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Supramolecular dendrimer chemistry: using dendritic crown ethers to reversibly generate functional assemblies

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Abstract—A series of crown ether derivatives functionalised with dendritic branching based on L-lysine repeat units has been synthesised. The ability of these receptors to interact with cationic guests has been investigated using NMR and mass spectrometric techniques. Binding constants have been evaluated, some using competitive binding assays, and these indicate that the strength of interaction between the encapsulated crown-ether and cationic guests decreases with increasing dendritic functionalisation. The interaction of these dendritic branches with ditopic ammonium cation functionalised templates has been investigated, and Job plot analysis indicates the formation of 2:1 (branch/template) stoichiometric complexes in MeOH solution. These supramolecular assemblies have been disassembled by the addition of potassium cations, hence achieving controlled release of the template back into solution. This process has been investigated by NMR methods and the effect of counteranion on these studies is reported. The use of ditopic ammonium cations possessing long alkyl spacer chains as templates has also been investigated, and in this case, the 2:1 assembly that forms, goes on to achieve higher order levels of organisation, hence gelating the solvent. This particular system is therefore a rare example in which discrete, characterisable dendritic supermolecules possess an inherent potential for further supramolecular assembly, to yield new materials.

1. Introduction

Dendrimer chemistry has developed rapidly since its inception during the 1980s.[1] In general, synthetic chemists now have an excellent degree of control over the covalent synthesis of dendritic superstructures using a wide range of organic and inorganic methodologies. Recently, attention has increasingly turned to the construction of dendritic structures using supramolecular synthetic methods—in other words, synthesising dendrimers which are held together by non-covalent (or supramolecular) interactions.[2] Such systems are easy to construct, with components being simply mixed in solution. In addition, chemical information can easily be programmed into the different building blocks used in the construction of the assembly. Finally, because the connections between the building blocks are non-covalent, they are reversible, and can, in principle, be broken at a precise moment of choice.

Both fully formed spherical dendrimers and individual dendritic branches (or dendrons) have been of interest for their application in supramolecular dendrimer chemistry. Molecular recognition at the multiple surface groups of a spherical dendrimer has been used to achieve multivalent binding.[3] It has been shown that such multivalent recognition offers enhanced binding strength, providing a clear advantage when binding biologically important macromolecules, where the individual binding interactions are weak.[4] Multiple binding events at a dendritic surface have also been shown to dramatically alter the solubility profile of the dendrimer,[5] as the supramolecular assembly generated by this process is surface modified, and it is this modified surface which interacts with the surrounding bulk solvent environment.

Distinct from the surface, the core of spherical dendrimers has been used in supramolecular chemistry to act as an encapsulated binding site. In such cases, the dendritic shell has been shown to have an impact on both the strength and selectivity of guest binding in an analogous way to the manner in which the tertiary structure of a protein can control binding at the active site.[6] A variety of receptors such as dendritic porphyrins,[7] dendroclefts[8] and dendrophanes[9] have been used to bind diverse guests. This approach has also been used to assemble multiple spherical dendrimers. In a keynote example,[10] Diederich and co-workers used a dendrophane receptor to interact with a ditopic guest containing one steroid attached to each end of a rigid molecular rod. This gave rise to a 2:1 supramolecular assembly, with the length of the rod being crucial in controlling the thermodynamics of the assembly process. Dendritic cyclodextrins have been used to generate supramolecular assemblies in a similar way.[11]

Individual dendritic branches (or dendrons) are of increasing interest in supramolecular assembly processes, in part due to the wide variety of structures that can readily be

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synthesised. Zimmerman and co-workers illustrated that well-designed branches could self-assemble through hydrogen bond formation to form a hexameric rosette type structure.[12] This hydrogen bond mediated approach to dendritic assembly has also been applied by other researchers.[13] Meanwhile, Percec and co-workers have exploited the ability of dendrons to assemble into cylindrical and spherical structures with liquid crystalline properties—an approach also exploited by numerous other groups.[14] Dendritic branches have also been shown to assemble in solution to give gel phase materials.[15]

In addition to these dendron-only processes, however, it is also possible to direct the assembly of dendrons through the use of a template (see Figure 1). This approach requires that the focal point of the dendritic branch is capable of interacting with a functional group on the template. Several groups have employed hydrogen bonds for this purpose,[16] others have used ligand–metal interactions,[17] and yet another example cites the use of electrostatically attractive interactions.[18] Gibson and co-workers have recently employed interactions between [24]crown-8 and protonated secondary amine groups to construct supramolecular dendrimers via the formation of rotaxane-type interactions.[19] Stoddart and co-workers have also generated supramolecular dendritic structures using a similar approach.[20]

We have recently exploited acid–amine interactions to assemble dendritic superstructures. We illustrated that the acid functionalised dendritic branches were able to solubilise and transport hydrophilic amine functionalised dyes into and through non-polar solvents.[21] Enhanced solubilisation was achieved by higher generation dendrimers, and furthermore, the optical properties of the dye were also controlled by the degree of dendritic encapsulation. In a separate paper,[22] we also indicated that certain assemblies of dendritic branch and aliphatic diamines were able to assemble yet further in solution, generating gel phase materials.

However, acid–amine interactions are relatively weak, and the assemblies generated were not particularly well defined or easy to characterise. In order to improve on this, we have developed dendritic crown ethers. In a recent preliminary communication[23] we described the ability of these dendritic crowns to bind cationic guest species, in particular, their ability to assemble into supramolecular dendrimers with ditopic ammonium cation guests. These supramolecular assemblies could then be disassembled by the addition of potassium cations, providing us with a means of achieving reversible dendritic encapsulation. This paper reports further details of these investigations, in particular, additional binding data, mass spectral evidence for complexation, the effect of counteranion on the disassembly process and the ability of some of the assembled systems to form novel gel-phase materials.

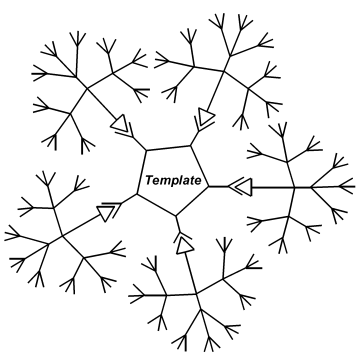
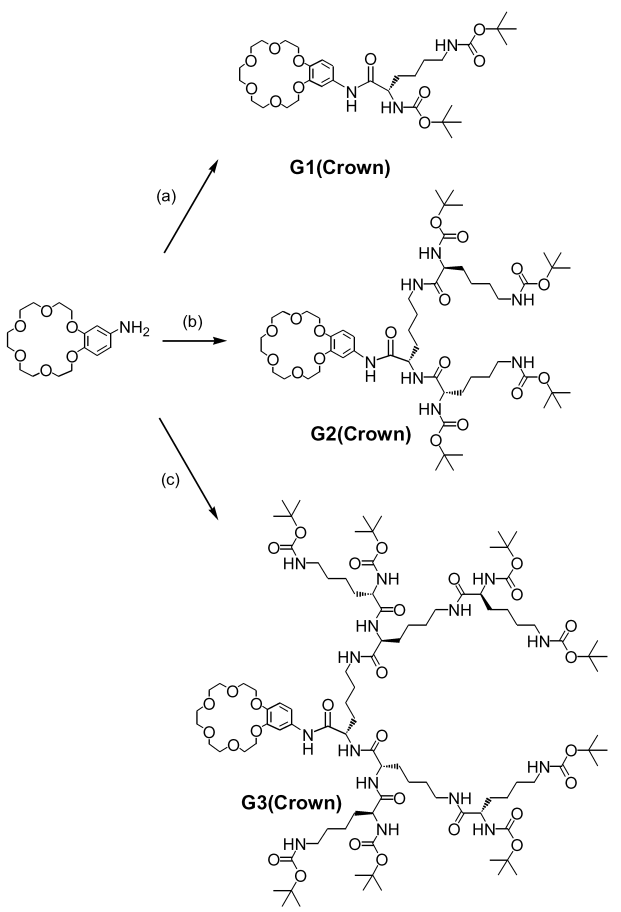


Figure 1. Schematic of a supramolecular dendrimer with individual dendritic branches (dendrons) assembled around a molecular template.

2. Results and discussion

2.1. Synthesis

Target molecules G1(Crown), G2(Crown) and G3(Crown) were synthesised as illustrated in Scheme 1. Commercially available 4′-nitrobenzo-[18]crown-6 was reduced in near quantitative yield according to literature methodology[24] with Pd/C and H_2 in EtOH. The resultant amine was then coupled to L-lysine derived dendritic branches with a carboxylic acid group at the focal point (Gn(COOH)), the synthesis of which has been described by us previously.[21b] For the first generation dendritic branch (G1(COOH)), this coupling reaction could be performed using the classic peptide coupling conditions of DCC/HOBt.[25] The product G1(Crown) was obtained in an excellent yield of 87%.



Scheme 1. Synthesis of the crown ether functionalised dendritic branches: (a) G1(COOH), DCC, HOBt, Et_3N, EtOAc, 87%; (b) G2(COOH), HATU, Et_3N, EtOAc, 91%; (c) G3(COOH), HATU, Et_3N, EtOAc, 63%.

However, for the second generation dendritic branch (G2(COOH)), the coupling reaction became sluggish, and the yield was poor (40%). For third generation dendritic branch (G3(COOH)), the reaction was incomplete and the desired product, present in about 20% yield, could not be purified. This is a common problem associated with convergent coupling methodology,[1e] in which the bulk of the dendritic branches effectively buries the focal point, hence decreasing its reactivity. Consequently, more strongly activating conditions using HATU[26] as coupling reagent were employed, and this approach gave rise to the target second (G2(Crown)) and third (G3(Crown)) generation dendritic crown ethers in excellent yields of 91 and 63%, respectively. Even still, the synthesis of G3(Crown) required heating and a prolonged reaction time. During the synthesis of all three dendritic crown ethers, an excess of 4′-aminobenzo-[18]crown-6 was employed. This was to ensure that there was no remaining Gn(COOH) in the reaction mixture. It would have been very difficult to separate Gn(Crown) from unreacted Gn(COOH) on the basis of molecular size using gel permeation chromatography as they have similar molecular masses, whereas Gn(Crown) could easily be separated from the excess of 4′-aminobenzo-[18]crown-6 using this approach (Biobeads, SX-1, 90:10, CH_2Cl_2–MeOH). Hence the novel dendritic crown ethers were obtained in pure form.

2.2. Characterisation

Characterisation of the novel dendritic crowns was achieved using all standard techniques. Mass spectrometry, which is particularly important for dendritic systems, was performed using electrospray ionisation, and the ions were observed for $[M+Na]^+$ for G1(Crown) and G2(Crown)—no significant fragment peaks or impurities were present. The detection limit of our apparatus was *m/z* 2000, and hence G3(Crown) was observed as a doubly charged ion corresponding to $[M+2Na]^{2+}$. The isotope distributions observed for the mass spectral ions of the larger molecules were consistent with data calculated from isotopic abundances.

^1H and ^{13}C NMR spectra were also fully consistent with the proposed structures. It is interesting to note that the peaks corresponding to the aromatic ring were perturbed by the presence of the dendritic branching, an effect particularly noticeable for the ^{13}C NMR resonances (Table 1), especially with third generation branching. A similar, but less marked effect could be observed for the CH_2–O resonances of the crown ether ring. This is the first indication that the dendritic branching does indeed have an impact on the binding site located at the focal point—in other words the dendritic branching generates a microenvironment at the focal point, an effect often seen in dendritic systems.[27]

Table 1. ^{13}C NMR data (ppm, MeOD) for the resonances of the aromatic ring of Gn(Crown) indicating the effect of dendritic generation on NMR shift

G1(Crown)	G2(Crown)	G3(Crown)
108.7	108.5	106.0
114.3	114.2	112.1
115.7	115.5	113.8
133.6	133.5	133.1
147.1	146.9	145.4
150.3	150.2	148.4

Further characterisation data, including IR, $[\alpha]_D$, R_f, mp and HRMS (where appropriate) can be found in Section 4.

2.3. Binding studies with cationic guests

In the first instance, we were interested in the ability of these dendritic crown ethers to bind simple un-functionalised cationic guests. Given the high affinity and selectivity of [18]crown-6 derivatives for potassium ions,[28] we chose K^+ as a suitable target. As described in Section 1, there has been considerable interest in the ability of an encapsulated binding site to recognise guest species, with the effect of encapsulation on the binding strength being of key interest.[7–9] Surprisingly, however, to the best of our knowledge, this is the first occasion that the ability of a single dendritically encapsulated binding site to bind a single charged guest ion has been described.

^1H NMR titrations in methanolic solution allowed us to unambiguously assign the stoichiometry of binding as 1:1, with clear titration profiles for the aromatic resonances of Gn(Crown) indicating saturation of the receptor on the addition of one equivalent of K^+ (Fig. 2). The binding stoichiometry was independent of dendritic generation. However, the binding constants were too large to be determined by regression analysis of the data. Nonetheless, it was clear that the aromatic protons of G1(Crown), were more strongly perturbed by K^+ than those of G2(Crown), which in turn were shifted further than those of G3(Crown).

In order to determine accurate binding strengths, we developed a new calibrated competitive binding assay, the full details of which have been reported elsewhere.[29] It is well-known that competitive binding experiments allow the elucidation of binding constants for strongly bound complexes.[30] In this case, we used dibenzo-[18]crown-6 as a competing receptor for K^+ ions, and hence determined the binding constants for G1(Crown), G2(Crown) and G3(Crown) (Table 2).

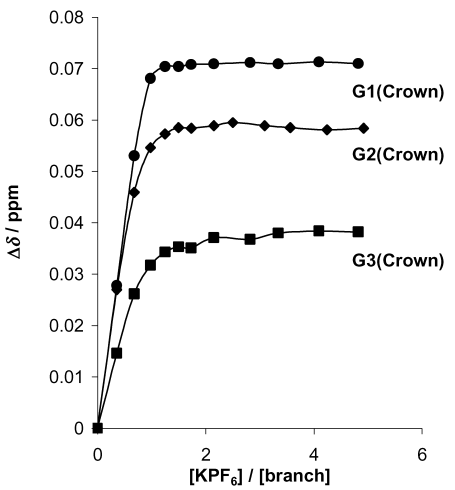


Figure 2. NMR titration curves for G1(Crown), G2(Crown) and G3(Crown) with K^+, monitoring the shift of the aromatic peak (at ca. 6.9 ppm).

Table 2. Binding constants (log K_a, MeOD, T=300 K) elucidated by ^{1}H NMR competition experiments and titration methods for 1:1 complexes of dendritic crown ethers with K^+ and **1** (K_a: units mol^{-1} dm^3, estimated error in K_a values is ±10%)

Receptor	Guest	log K_a	$\Delta\delta_{sat}$ (ppm)
G1(Crown)	K^+	5.01[a]	0.070[b]
G2(Crown)	K^+	4.86[a]	0.050[b]
G3(Crown)	K^+	4.40[a]	0.038[b]
G1(Crown)	1	3.58[c]	0.115[d]
G2(Crown)	1	3.28[c]	0.104[d]
G3(Crown)	1	2.31[c]	0.108[d]

[a] Determined by calibrated competitive method as described in the text.
[b] Saturation shift in the aromatic peak (at ca. 6.9 ppm) of the benzo crown ether induced by the addition of potassium cations.
[c] Determined by NMR titration methods with regression analysis of the data using HYPNMR.[33]
[d] Saturation shift in the CH_2 (benzyl) peak (at 4.10 ppm) on guest **1** induced by the addition of the dendritic crown ether.

The assay developed involved the careful calibration of the recognition process between a reference receptor (dibenzo-[18]crown-6) and K^+. This allowed the determination of a straight-line relationship connecting the concentration of the reference complex and the NMR shift of the aromatic protons of dibenzo-18-crown-6 induced by K^+. Once the calibration had been performed, an NMR spectrum was then measured of a solution containing equimolar concentrations of Gn(Crown), dibenzo-[18]crown-6 and K^+. The induced NMR shift of the aromatic protons of the reference receptor was observed, with the presence of Gn(Crown) diminishing this shift, because it competes for the guest cation. The straight-line relationship previously generated then allowed the concentration of the reference complex in the presence of an equimolar amount of competitive Gn(Crown) to be determined. From this concentration, and the known literature value of the binding constant (K_a) between dibenzo-[18]crown-6 and K^+, the unknown binding constant between Gn(Crown) and K^+ could be calculated using straightforward thermodynamic relationships. In summary, this method allowed us to determine binding constants for each of the novel receptors using a single NMR spectral measurement. This new competitive assay is ideal for rapid screening of large numbers of potential receptors (e.g. combinatorial libraries) and full details can be found elsewhere.[29]

Interestingly, the binding constants indicate that as the extent of dendritic functionalisation of the crown ether increases, so the strength of K^+ binding decreases, with an order of magnitude difference between G1(Crown) and G3(Crown). There are several potential reasons for this negative dendritic effect: (a) donor atoms in the dendritic branching are also able to interact with K^+ and compete with the crown ether for the guest; (b) steric hindrance of the crown ether cavity is provided by the dendritic branches, hence hindering guest binding; (c) the micro-environment generated by the dendritic branching is apolar and therefore less favourable for a charged entity than the surrounding bulk solvent, which in this case is relatively polar methanol. Which of these reasons is dominant in this case could not be determined, but it is interesting to note there is a direct parallel with investigations of encapsulated redox probes, the overwhelming majority of which indicate that the build up of charge inside dendritic structures is a thermodynamically disfavoured process due to the relatively low micropolarity of the internal dendritic microenvironment when compared to the more polar bulk solvent environment.[31]

Binding studies were then performed with a simple, commercially available benzylammonium guest cation (**1**, Figure 3), also in methanol solution. It is well known that [18]crown-6 forms strong complexes with protonated primary amines, with the complex formed having three N^+–H···O hydrogen bonds (Fig. 4).[32] In this case, we followed the binding of dendritic crown ethers to the ammonium cation by monitoring the shift of the Ar–CH_2 protons of the ammonium cation on the addition of increasing amounts of Gn(Crown). Titration curves were obtained, and binding constants determined using HYPNMR (Table 2).[33] The binding constants were approximately two orders of magnitude less than for the simple K^+ cation. This is also the case for unfunctionalised [18]crown-6, and is primarily a consequence of the very high binding affinity of this type of crown for K^+ ions. Interestingly, as for the binding of K^+, it was again observed that the binding constant decreased with the increasing degree of dendritic functionalisation—it might be expected that this is at least partially due to steric effects.

To support these NMR investigations, binding studies were also performed between Gn(Crown) and compound **1** using mass spectrometric techniques. It is possible to perform quantitative mass spectral studies in order to obtain binding constant data,[34] however, in this case a qualitative approach was applied to see whether the proposed complexes could be detected by this method.

After mixing an equimolar amount of Gn(Crown) and ammonium cation **1**, an electrospray mass spectrum was determined. In the case of G1(Crown), the major peak in the mass spectrum corresponded to the complex [G1(Crown)+**1**]$^+$ (Table 3). For G2(Crown), however, this peak had decreased in intensity relative to the peak for [G2(Crown)+Na]$^+$. For G3(Crown), doubly charged

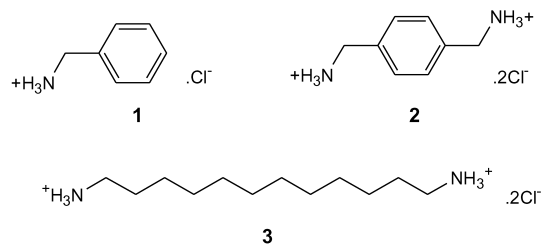


Figure 3. Ammonium cation guests.

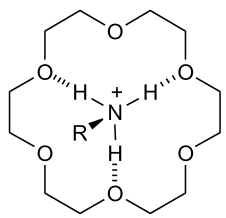


Figure 4. Interaction between 18-crown-6 and an alkylammonium cation.

Table 3. Major mass spectral peaks [with intensities] observed on electrospray MS determination of equimolar amounts of Gn(Crown) and compound **1** in methanol

Compounds	Major mass spectral peaks [intensity]
G1(Crown)+**1**	763 [100%] [G1(Crown)+**1**]$^{+}$
	678 [10%] [G1(Crown)+Na]$^{+}$
G2(Crown)+**1**	1219 [100%] [G2(Crown)+**1**]$^{+}$
	1135 [22%] [G2(Crown)+Na]$^{+}$
G3(Crown)+**1**	1120 [32%] [G3(Crown)+2×**1**]$^{2+}$
	1078 [97%] [G3(Crown)+**1**+Na]$^{2+}$
	1036 [100%] [G3(Crown)+2×Na]$^{2+}$
	1024 [27%] [G3(Crown)+Na+H]$^{2+}$

ions were observed, with the peak for [G3(Crown)+2Na]$^{2+}$ being dominant over those which included compound **1**. This qualitative result agrees with the NMR investigations that illustrate that with increasing dendritic functionalisation, cationic guest **1** becomes less strongly bound.

2.4. Binding studies with a ditopic guest cation—assembly of a supramolecular dendrimer

In order to extend the binding studies, we investigated the ability of these novel dendritic crown ethers to assemble around a ditopic guest cation: 1,4-bis(aminomethyl) benzene dihydrochloride (**2**, Figure 3). Compound **2** was prepared by the treatment of commercially available 1,4-bis(aminomethyl) benzene with HCl(g) in Et_2O. NMR binding titration experiments were performed in methanol, with G2(Crown) being added to a solution of compound **2** and the NMR shift of the Ar–CH_2 protons being followed (Fig. 5). The profile was relatively uninformative, however, it could be fitted to a mixture of 1:1 and 2:1 (G2(Crown):**2**) stoichiometries using HYPNMR and binding constants of $\log K_{11}$=2.06 (0.37) and $\log K_{21}$=1.27 (0.16) were obtained. Given the poor NMR profile, there is some doubt about these values. It is, however, interesting to note that the first binding event (K_{11}) is weaker than that for G2(Crown) binding compound **1** ($\log K_{11}$=3.28 (0.23)). This is perhaps surprising, however, this could be a consequence of the dendritic branching and the fact that it disfavours the build up of charge within the superstructure. Log K_{21} is lower than log K_{11}, as would be expected on the

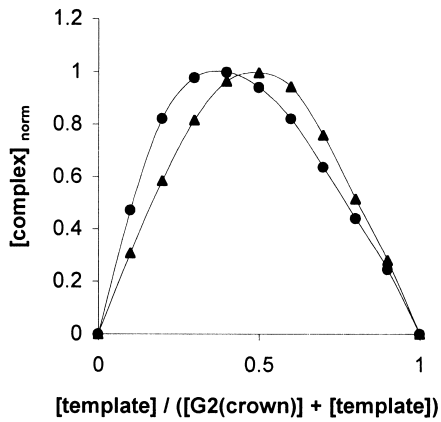


Figure 5. Job plot determined by ^{1}H NMR indicating the 2:1 stoichiometry of the complex formed between G2-crown and compound **2** (circles), and the 1:1 stoichiometry of the complex formed between G2-crown and compound **1** (triangles).

Table 4. Major mass spectral peaks [with intensities] observed on electrospray MS determination of equimolar amounts of G1(Crown) and compound **2** in methanol

Compounds	Major mass spectral peaks [intensity]
G1(Crown)+**2**	1447 [11%] [2×G1(Crown)+**2**–H]$^{+}$
	1333 [20%] [2×(G1Crown)+Na]$^{+}$
	792 [100%] [(G1Crown)+**2**–H]$^{+}$
	724.5 [50%] [2×(G1Crown)+**2**]$^{2+}$
	678 [48%] [G1(Crown)+Na]$^{+}$
	397 [27%] [G1(Crown)+**2**]$^{2+}$

grounds of the increased steric crowding experienced on the formation of the 2:1 assembly.

Convincing evidence for the formation of a 2:1 complex was found by performing a Job plot for G2(Crown) and compound **2**, and comparing it to that for G2(Crown) and compound **1** (Fig. 5). The maximum of this plot occurs at 0.5 for compound **1**, whereas it occurs at 0.33 for compound **2**. This clearly indicates the formation of complexes with 1:1 and 2:1 stoichiometries respectively. This proves that under the concentration regime of the NMR experiments performed, supramolecular dendrimers (2:1 assemblies) are indeed present.

Finally, mass spectrometry was used to investigate whether these supramolecular dendrimers could be observed. The mass spectral peaks are tabulated (Table 4). Mass spectral ions for the doubly charged 1:1 and 2:1 complexes were observed, as were the corresponding singly charged ions in which a proton had been lost. These peaks indicated a mixture of 1:1 and 2:1 complexes. This may be due to partial complexation, or fragmentation of the 2:1 assembly under electrospray ionisation conditions. These results are therefore in broad agreement with what would have been expected from the NMR investigations. Peaks corresponding to one and two equivalents of G1(Crown) complexed to sodium were also observed.

2.5. Disassembly of the supramolecular assemblies

Perhaps the major advantage of using supramolecular chemistry to assemble dendrimers, apart from its relative ease, is the fact that the process is a reversible one, and the interaction between template and dendritic branch can, in principle, be broken at a controlled moment of choice. This opens the possibility of dendritically encapsulating a template molecule in a supramolecular manner, modifying its behaviour, and then releasing it again into solution. There are two potential strategies for the disassembly of the supramolecular dendrimers formed above. The first approach is to add a base to the solution, a concept previously suggested by Gibson and co-workers for related systems.[19b] This would release the template as the free base, rather than in the protonated form. The second approach is to use potassium ions as competitive species. This method would release the protonated template into solution. As shown above, K^{+} ions bind 2–3 orders of magnitude more strongly than the NH_3^{+} functionalised templates, and hence should be able to displace them from the assembly. In this way, controlled encapsulation and release of the template species would be achieved.

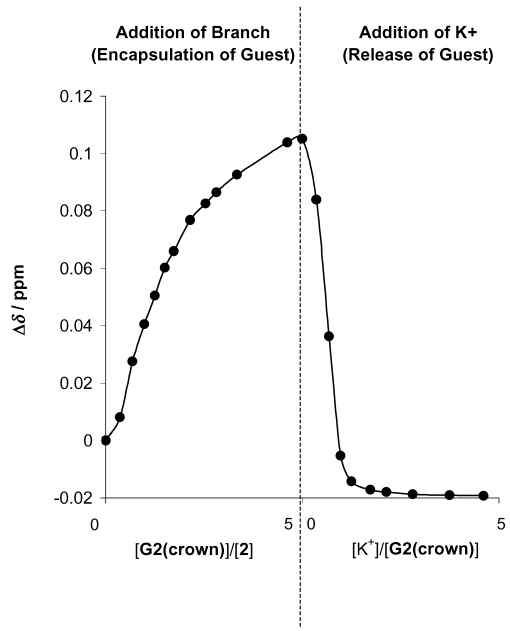


Figure 6. NMR shift of the ArCH_2 peak (at 4.10 ppm) of guest **1** on the addition of G2-crown followed by the addition of KPF_6.

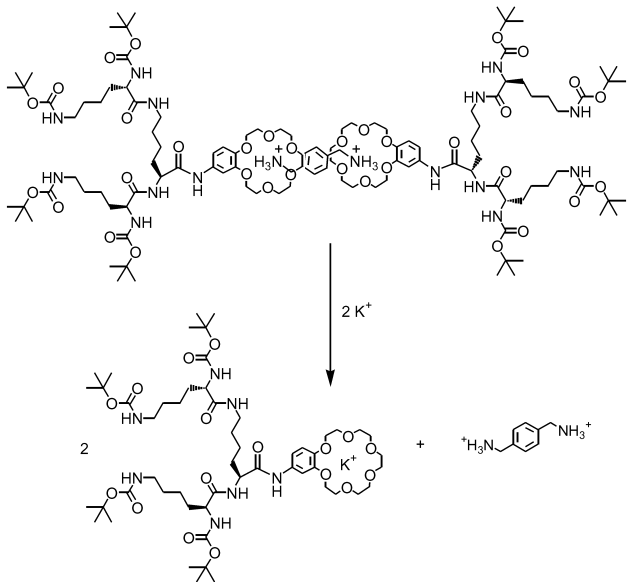


Figure 7. Disassembly of the supramolecular dendrimer induced by the addition of KPF_6.

In order to monitor this encapsulation–release process, NMR experiments were performed with G2(Crown) and compound **1** in methanol (Fig. 6). Firstly, 5 equiv. of G2(Crown) were added to compound **1**, and the downfield ^{1}H NMR shift of the Ar–CH_2 peaks of **1** reported on the formation of the molecular complex (as described above). Potassium ions were then added to the solution in the form of KPF_6. The NMR peaks of compound **1** were again monitored, and this time an upfield shift of the protons was observed. This indicates that the complex is being disassembled, and cation **1** released into solution (Fig. 6).

It was observed that the NMR shift for the Ar–CH_2 peak did not quite return to its original value (4.097 ppm), returning instead to 4.114 ppm. It was proposed that this was the result of the presence of an excess of KPF_6. The original counter-ion to compound **1** was chloride, but in the presence of an excess of KPF_6, the counter ion will predominantly be hexafluorophosphate. In order to check this was indeed the reason, 50 equiv. of KPF_6 were added to compound **1** at NMR titration concentrations and the ^{1}H NMR shift of the Ar–CH_2 peak was monitored. As expected, the peak was shifted from 4.097 ppm to 4.114 ppm, confirming our hypothesis. It is possible that this could simply be an ionic strength effect induced by KPF_6, but it is more likely that the reason for the effect is a consequence of the ability of chloride anions to interact with NH_3^+ better than the PF_6^- anion can, hence modifying the NMR shift of the adjacent CH_2 protons.

The same experiment to monitor assembly followed by potassium ion induced disassembly was then performed using compound **2**, but this time 10 equiv. of G2(Crown) were added to ensure formation of the 2:1 complex. Once again, the addition of KPF_6 had a dramatic effect on the ^{1}H NMR spectrum of encapsulated template **2**, indicating that the template was being released from the interior of the supramolecular dendrimer and into solution (Fig. 7). On this occasion, the NMR shift of the Ar–CH_2 peak returned to 7.547 ppm, having started at 7.303 ppm. This difference was again rationalised as the effect of excess KPF_6 on the NMR spectrum of template **2**, and this was proven by the appropriate control experiment.

This experiment illustrates that supramolecular assembly is a reversible process, and furthermore indicates that the NMR properties of the template are modified by the encapsulation/release process. We are now extending this research to reversibly modify the behaviour of other functional templates. This will hopefully allow this type of supramolecular dendrimer to be used for the reversible storage of information on a molecular scale.

2.6. Gel formation with supramolecular dendrimers

In order to extend the scope of this methodology, we decided to investigate the complexes formed between G2(Crown) and protonated long chain aliphatic diamine **3**. This ammonium salt was prepared by treating 1,12-diaminododecane with HCl(g) in Et_2O. From our previous investigations of supramolecular dendrimers constructed using acid–base interactions, we knew that the combination of G2(COOH) with 1,12-diaminododecane in organic solvents led to the formation of new two-component gel-phase materials (Fig. 8).[21] These gel phase materials form because the dendritic supermolecule has the inherent potential to assemble yet further, creating networks running through the solvent. Both the length of the hydrophobic spacer, and hydrogen bond interactions between the peptidic branches have been shown to be important for the formation of strong gel phase materials.

Given this precedent for dendrimers with a similar supramolecular structure to form gels, and the general interest in the structure activity relationships of gel-phase materials,[15,35] we were therefore very interested to know

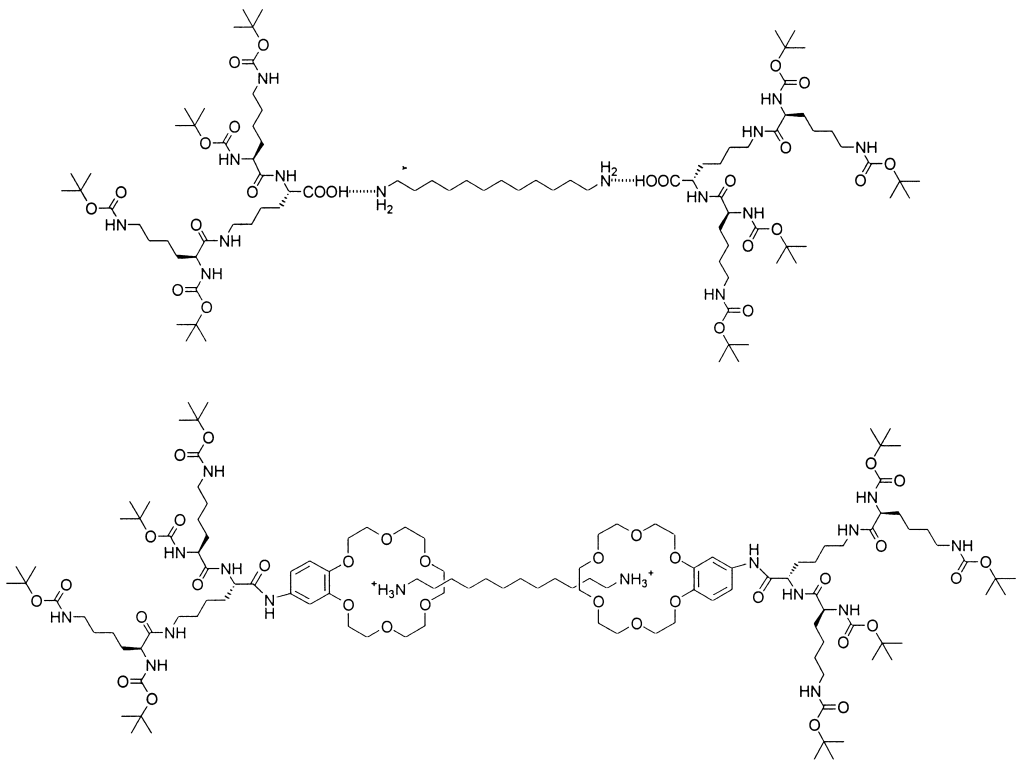


Figure 8. Two-component supramolecular dendritic gels based on either acid–amine or crown-NH_3^+ interactions between the components.

whether the combination of G2(Crown) with cationic **3** would have the same effect. G2(Crown) was dissolved in organic solvents (30 mM), and 1 mL of the resultant solution was added to solid bis-ammonium cation **3** (14 mg). This experiment was performed in several different solvents—dichloromethane, toluene and methanol.

In toluene, the dendritic branch on its own formed a very weak gel which could be broken by lightly shaking (behaviour not previously observed with G2(COOH)). It has been previously reported that crown ethers can lead to some hierarchical ordering of dendritic systems, and presumably that is occurring in this case.[36] Compound **3** was insoluble in toluene. On the addition of G2(Crown), however, the bis-ammonium cation was solubilised. A similar effect on the solubility of diaminododecane caused by dendritic carboxylic acids was reported previously.[22] As before, the result in this case was a strong gel, which could not be broken on shaking. This indicates that the two-components when combined form a complex which is capable of forming a hierarchical network that rigidifies the solvent. In this way, the two individual components act in a synergistic way. In dichloromethane, however, the mixture did not form a gel-phase material, and in methanol, both components were freely soluble at the outset, and once again, no gel-phase material resulted.

The results in different solvents indicate that the solvent plays a key role in mediating the interactions between the individual components that allow the hierarchical assembly of individual supramolecular dendrimers to take place, hence forming a gelated network. The solvent in which strong gelation of the two-component mixture occurred was toluene, which is a poor hydrogen bond donor or acceptor. This indicates that hydrogen bond interactions between the peptidic groups of the dendritic branching in adjacent complexes may play a key role in allowing further assembly. Furthermore, the addition of small amounts of hydrogen bond competitive solvents to the gels destroyed them, once again indicating the importance of hydrogen bonds in maintaining the assembly.

It should be pointed out that such two-phase supramolecular organogelators are still comparatively rare.[37–40] It was therefore very pleasing that our expectations were fulfilled, and that the complexes formed through crown-NH_3^+ interactions did indeed assemble further into gel-phase networks. This indicates that the structural motif discovered in our previous investigations[22] (Fig. 8) is of general applicability in the development of novel dendritic gelation systems.

Further studies to elucidate other structure–activity properties of these assemblies have thus far been limited by lack of material, but work is currently ongoing to fully evaluate the behaviour and potential applications of this type of tunable two-component gel phase system. These materials clearly illustrate the ability of supramolecular assemblies of dendrimers to demonstrate behaviour that is more than the sum of their individual parts. This system is therefore a rare example in which discrete, characterisable dendritic supermolecules possess an inherent potential for further supramolecular assembly on the mesoscale, to yield new materials. In addition, these gel phase materials should be reversibly broken down simply by the addition of K^+ ions—a property which may give rise to interesting applications.

3. Conclusions

A series of dendritic crown ethers has been synthesised, and their ability to bind simple cationic guests has been investigated. It has been shown that increasing the extent of dendritic functionalisation decreases the strength of the host–guest complex. These dendritic crowns have also been used to assemble supramolecular dendrimers around bis-ammonium cations. These supramolecular dendrimers can be disassembled by the addition of potassium ions, a process investigated by NMR methods. Disassembly achieves controlled release of the template into solution and indicates the potential of this system for reversible encapsulation and release of functional species. In the case where the template bis-ammonium cation has a long aliphatic chain between the NH_3^+ groups, the supramolecular assemblies which form give rise to gel phase hierarchical assemblies in non-hydrogen bond competitive solvents, indicating the ability of such assemblies to behave as more than the sum of their individual parts.

We are currently extending this research through the encapsulation of functional templates, the supramolecular synthesis of dendrimers with a variety of three dimensional shapes and structures, and the further determination of the key factors controlling the gelation process for this type of supramolecular dendrimer.

4. Experimental

4.1. General

Solvents and reagents were used as supplied. Thin layer chromatography was performed on commercially available Merck aluminium backed silica plates. Preparative gel permeation chromatography (GPC) was carried out using a 2 m glass column packed with Biobeads SX-1, supplied by Biorad. Analytical GPC traces were recorded using a Waters instrument incorporating two Shodex columns in series (KF-802.5 and KF-803) using THF as eluent. Proton and carbon NMR spectra were recorded on either a Jeol EX-270 (^{1}H 270 MHz, ^{13}C 67.9 MHz) or a Bruker AMX-500 (^{1}H 500 MHz, ^{13}C 125 MHz) at 25°C. Chemical shifts (δ) are quoted in parts per million, referenced to residual solvent. Coupling constant values (J) are given in Hz. DEPT experiments were used to assist in the assignment of ^{13}C NMR spectra. Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus and are uncorrected. Optical rotation was measured as $[\alpha]_D$ on a JASCO DIP-370 digital polarimeter. Positive ion electrospray mass spectra were recorded on a Finnigan LCQ mass spectrometer. Positive ion fast atom bombardment mass spectra were recorded on a Fisons Instruments Autospec mass spectrometer. The isotope distributions observed for mass spectral ions of the larger molecules are consistent with data calculated from isotopic abundances. Infra-red spectra were recorded using an ATI Mattson Research Series 1 FTIR spectrometer. Compound G1(COOH) was prepared according to a literature method,[41] as were dendritic branches G2(COOH) and G3(COOH).[21b]

4.1.1. G1(Crown). 4′-Aminobenzo-[18]crown-6 (0.274 g, 0.839 mmol, 1.5 equiv.) was dissolved in ethyl acetate (25 mL). Triethylamine (0.12 mL, 0.839 mmol) and G1(COOH) (0.194 g, 0.559 mmol, 1.0 equiv.) were added and the solution stirred under nitrogen for 2 min, before being cooled to 0°C. Hydroxybenzotriazole (HOBt, 0.076 g, 0.559 mmol) and dicyclohexylcarbodiimide (DCC, 0.115 g, 0.559 mmol, 1 equiv.) were then added simultaneously as a mixture of solids. The reaction mixture was allowed to warm to room temperature and stirred for 40 h. The solvent was removed by rotary evaporation and the mixture purified by gel permeation chromatography (Biobeads, 90:10, CH_2Cl_2–MeOH) to give the product with a yield of 0.318 g (0.485 mmol, 87%). White solid; mp 140–141°C; R_f 0.47 (CH_2Cl_2–MeOH 80:20); $[\alpha]_D^{293}=-19.3$ (c=1.0, $CHCl_3$); HRMS (FAB) $C_{32}H_{53}N_3O_{11}Na$ calcd 678.3578, found 678.3575; m/z (ESI) (M_r=678.8) 678 ([M+Na]$^+$, 100%), 679 (30%); δ_H (500 MHz, CD_3OD) 7.29 (1H, br s, ArH), 7.04 (1H, dd, J=8.5, 2.5 Hz, ArH), 6.88 (1H, d, J=8.5 Hz, ArH), 4.13–4.10 (5H, m, CH_2O, C*H*CONH), 3.88–3.84 (4H, m, CH_2O), 3.73–3.70 (4H, m, CH_2O), 3.69–3.67 (4H, m, CH_2O), 3.65 (4H, s, CH_2O), 3.06–3.03 (2H, m, CH_2CH_2NH), 1.90–1.30 (24H, m, CH_2, CH_3); δ_C (125 MHz, CD_3OD) 173.3 (CONH), 158.6 (NH*C*OBoc), 157.9 (NH*C*OBoc), 150.3, 147.1, 133.6, 115.7, 114.3, 108.7 (Ar×6), 80.7 (O*C*(CH_3)$_3$), 79.9 (O*C*(CH_3)$_3$), 71.8, 71.8, 71.7, 71.7, 71.7, 71.7, 70.8, 70.7, 70.6, 70.1 (CH_2O×10), 56.7 (*C*HCONH), 41.0 (CH_2CH_2NH), 33.3 (CH_2), 30.7 (CH_2), 28.8 (C*C*H_3), 28.7 (C*C*H_3), 24.2 (CH_2). ν_{max} (KBr disc) 3343s, 3326s, 2971w, 2932m, 2867w, 1681s, 1660s, 1604w, 1517s, 1456w, 1365m, 1130s, 1248s, 1169s, 1056m.

4.1.2. G2(Crown). 4′-Aminobenzo-[18]crown-6 (0.274 g, 0.839 mmol, 1.5 equiv.) was dissolved in ethyl acetate (25 mL). Triethylamine (0.12 mL, 0.839 mmol) and G2(COOH) (0.449 g, 0.559 mmol, 1.0 equiv.) were added. The solution was stirred under nitrogen for 2 min, before being cooled to 0°C. *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium hexafluorophosphate (HATU, 0.256 g, 0.672 mmol, 1.2 equiv.) was then added and the reaction mixture was stirred at room temperature for 40 h. The solvent was removed by rotary evaporation and the mixture purified by gel permeation chromatography (Biobeads, 90:10, CH_2Cl_2–MeOH) to give the product with a yield of 0.564 g (0.507 mmol, 91%). White solid; melting range 90–110°C; R_f 0.08 (CH_2Cl_2–MeOH 90:10); $[\alpha]_D^{293}=+21.1$ (c=1.0, $CHCl_3$); HRMS (FAB) $C_{54}H_{93}N_7O_{17}Na$ calcd 1134.6520; found 1134.6526; m/z (ESI) (M_r=1135.36) 1134.5 ([M+Na]$^+$, 100%), 1135.5 (65%), 1136.6 (20%); δ_H (270 MHz, CD_3OD) 7.31 (1H, d, J=2.5 Hz, ArH), 7.08 (1H, dd, J=8.5, 2.5 Hz, ArH), 6.88 (1H, d, J=8.5 Hz, ArH), 4.45–4.41 (1H, br s, COC*H*(R)NH), 4.14–4.10 (4H, m, CH_2O), 4.07 (1H, br s, COC*H*(R)NH), 3.96 (1H, br s, COC*H*(R)NH), 3.89–3.86 (4H, m, CH_2O), 3.72–3.69 (8H, m, CH_2O), 3.65 (4H, s, CH_2O), 3.21–3.18 (2H, m, CH_2CH_2NH), 3.04–2.99 (4H, m, CH_2CH_2NH), 1.90–1.40 (54H, m, CH_2, CH_3); δ_C (67.9 MHz, CD_3OD) 175.3, 175.1, 172.0 (CONH×3), 158.5, (NH*C*OBoc), 158.1, (NH*C*OBoc), 158.0, (NH*C*OBoc), 157.7 (NH*C*OBoc), 150.2, 146.9, 133.5, 115.5, 114.2, 108.5 (Ar×6), 80.8 (O*C*(CH_3)$_3$), 80.6 (O*C*(CH_3)$_3$), 79.8 (O*C*(CH_3)$_3$×2), 71.7, 71.7, 71.6, 71.6, 71.6, 71.6, 70.8, 70.6, 70.4, 70.0 (CH_2O×10), 56.3 (COCH(R)NH), 56.2 (COCH(R)NH), 55.1 (COCH(R)NH),

41.0 ($CH_2CH_2NH\times2$), 40.0 (CH_2CH_2NH), 33.2 (CH_2), 32.9 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 28.9 ($CCH_3\times6$), 29.8 ($CCH_3\times6$), 24.2 ($CH_2\times2$), 24.0 ($CH_2\times2$). ν_{max} (KBr disc) 3335m, 2976m, 2936m, 2870w, 1688s, 1655s, 1604w, 1517s, 1457w, 1366m, 1124m, 1250m, 1171s.

4.1.3. G3(Crown). 4′-Aminobenzo-[18]crown-6 (0.274 g, 0.839 mmol, 3.0 equiv.) was dissolved in ethyl acetate (25 mL). Triethylamine (0.12 mL, 0.839 mmol) and G3(COOH) (0.480 g, 0.280 mmol, 1.0 equiv.) were added. The solution was stirred under nitrogen for 2 min, before being cooled to 0°C. HATU (0.213 g, 0.559 mmol, 2.0 equiv.) was then added and the reaction mixture was stirred at room temperature for 72 h. Thin layer chromatography indicated an incomplete reaction and hence a further aliquot of HATU was added (0.106 g, 0.280 mmol, 1.0 equiv.), and the reaction was heated at 45°C until TLC indicated completion (42 h). The solvent was then removed by rotary evaporation and the mixture purified by gel permeation chromatography (Biobeads, 90:10, CH_2Cl_2–MeOH) to give the product with a yield of 0.356 g (0.176 mmol, 63%). Mp 132–136°C; R_f 0.21 (CH_2Cl_2–MeOH 90:10); $[\alpha]_D^{293}=-5.8$ ($c=1.0$, $CHCl_3$); *m/z* (ESI) $C_{98}H_{173}N_{15}O_{29}Na_2$ ($M_r=2071.6$—observed as dipositive ion at 1035.8); 1035.0 (80%), 1035.5 ($[M+2Na]^{2+}$, 100%), 1036.0 (60%), 1036.5 (25%); δ_H (500 MHz, CD_3OD) 7.47–7.40 (1H, m, Ar*H*), 7.17–7.10 (1H, m, $J=8.5$ Hz, Ar*H*), 6.93 (1H, d, $J=8.5$ Hz, Ar*H*), 4.41–4.36 (2H, m, COC*H*(R)NH), 4.27–4.24 (1H, m, COC*H*(R)NH), 4.19–4.17 (4H, m, CH_2O), 4.05–4.01 (2H, m, COC*H*(R)NH), 3.98–3.95 (2H, m, COC*H*(R)NH), 3.91–3.88 (4H, m, CH_2O), 3.72–3.70 (4H, m, CH_2O), 3.67–3.66 (4H, m, CH_2O), 3.64 (4H, s, CH_2O) 3.21–3.15 (6H, m, CH_2CH_2-NH), 3.04–3.01 (8H, m, CH_2CH_2NH), 1.80–1.30 (114H, m, CH_2, CH_3); δ_C (125 MHz, CD_3OD) 175.4, 175.3, 175.2, 175.1, 174.0, 173.9, 172.2 (CONH×7), 158.5 (NH*C*OBoc×4), 158.0 (NH*C*OBoc×2), 157.7 (NH*C*OBoc×2), 148.4, 145.5, 133.1, 113.8, 112.1, 106.0 (Ar×6), 80.7 ($OC(CH_3)_3\times2$), 80.5 ($OC(CH_3)_3\times2$), 79.8 ($OC(CH_3)_3\times4$), 70.9, 70.8, 70.7, 70.7, 69.9, 69.9, 67.9, 66.8 ($CH_2O\times10$), 56.5, 56.2, 55.4, 54.8, 54.6 (COC*H*(R)NH×7), 41.0 ($CH_2CH_2NH\times4$), 40.0 (CH_2CH_2-NH×3), 33.2, 32.6, 32.4, 30.6, 29.9 (all CH_2), 28.8 ($CCH_3\times24$), 24.2 (CH_2). ν_{max} (KBr disc) 3420s, 2977m, 2933m, 2868w, 1692s, 1517s, 1454w, 1392w, 1367m, 1121m, 1251m, 1170s.

4.1.4. Protonated diamines 2 and 3. 1,4-Bis(aminomethyl)benzene or 1,12-diaminododecane was dissolved in Et_2O and stirred. An excess of HCl(g) was bubbled through the solution, with a white precipitate being formed. The precipitate was filtered, washed with diethyl ether and dried to give products **2** or **3** as a white solid. ^1H NMR characterisation indicated that the bis-protonated HCl salts had been formed—the spectra indicated the symmetry in the molecules, with the $CH_2NH_3^+$ peaks being shifted with respect to the same peaks in the spectra of the free amines.

Compound **2**. δ_H (270 MHz, D_2O) 7.53 (4H, s, ArH), 4.22 (4H, s, Ar–CH_2); δ_C (67.9 MHz, D_2O) 134.1 (Ar×2); 130.1 (Ar×4); 43.3 (Ar$CH_2\times2$).

Compound **3**. δ_H (270 MHz, D_2O) 3.02 (4H, t, $J=7.5$ Hz, $CH_2NH_3^+$); 1.69 (4H, qn, $J=7.5$ Hz, $CH_2CH_2NH_3^+$); 1.42–1.32 (16H, m, CH_2).

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