.; Fréchet, J. M. J. *J. Controlled Release* **2000**, *65*, 121. (d) Eichman, J. D.; Bielinska, A. U.; Kukovska-Latallo, J. F. K.; Baker, J. R. *Pharmaceut. Sci. Technol. Today* **2000**, *7*, 232.
7. (a) Tomalia, D. A. *Nature* **1994**, *372*, 617. (b) Bhyrappa, P.; Young, J. K.; Moore, J. S.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5708. (c) Mak, C. C.; Chow, H. F. *Macromolecules* **1997**, *30*, 1228. (d) Zhao, M.; Crooks, R. M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 364. (e) Piotti, M. E.; Rivera, F.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9471. (f) Bolm, C.; Derrien, N.; Seger, A. *Synlett* **1996**, 387. (g) Kimura, M.; Sugihara, Y.; Muto, T.; Hanabusa, K.; Shirai, H.; Kobayashi, N. *Chem. Eur. J.* **1999**, *5*, 5495.
8. (a) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4374. (b) Devadoss, C.; Bharathi, P.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1633. (c) Smith, D. K.; Müller, L. *J. Chem. Soc., Chem. Commun.* **1999**, 1915. (d) Issberner, J.; Vögtle, F.; De Cola, L.; Balzani, V. *Chem. Eur. J.* **1997**, *3*, 706. (e) Vögtle, F.; Plecoets, M.; Nieger, M.; Azzallini, G. C.; Credi, A.; De Cola, L.; De Marchis, V.; Venturi, M.; Balzani, V. *J. Am. Chem. Soc.* **1999**, *121*, 6290.
9. Voit, B. I.; Wolf, D. *Tetrahedron* **1997**, *53*, 15535.
10. Murer, P. K.; Lapierre, J.-M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 1648.
11. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.
12. (a) Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010. (b) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
13. Ramalingam, K.; Raju, N.; Nanjappan, P.; Nowotnik, D. P. *Tetrahedron* **1995**, *51*, 2875.
14. Kane, S. A.; Sasaki, H.; Hecht, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 9107.
15. Lindsey, J. S.; Prathapan, S.; Johnson, T. E.; Wagner, R. W. *Tetrahedron* **1994**, *50*, 8941.
16. Wang, S. S.; Tam, J. P.; Wang, B. S. H.; Merrifield, R. B. *Int. J. Pept. Protein Res.* **1981**, *18*, 459.
17. Hu, H.; Mendoza, J. S.; Lowden, C. T.; Ballas, L. M.; Janzen, W. P. *Bioorg. Med. Chem.* **1997**, *5*, 1873.
18. Tecilla, P.; Tonellato, U.; Veronese, A. *J. Org. Chem.* **1997**, *62*, 7621.
19. (a) Rannard, S. P.; Davis, N. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 63. (b) Rannard, S. P.; Davis, N. J. PCT/GB96/03189. (c) Rannard, S. P.; Davis, N. J. *Org. Lett.* **1999**, *1*, 933.
20. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.
21. Pan, Y.; Ford, W. T. *J. Polym. Sci. Polym. Part A: Polym. Chem.* **2000**, *38*, 1533.
22. Ambrovici, S.; Neumann, R.; Sasson, J. *J. Mol. Catal.* **1985**, *29*, 291.
23. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
24. Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
25. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
26. Bodansky, M.; Bodansky, A. *The Practice of Peptide Synthesis*; 2nd ed. Springer Laboratory Manual: Berlin, 1994; pp 124.
27. Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202.
28. Backson, S. C. E.; Bayliff, P. M.; Feast, W. J.; Kenwright, A. M.; Parker, D.; Richards, R. W. *Macromol. Symp.* **1994**, *77*, 1.
29. Appelhans, D.; Komber, H.; Vogt, D.; Häussler, L.; Voit, B. I. *Macromolecules* **2000**, *33*, 9494.
30. Uhrich, K. E.; Fréchet, J. M. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1623.
31. Hayes, W.; Osborn, H. M. I.; Osborne, S. D.; Rastall, R. A.; Romagnoli, B. *Tetrahedron Lett.* **2002**, *43*, 7683.
32. Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 1750.
33. Jikei, M.; Chon, S.-H.; Kakimoto, M.; Kawauchi, S.; Imase, T.; Watanebe, J. *Macromolecules* **1999**, *32*, 2061.
34. Kraft, A.; Osterod, F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1019.
35. Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 512.
36. Klopsch, R.; Koch, S.; Schlüter, A. D. *Eur. J. Org. Chem.* **1998**, 1275.
37. Mong, T. K.-K.; Niu, A.; Chow, H.-F.; Wu, C.; Li, L.; Chen, R. *Chem. Eur. J.* **2001**, *7*, 686.
38. Mizrahi, D. M.; Gottlieb, H. E.; Marks, V.; Nudelman, A. *J. Org. Chem.* **1996**, *61*, 8402.
39. (a) Köllner, C.; Togni, A. *J. Chem.* **2001**, *79*, 1762. (b) Clark, A. J.; Coleshill, A. A.; Haddleton, D. M.; Isles, S. J.; Sahota, H. S.; Taylor, P. C. *Eur. Mass. Spectrom.* **1999**, *5*, 273. (c) Hobson, L. J.; Feast, W. J. *Polymer* **1999**, *40*, 1279.
40. Lach, C.; Hanselmann, R.; Frey, H.; Mülhaupt, R. *Macromol. Rapid Commun.* **1998**, *19*, 461.
41. (a) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689. (b) Stoddart, F. J.; Welton, T. *Polyhedron* **1999**, *18*, 3575. (c) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181.
42. Hanus, L. H.; Sooklal, K.; Murphy, C. J.; Ploehn, H. J. *Langmuir* **2000**, *16*, 2621.
43. Romagnoli, B.; Harwood, L. M.; Hayes, W. *Tetrahedron Lett.* **2003**, *44*, 37.
44. Cerius2 v4.2- Molecular Simulation Incorporated, 9685 Scranton Road, San Diego, CA, USA.
45. UFF v1.02, see Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard-III, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.