Crown ether functionalised dendrons—controlled binding and release of dopamine in both solution and gel-phases†

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This paper reports the use of first (G1), second (G2) and third (G3) generation dendritic branches based on L-lysine building blocks with an [18]crown-6 unit at the focal point to bind protonated dopamine. The binding strength in CD_3OD is dependent on dendritic generation (G1 > G2 < G3). As expected, the presence of water (10%) disrupts the binding of dopamine; however, this effect is smaller for the G2 system than its G1 analogue, a result which may indicate a degree of dendritic protection from competitive solvents. The addition of K^+ causes release of protonated dopamine, whilst the use of a base releases deprotonated dopamine. A key advantage of dendritic functionalisation in these crown ether derivatives is that it enables them to assemble *via* intermolecular hydrogen bond interactions and consequently form gels in non-hydrogen bonding solvents. Indeed, the G2 and G3 crown ethers (but not G1) form gels in toluene, as well as in oils used in pharmaceutical formulation (*e.g.* isopropyl palmitate). The thermal properties of these gels are reported, and a tape-like morphology imaged by scanning electron microscopy. Dopamine modifies the thermal stability of the gel-phase material and the subsequent addition of potassium ions breaks down the structure of the gel completely. This system therefore offers a demonstration of the way supramolecular gels can respond to specific ionic/molecular triggers, and indicates how controlled release applications may be developed for such materials in formulation science.

Introduction

Dendritic molecules, which have well-defined, branched molecular architectures, constitute a fascinating nanoscale toolkit for the fabrication of intriguing host–guest complexes and self-assembled architectures.[1] Indeed, supramolecular dendrimer chemistry is one of the key frontiers of nanochemistry.[2]

There has been considerable interest in molecular recognition processes that occur within a dendritic environment, with the impact of the branching on the binding being of particular interest. For example, dendrophanes bind hydrophobic guests such as steroids,[3] dendritic cyclotriveratrylenes bind C_{60} fullerenes with the branches assisting the binding process,[4] dendroclefts have been used to achieve enantio- and diastereoselective binding,[5] and dendritic metalloporphyrins have been used for small molecule binding.[6] A number of hydrogen bonding dendritic receptors have been reported,[7] and encapsulated dendritic amidoferrocenes have been exploited for their ability to bind, and electrochemically sense, anionic targets.[8] In recent years, dendritic crown ethers have been developed by several different research groups. Dendritic crowns with multiple crown ethers either in the branches or on the surface have been reported.[9] Gibson and co-workers have reported dendritic branches (dendrons) with a dibenzo[24]crown-8 unit at the focal point.[10] This crown ether interacts with secondary ammonium cations and, using this interaction, non-covalent dendrimers were assembled around multi-functional templates. We have reported previously chiral dendritic crown ethers, in which a benzo[18]crown-6 unit is connected to the focal point of a dendron based on L-lysine (Fig. 1).[11] We showed the ability of these dendrons to assemble around an appropriate template cation in solution, forming supramolecular dendrimers, and, using NMR methods, showed that the complex could be disassembled in a controlled manner through the addition of competitive K^+ cations.

The self-assembly of multiple individual dendritic molecules into extended assemblies capable of underpinning supramolecular gel-phase materials has also been of considerable interest in the area of dendritic nanochemistry.[12] Since early initial

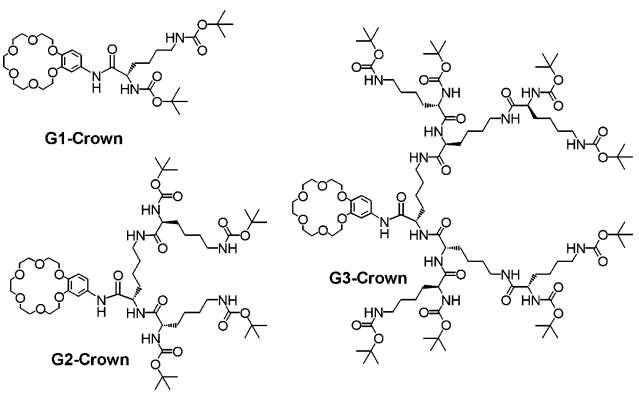

Fig. 1 Structure of dendritic crown ethers (G*n*-Crown) with branching based on L-lysine.

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reports by Newkome and co-workers of dendritic bola-amphiphiles which self-assemble in aqueous solution,[13] there have been a number of reports of dendritic gelators which operate in organic solvents, including research from the groups of Aida,[14] Kim[15] and Stupp,[16] as well as ourselves.[17] The effect of dendritic generation on the self-assembly process which underpins gelation has been widely explored—indeed the multiple functional groups inherent within dendritic compounds provide an advantage in terms of self-assembly, by multiplying intermolecular interactions and hence enhancing their strength.

A key frontier in the chemistry of gels is the development of materials which respond to specific stimuli.[18] Indeed, supramolecular gels based on the self-assembly of low molecular weight gelators are ideal for applications as responsive gels, as they are held together by multiple weak non-covalent interactions, are thermally reversible, and can potentially respond to specific molecular or ionic triggers. Such gel-phase materials therefore have considerable potential in controlled release applications.

Bearing in mind the intense interest focused on the controlled binding and release of biologically active molecules,[19] we decided to use dopamine as a simple model system and investigated the ability of our dendritic crown ethers to bind, encapsulate and release this target (Fig. 2). Dopamine is an important molecule because it is a neurotransmitter, associated with Parkinson's disease, Tourette's syndrome, schizophrenia, and attention deficit hyperactivity disorder (ADHD).[20] Patients with Parkinson's are often treated with L-dopa, a prodrug which is converted to dopamine *in vivo* by decarboxylation.[21] Dopamine is not itself administered because of its inappropriate biodistribution and poor delivery profile. In this paper, we describe the use of our dendritic crown ethers to elucidate the impact of the dendritic branching on the binding of the substrate in different solvents. Furthermore, we investigate the controllability of the complexation process by releasing the bound dopamine from the complex using different triggering systems. Finally, we harness the ability of dendritic systems based on L-lysine to form gels, in order to develop responsive soft materials capable of dopamine binding and triggered release.

Results and discussion

Synthesis

Compounds G1-Crown, G2-Crown and G3-Crown were synthesised using the convergent strategy reported previously,[11] in which pre-formed dendrons, synthesised using L-lysine amino acid building blocks (using published solution phase methodology),[22] were grafted onto 4′-aminobenzo[18]-crown-6 in good yield *via* simple peptide coupling reactions. All compounds were characterised using appropriate methods and the data shown to be in agreement with those previously published.

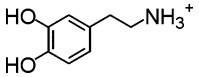

Fig. 2 Structure of protonated dopamine.

Dopamine binding in the solution phase

The binding of dopamine was investigated initially in the solution phase, using ^{1}H NMR titrations in CD_3OD. The titration was performed by addition of aliquots of the crown ether to a solution of the dopamine, and following the NMR peaks of the dopamine guest. For example, on the addition of G1-Crown (M_r = 655.8), the dopamine became bound by the dendron, and its NMR resonances were perturbed. As expected, the CH_2 group adjacent to the protonated amine was the most heavily perturbed resonance ($\Delta\delta$ = 0.15 ppm for the addition of 5 equivalents of G1-crown), whilst those on the aromatic ring, more distant from the binding site, were less strongly affected. The data could be fitted to a 1 : 1 model, with dopamine binding taking place at the focal point of the dendritic branch within the crown ether ring. Fitting the data using HypNMR[23] gave rise to a binding constant, K_a, of 1200 mol^{-1} dm^3, as shown in Table 1.

Titrations were then performed with the higher generation dendrons, G2-Crown (M_r = 1112.4) and G3-Crown (M_r = 2025.6). The NMR spectrum of dopamine was perturbed in a very similar manner ($\Delta\delta$ = 0.15 ppm), and the binding curves fitted to a 1 : 1 binding model. As anticipated, compound G2-Crown (K_a = 480 mol^{-1} dm^3) bound dopamine less strongly than G1-Crown. As dendritic generation increases, the binding site at the focal point of a dendritic structure becomes increasingly sterically crowded. Furthermore, the dendrons provide an electronic environment which is less favourable for the introduction of a charged species, which would rather remain in the bulk solvent. Both of these dendritic effects will decrease the strength of binding with an ionic guest.[8,11] We were therefore surprised to note that G3-Crown (K_a = 690 mol^{-1} dm^3) bound dopamine more effectively than G2-Crown. This has not previously been observed for a dendritic system. Specifically, this was not the case for the previously reported binding of benzylammonium or potassium cations to these dendrons (Table 1).[11b] In both of these previous cases, G3-Crown bound the cationic substrate significantly less strongly than G2-Crown. We argue that, in the case of G3-Crown binding dopamine, it is possible that secondary interactions (*e.g.* hydrogen bonds) between the extended dendritic branching and the catechol unit may occur, and that these would act

Table 1 Binding constants for G*n*-Crown with different guest molecules. Mixtures of MeOH-d_4–D_2O had a composition of 90 : 10. Estimated error in K_a values is ±10%

Receptor	Guest	Solvent	K_a/mol^{-1} dm^3
G1-Crown	$K^+PF_6^-$	MeOH-d_4	1.0×10^5 [11b]
G2-Crown	$K^+PF_6^-$	MeOH-d_4	7.2×10^4 [11b]
G3-Crown	$K^+PF_6^-$	MeOH-d_4	2.5×10^4 [11b]
G1-Crown	Benzylamine · HCl	MeOH-d_4	3800 [11b]
G2-Crown	Benzylamine · HCl	MeOH-d_4	1900 [11b]
G3-Crown	Benzylamine · HCl	MeOH-d_4	200 [11b]
G1-Crown	Dopamine · HCl	MeOH-d_4	1200
G2-Crown	Dopamine · HCl	MeOH-d_4	480
G3-Crown	Dopamine · HCl	MeOH-d_4	690
G1-Crown	Dopamine · HCl	MeOH-d_4–D_2O	280
G2-Crown	Dopamine · HCl	MeOH-d_4–D_2O	260

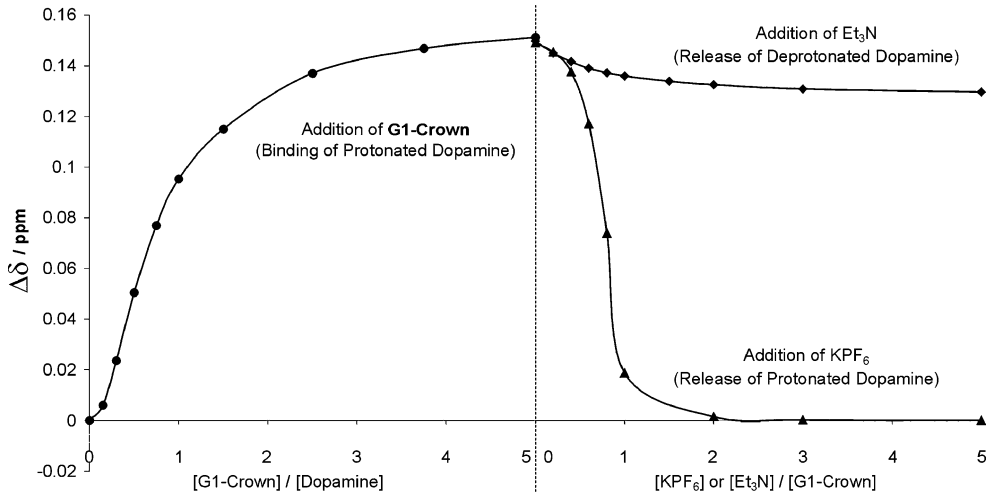

Fig. 3 Graph showing the NMR titration experiments used to demonstrate the binding of protonated dopamine to G1-Crown and either the release of protonated dopamine from the complex using K^+ as an ionic trigger, or the release of free base dopamine using Et_3N as a molecular trigger. Solvent: MeOH-d_4. [Dopamine] = 2.0 mM throughout the experiment. For the release curves, [G*n*-Crown] = 10 mM. Temperature = 298 K.

to reinforce the formation of the host–guest complex, counteracting the increased steric hindrance which would be expected with the higher generation system.

We then went on to investigate the binding of these compounds with dopamine in the presence of increasing amounts of D_2O, in order to determine the effect of solvent composition on binding. As expected for binding based on a combination of electrostatic and hydrogen bonding interactions, the addition of water decreased the strength of binding and decreased the induced chemical shift on dopamine. Indeed, in 50 : 50 CD_3OD–D_2O, binding could not be detected by NMR spectroscopy with either dendron. Interestingly, however, in 90 : 10 CD_3OD–D_2O, binding was still observed. It is noteworthy that the ability of G1-Crown to bind dopamine was more affected by the presence of water than that of G2-Crown. For G1-Crown, the binding constant decreased from 1200 to 280 mol^{-1} dm^3, and $\Delta\delta$ = 0.11 ppm, whilst for G2-Crown the introduction of 10% D_2O only changed the binding constant from 480 to 260 mol^{-1} dm^3, with a larger $\Delta\delta$ value of 0.13 ppm. This result appears to indicate that G2-Crown is better able to shield the crown ether binding site from the competitive solvent than G1-Crown, and indicates that, whilst dendritic branching generally appears to disfavour binding at an encapsulated binding site, it may in some cases have a proactive effect on molecular recognition. Unfortunately, it was not possible to investigate G3-Crown under these conditions due to its lower solubility in the mixed solvent system.

Dopamine release in the solution phase

We then went on to investigate the controlled release of dopamine from the solution-phase complexes formed with the different dendrons (Fig. 1). Initially, we used the addition of K^+ to drive the decomplexation of protonated dopamine as a consequence of its competitive binding strength (Table 1). The binding strengths of K^+ ions with G1-Crown, G2-Crown and G3-Crown are several orders of magnitude larger than the binding constants reported here with dopamine. K^+ ions were therefore titrated into a dopamine–dendrimer complex and the NMR shift of the bound dopamine was followed. Fig. 3 illustrates the NMR shifts induced during the overall binding and release experiment for G1-Crown. Similar binding and release profiles were obtained using G2-Crown and G3-Crown. It can clearly be seen that the initial downfield shift of the dopamine NMR peaks is reversed on the addition of K^+ ions. Indeed, the addition of one equivalent of potassium cations (relative to the dendron) is sufficient to almost completely release protonated dopamine from the complex.

In addition, we decided to use an organic base to release dopamine from the complex. Triethylamine was titrated into the dendritic crown–dopamine complex and once again a 'release' curve was obtained (Fig. 3). It will be noted that the NMR spectrum of the released dopamine was different from that of the dopamine at the start of the binding-release experiment. This is a consequence of the fact that, whilst protonated dopamine is initially bound by the crown, it is deprotonated dopamine that is finally released, and deprotonated dopamine has a different NMR spectrum from that observed when protonated. Measuring the NMR spectrum of deprotonated dopamine under equivalent conditions of solvent and ionic strength confirmed that the species being released was the deprotonated form.

Formation of gel-phase materials using G*n*-crown

Having established that our dendrons were capable of achieving controlled binding and release of dopamine in solution, we became interested in their ability to generate soft materials capable of exhibiting controlled release properties. In a number of studies we have established that employing dendritic L-lysine units can be a useful way of endowing a range of molecules with the ability to self-assemble into gel-phase materials.[17] Hydrogen bonds between the dendritic peptides lead to nanoscale fibrillar assemblies capable of 'immobilising' organic solvents. There are a number of gel-phase materials in the literature which incorporate crown ether building blocks.

In particular, Shinkai and co-workers have demonstrated that functionalisation of crown ethers with cholesterol units—known for their ability to promote the formation of nanoscale assemblies—can give rise to effective gelation.[24] We therefore decided to explore the ability of G*n*-Crown to form gels, with the hope of developing stimulus-responsive supramolecular gels ultimately capable of triggered dopamine release.

Initially, gelation was investigated in toluene. Sonication followed by a heat–cool cycle led to gelation in the cases of G2-Crown and G3-Crown but not for G1-Crown. The dendritic branching based on L-lysine clearly plays a pro-active role in encouraging gelation. It seems likely that only the more extensive, higher generation dendritic branches can form sufficient dendron–dendron hydrogen bonds to generate a stable nanoscale fibrillar assembly (*i.e.*, G1-Crown cannot form enough dendron–dendron hydrogen bonds to support a sample spanning network).

The thermal properties of G2-Crown and G3-Crown were then investigated in more detail as a function of concentration, by studying the transition from an immobile to a mobile self-assembled state in toluene using tube inversion experiments. This reproducible method (±1 °C) served to define a mobile–gel transition temperature (*i.e.*, a gel 'boundary'),[25] and is described in detail in the experimental. The gel 'boundary' is analogous to the thermally reversible gel–sol transition temperature (T_{gel}). T_{gel} values were measured at different concentrations of gelator (Fig. 4). As previously reported for our other gelators, when the molar concentration of the gelators was increased, the T_{gel} values also increased, until a concentrated regime (the 'plateau region') was reached, denoted by a concentration independent T_{gel}. This indicates a 'gel-building' concentration regime, followed by a regime in which the formation of a gel-phase network can be considered to be effectively complete.

Interestingly, G2-Crown has a T_{gel} value of 80 °C in the plateau region, whilst that of G3-Crown has increased to 100 °C. This indicates that, for these systems, more extensive dendritic branching has a pro-active effect on the thermal stability of the gel. G2-Crown reaches its plateau region at a concentration of approximately 17.5 mM. This corresponds to 1.95% wt/vol. Room temperature gelation can be observed at concentrations of 5 mM (0.56% wt/vol). For G3-Crown, the onset of the plateau region occurs across a range of concentrations; however, even at concentrations of 1 mM (0.20% wt/vol) room temperature gelation can readily be achieved (indeed, $T_{gel} > 50$ °C).

We have previously reported differing dendritic effects on gelation,[12,17d] and believe that the control of such effects is mediated by a subtle balance between the additional interactions that are possible between more extensive dendritic structures (favourable) and the steric repulsion which occurs between higher generation dendritic systems (unfavourable). In this case, therefore, we propose that the additional dendron–dendron hydrogen bonds that are possible for higher generation G3-Crown dominate in controlling the thermal properties of the assembly (in fact, G3-Crown contains 15 N–H groups, whilst G2-Crown only contains 7). However, given that G2-Crown was more readily synthetically available in large quantities than the third generation analogue, we decided to continue our investigations using G2-Crown, as its gelation properties were more than adequate for this study.

Molecular self-assembly at the nanoscale level was probed using scanning electron microscopy (SEM)—a useful comparative technique to assess the impact of dendritic branching on the mode of self-assembly. SEM was performed on a sample of the gel dried from toluene (Fig. 5). As expected for a gel-phase material, G2-Crown exhibited an extended 'one dimensional' nanoscale morphology. Indeed, the morphology was 'tape-like', with tapes comprised of aligned smaller fibres. The majority of gel-phase materials are underpinned by fibrillar architectures. Indeed, it is becoming apparent from the literature that gelation occurs (rather than crystallisation), when the 'growth' (or 'crystallisation') of a nanostructure is constrained in one or two dimensions (hence preventing bulk 'three-dimensional' crystallisation and encouraging the formation of nanoscale networks).[26]

Response of gels to guests—controlled disassembly

Given that we had access to a gel based on our crown ether dendrons, we were interested to observe whether it had responsive properties. We therefore dissolved G2-Crown in

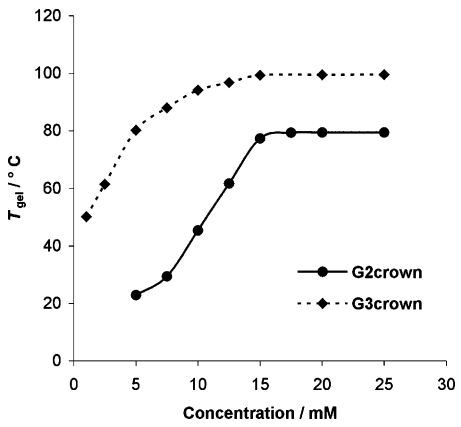

Fig. 4 Effect of [dendron] on the T_{gel} value for G*n*-Crown as measured by tube-inversion methodology, demonstrating the dendritic effect on the thermal stability of the gel. Solvent: toluene.

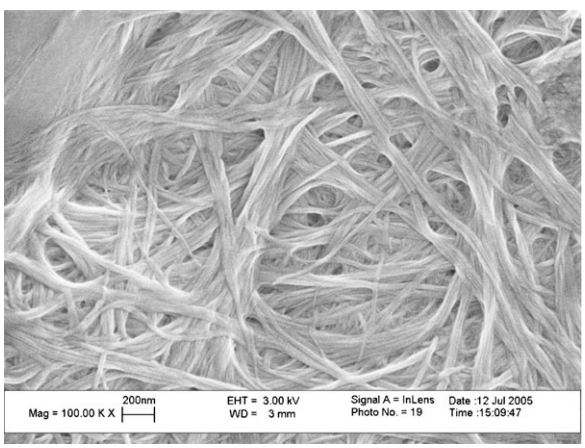

Fig. 5 Scanning electron microscopy image of G2-Crown in a sample allowed to dry from toluene. Image demonstrates a tape-like morphology.

toluene and added one equivalent of protonated dopamine, which remained as an insoluble solid. The mixture was sonicated and a heat–cool cycle applied. Not all of the dopamine dissolved and some solid material was left as a solid suspended towards the bottom of the gel. However, we decided to investigate the thermal behaviour of the resultant gel. Interestingly, the T_{gel} value had decreased from 80 °C (for G2-Crown alone) to 43 °C for the mixture of G2-Crown and dopamine. This would be consistent with a model in which the crown ether has dissolved sub-stoichiometric amounts of the dopamine which has become complexed by the gel. Electrostatic repulsion between the protonated dopamine units may give rise to the reduction in the thermal stability of the gel.

The solvent was then changed from toluene to isopropyl palmitate—a long chain fatty acid ester which is used in pharmaceutical formulation.[27] Isopropyl palmitate is apolar and G2-Crown was capable of supporting an effective gel-phase material in this solvent. A gel was then formed from a mixture of G2-Crown and protonated dopamine in a similar way to the gel in toluene described above. Acetonitrile containing $KBPh_4$ was then layered on top of the gel. This resulted in a complete *breakdown of the gel* over a period of ten minutes. However, if acetonitrile alone was placed on top of the gel, the gel maintained its structure, and even after 24 hours was effectively unchanged. This indicates that it is not the solvent which gives rise to breakdown of the gel in isopropyl palmitate, but rather the K^+ ions which trigger disassembly. We propose that K^+ ions diffuse into the gel and bind strongly to the crown ethers, leading to electrostatic repulsion and hence disassembly of the gel. In order to confirm this hypothesis, attempts were made to form gel-phase materials using G2-Crown in the presence of $KBPh_4$. All such attempts were unsuccessful, demonstrating that K^+ ion complexation does indeed inhibit the ability of G2-Crown to form gels.

We therefore report that gels based on G2-Crown undergo K^+ ion triggered disassembly. Responsive gels of this type are of intense interest, and in this case it is clear that the crown ether functionality built into the gel is playing an active role in the disassembly process. In the case of gels formulated using a mixture of G2-Crown and dopamine, K^+ ions can lead to triggered release of the active ingredient from the gel, as the integral structure of the material breaks down. Indeed, this approach releases both the dopamine complexed within the gel and the excess solid dopamine suspended within the gel. Given that these gels can be formed in biocompatible solvents such as isopropyl palmitate, this system has potential for development in a range of controlled release applications.

Conclusions and outlook

In summary, this paper demonstrates that dendritic crown ethers offer an effective way of achieving the controlled binding and release of an active compound, in this case one of pharmaceutical interest (*i.e.*, dopamine). As such, these dendritic systems can be considered as prototype 'carrier systems'. The binding strengths of dopamine depend on dendritic generation in a non-trivial way, with G1-crown > G2-crown < G3-crown. The binding exhibited by G2-crown appears to be better able to resist the addition of 10% water than that of G1-Crown.

Both G2-Crown and G3-Crown are capable of forming sample-spanning gel-phase networks in organic solvents such as toluene. G3-Crown forms gels with higher thermal stability than G2-Crown, presumably due to the presence of additional dendron–dendron hydrogen bonds. Furthermore, we have illustrated that the presence of dopamine within the gel modifies the thermal properties of the gel in toluene—reducing the T_{gel} value. Finally, we have demonstrated that a gel formulated from G2-Crown and dopamine in the biocompatible solvent isopropyl palmitate undergoes K^+ ion triggered disassembly, with the structure of the gel being broken down and releasing dopamine from its encapsulated location within the gel.

The lysine-derived dendritic branching plays a pro-active role in enabling the self-assembly of soft materials in this case, whilst the incorporation of a crown ether builds a triggering mechanism into the nanostructure. We postulate that dendritic systems of this general type may be of interest for applications in controlled release applications, and further experiments in this direction are currently in progress in our laboratory.

Experimental

Materials

The L-lysine based crown ether dendrons were synthesised in high yields, using a solution phase approach previously reported by us,[11] with column chromatography being employed to isolate the purified material. All compounds were of high purity (>95%) as assessed by NMR methods. It is possible that some epimerisation occurs during the grafting of the lysine dendrons onto the 4′-aminobenzo[18]crown-6 building block, although no evidence of this was detected.

NMR titration method

NMR binding titrations were performed in undried CD_3OD solution (or CD_3OD–D_2O mixtures of appropriate composition) using a dopamine·HCl concentration of 2.0 mM. A solution containing the dendritic crown ether at a concentration of 50 mM, and dopamine·HCl at a concentration of 2.0 mM (in order to ensure a constant concentration of dopamine·HCl) was made up in the same solvent. This solution was added in aliquots to the host solution and NMR spectra recorded. All solutions were prepared using accurate (5 figure) balances and Gilson pipettes were used to deliver all solvent volumes (including adding aliquots to the NMR samples during titration experiments). Data were analysed by non-linear least squares fitting methods using a commercially available program (HypNMR).[23]

Release experiments were performed by the addition of a solution containing dopamine·HCl (2.0 mM), and either KPF_6 (100 mM) or Et_3N (100 mM) depending on whether K^+ ion or base-mediated release was being performed.

Gelation experiments

A weighed amount of dendritic gelator was dissolved in a measured volume (Gilson pipette) of selected pure solvent. The mixture was sonicated at ambient temperature for 30 min

before heating and cooling produced a gel. The gel sample was left to stand overnight. Gelation was considered to have occurred when a homogenous 'solid-like' material was obtained that exhibited no gravitational flow. The thermally reversible gel–sol transition temperature (T_{gel}) was determined using a tube inversion methodology—the gel–sol transition temperature represents the point at which the stress exerted by the gel exceeds its yield strength, and a drop of solvent begins to run from the immobilised gel. All samples of gel-phase materials were prepared with a total volume of 1 ml in tubes with a diameter of 10 mm—this ensures that the stress generated by the gel on tube inversion is approximately constant in each case.

Scanning electron microscopy

Gel samples were applied to stainless steel stubs and allowed to dry. Prior to examination, the gels were coated with a thin layer of Pd/Pt. Scanning electron micrographs were recorded using a LEO 1530 FEGSEM instrument. Pd/Pt deposition was performed using a Denton vacuum LLC.

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