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Review

Single-Component Physical Hydrogels of Dendritic Molecules

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Abstract: Hydrogels are hydrophilic, three-dimensional networks able to imprison large amounts of water and are largely used in pharmaceutical formulations. Hydrogels are frequently obtained from hydrophilic polymers, either natural, biohybrid, or synthetic. Owing to their peculiar structure, dendrimers can be considered prospective building blocks for hydrogel networks. This review gathers the use of different types of amphiphilic dendritic structures able to generate physical hydrogels alone. Such dendritic structures comprise dendrimers, Janus dendrimers, and dendrons. The first part concerns different types of positively charged phosphorus dendrimers used to generate hydrogels, which are also suitable to form fibers, and for encapsulating diverse substances, or forming complexes with genetic materials for their slow delivery. The second part concerns PAMAM dendrimers functionalized with collagen mimetics. The third part concerns amphiphilic Janus dendrimers, whereas the fourth part displays different types of amphiphilic dendrons and their use, in particular in the fields of materials and drug delivery.

Keywords: dendrimer; dendron; amphiphilicity; hydrogel; encapsulation; fiber; biomaterial; drug delivery; nanomaterials

1. Introduction

Hydrogels are hydrophilic, three-dimensional networks able to imprison large amounts of water and resemble, to a large extent, biological tissue. For this reason, they are, in particular, widely used in pharmaceutical formulations [1], including for commercial uses [2]. Most of these biological properties concern drug delivery [3–6]. Hydrogels are frequently (but not only) obtained from hydrophilic polymers, either natural, such as collagen, gelatin, hyaluronate, fibrin, alginate, agarose, and chitin, or biohybrids, such as polypeptides, or synthetic, such as polyacrylic acid and derivatives, polyethylene oxide and copolymers, polyvinyl alcohol, and polyphosphazene [7,8]. Cross-linking strategies are also widely used to obtain hydrogels [9,10].

Owing to their peculiar structure, dendrimers, which are constituted of monomers as polymers but synthesized step-by-step, not by polymerization reactions, can be considered prospective building blocks for hydrogel networks. Indeed, the inherent multivalency of dendrimers makes it possible to expose multiple functional groups on the surface, whereas their highly symmetrical tree-like structure facilitates interactions between branches of different dendrimer molecules. Many hydrogels of dendrimers are based on their reaction with difunctional linkers, producing cross-linked polymeric networks [11]. However, the presence of both a hydrophobic interior together with hydrophilic terminal functions in some types of dendrimers and dendritic structures can induce the formation of physical hydrogels with no additional reagent used (single-component hydrogel). The very first examples of dendritic structures used for obtaining physical hydrogels concerned bolaform “arborols” constituted of two identical wedges bearing hydroxyl terminal groups linked through different types of hydrophobic chains. The first paper in this series, published in 1986 [12], described the use of a C10 alkyl chain as a linker between both hydrophilic wedges [13], then an alkyl chain with a central alkyne moiety [14]. Another example



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concerned a tetrathiafulvalene central moiety [15] (Figure 1). The self-association of the hydrophobic moieties in water resulted in gelation.

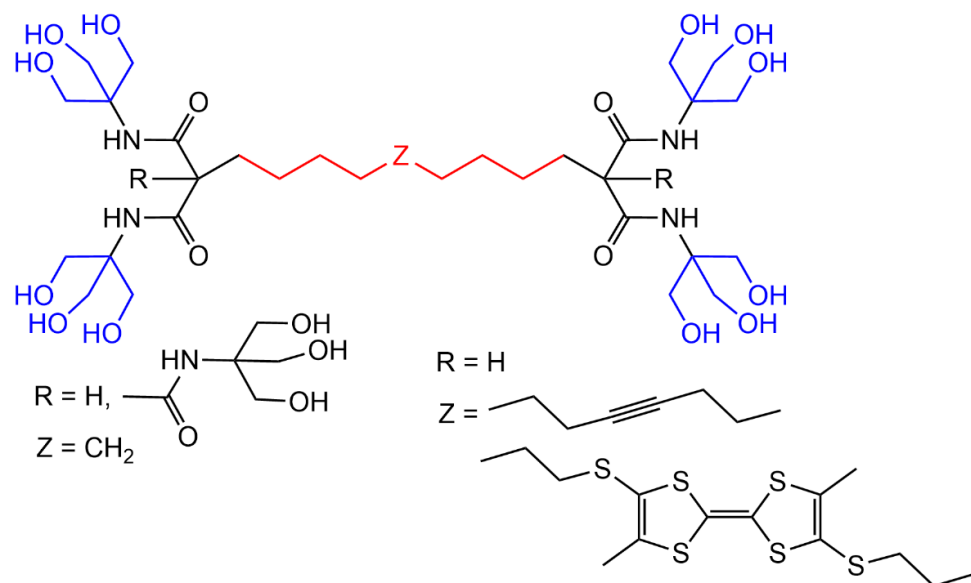


Figure 1. Structure of bolaform arborols suitable for forming hydrogels.

In this review, we will describe different well-defined dendritic structures that have been used to generate single-component physical hydrogels and also the different properties and uses of such hydrogels, beginning with phosphorus dendrimers. Indeed, a series of phosphorus dendrimers afforded the very first examples of fully symmetrical dendrimers suitable for generating physical hydrogels in 2001 [16]. Other types of dendritic structures used to generate physical hydrogels concerned polyamidoamine (PAMAM) dendrimers, amphiphilic Janus dendrimers, and different types of amphiphilic dendrons.

2. Phosphorus Dendrimers as Physical Hydrogels and Their Properties

Phosphorus dendrimers possessing high multivalency provide the favorable positioning of functional groups at the surface, as well as cavities, in the three-dimensional organization of the scaffold [17] and, therefore, can be considered potential gelators. The internal structure of phosphorus dendrimers is hydrophobic, whereas their terminal functions can be positively or negatively charged; thus, the whole structure becomes amphiphilic. In this Section, we will consider positively charged phosphorus dendrimers [18] as gelators by themselves in the first part and included in agarose gels (polymer composed of a disaccharide made of β -D-galactose and 3,6-anhydro-L-galactopyranose) in the second part, in particular dendrimers having gelation properties themselves.

2.1. Phosphorus Dendrimers as Building Blocks for Physical Hydrogels

The first examples of hydrogel-forming dendrimers concerned polycationic trimethylammonium acetohydrazone-terminated or pyridinium acetohydrazone-terminated phosphorus dendrimers of generations 0, 1, 2, and 4. They were synthesized by the grafting of the corresponding hydrazides (so-called Girard T and P reagents, respectively) to the aldehyde-terminated dendrimers, affording dendrimers **1a-G_n** (Girard T) and **1b-G_n** (Girard P) ($n = 0, 1, 2$ and 4), based on the trifunctional thiophosphate core [16]. The hydrazone bond stabilized with the aromatic fragment on one side and the carbonyl group on the other side appeared to be quite stable in water and did not require reduction. The full structure of the second-generation dendrimers **1a-G₂** and **1b-G₂** is shown in Figure 2, whereas the linear structure of all dendrimers of this series is shown in Figure 3.

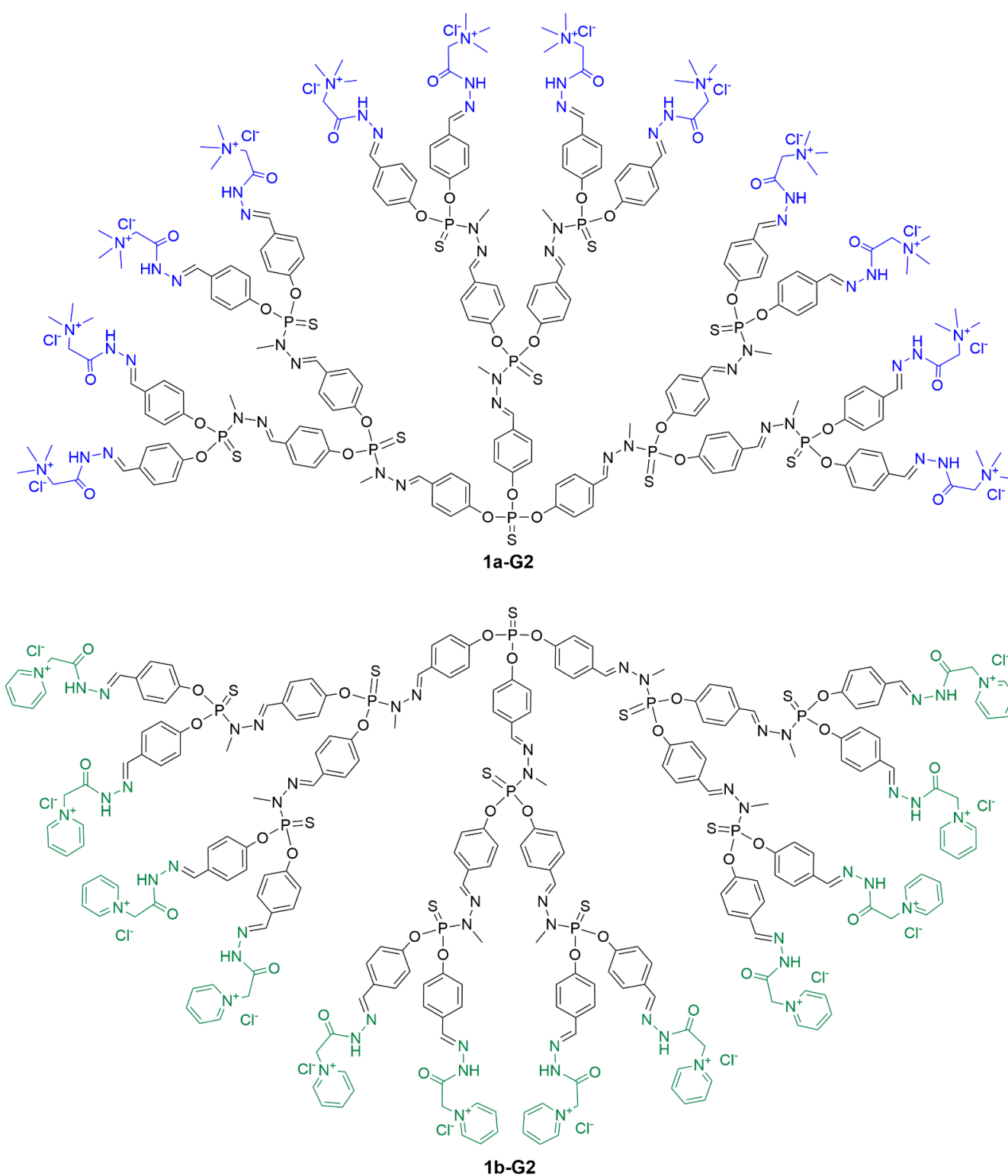


Figure 2. Full chemical structure of dendrimers **1a-G2** (functionalized with the Girard T reagent) and **1b-G2** (functionalized with the Girard P reagent).

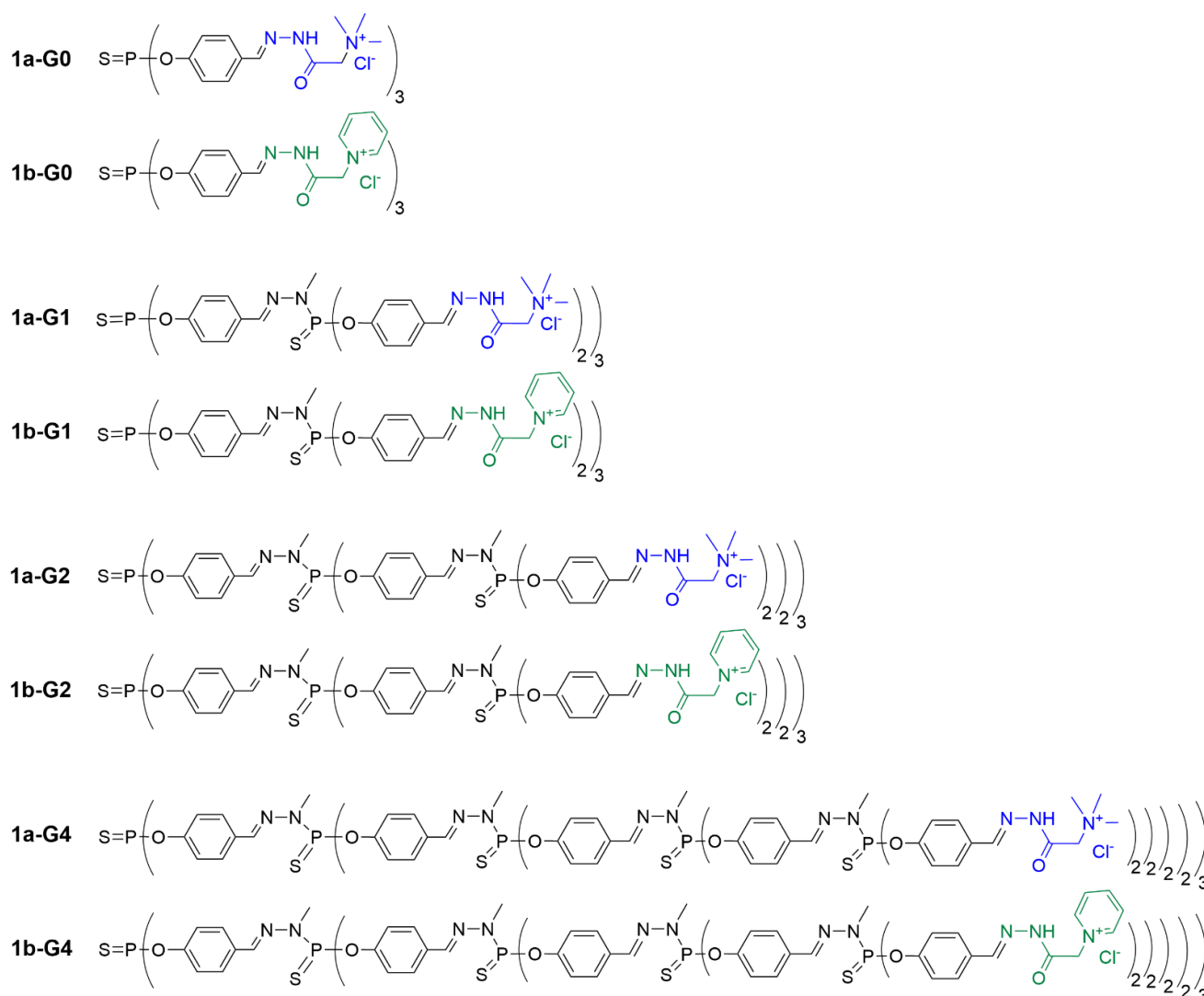


Figure 3. Linear representation of the chemical structure of phosphorus dendrimers built from a trifunctional core and functionalized with the Girard T reagent (series **a**, in blue) or the Girard P reagent (series **b**, in green) as hydrophilic terminal functions.

Polycationic aceto-hydrazone-modified dendrimers (1.8% in weight) formed stable physical hydrogels in water solutions when kept at 60 °C for several days. The formation of gels was driven by supramolecular interactions (hydrogen bonds, π - π aromatic stacking, and hydrophobic effects) of functional groups on the dendrimers' surface and in distal fragments of dendrimer branches. The gelation speed depended on the dendrimer generation (higher-generation dendrimers gelled faster), the nature of the functional groups on the surface (pyridinium aceto-hydrazone-terminated dendrimers gelled faster than trimethylammonium ones) and the nature of the counter-anion (acetates gelled easier than chlorides, as shown by anion exchange with **1b-G1**). Furthermore, the gelation was greatly accelerated in the presence of hydrophilic additives such as metal salts ($\text{Ni}(\text{Ac})_2$, $\text{Y}(\text{Ac})_3$, $\text{Er}(\text{Ac})_3$), organic acids (D,L-lactic acid, ascorbic acid, L-tartaric acid, citric acid), dithioerythritol, or EDTA (sodium salt of ethylenediaminetetraacetate). The hydrogels contained a considerable amount of water (7500–70,000 water molecules per dendrimer molecule, depending on the generation, from G1 to G4, respectively) and were able to encapsulate up to 30% of $\text{Ni}(\text{Ac})_2$ [16].

Since these dendrimer hydrogels are physical gels, the gelation could be reversed by the addition of acetonitrile; gels dissociated and could be recovered upon the removal of ace-

tonitrile. The gelation has been shown to be neither thermo-reversible nor pH-dependent. Interestingly, the three-dimensional hydrogel could be turned into an opaque aerogel by the freeze-drying-assisted removal of water, affording ramified fiber-like constructions, which look similar to green cabbage leaves.

Along with the formation of bulk hydrogels in the presence of additives, the directed gelation of these dendrimers was achieved using different modes of stimulated dendrimer gelation [19]. The formation of hydrogels has been found to be forced by the addition of a flocculating salt. The values of the sol-gel transition temperature T_g strongly depended on the dendrimer generation as well as concentrations of the dendrimer and the flocculating salt. The best gelation was achieved using the **1a-G4** dendrimer and NaI. The formation occurred at room temperature ($T_g \sim 17^\circ\text{C}$), which facilitated further handling.

Based on these data, dendrimer hydrogel fibers have been produced. The **1a-G4** dendrimer solution (10% in weight) was purged through a syringe into a flocculating bath containing salt (10% $\text{La}(\text{NO}_3)_3$). Upon purging, stable hydrogel fibers were formed instantly (Figure 4), and after 40 min of incubation, they could be taken from the flocculating bath and remained stable and resistant to air. Denaturation of the macro-fiber with NaOH revealed that they were composed of thinner fibers, similar to long hair. The dendrimer fibers exhibited an elastic behavior, contrary to polymer fibers, which displayed a plastic behavior (irreversible elongation). The rupture occurred above 9 GPa for the dendrimer fibers. The Young's modulus values were in the range of 0.5–3 GPa. It should be noted that such mechanical behavior is quite surprising for physical gels assembled exclusively by means of weak interactions [19].

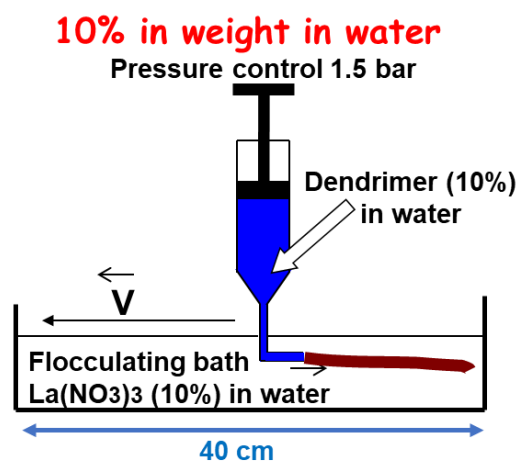


Figure 4. Schematization of the method used for producing dendrimer fibers with dendrimer **1a-G4**.

A series of cyclam-modified latex nanoparticles coated with phosphorus dendrons of generations 0, 1, and 2, bearing 2, 4 or 8 trimethylammonium acetohydrazone groups, respectively, was synthesized (Figure 5) [20]. The latex nanoparticles could accommodate on their surface about 300 molecules of the generation 0 dendron (**2a-G0**), 150 of the generation 1 dendron (**2a-G1**), and 90 of the generation 2 dendron (**2a-G2**). Exposure to multiple charged groups greatly increased the colloidal stability of the nanoparticles in water. The gelation occurred at room temperature for 1 week. The nanolatex samples could be freeze-dried and then re-dispersed in water into individual particles. Furthermore, nanoparticles decorated with dendrons imitated dendrimers of high generations (G10, for instance), and this greatly facilitated their gelation potential. Interestingly, coating with cationic dendrons did not prevent the successful complexation of Cu^{2+} ions by cyclam moieties on the surface of nanolatexes to form copper-containing hydrogels.

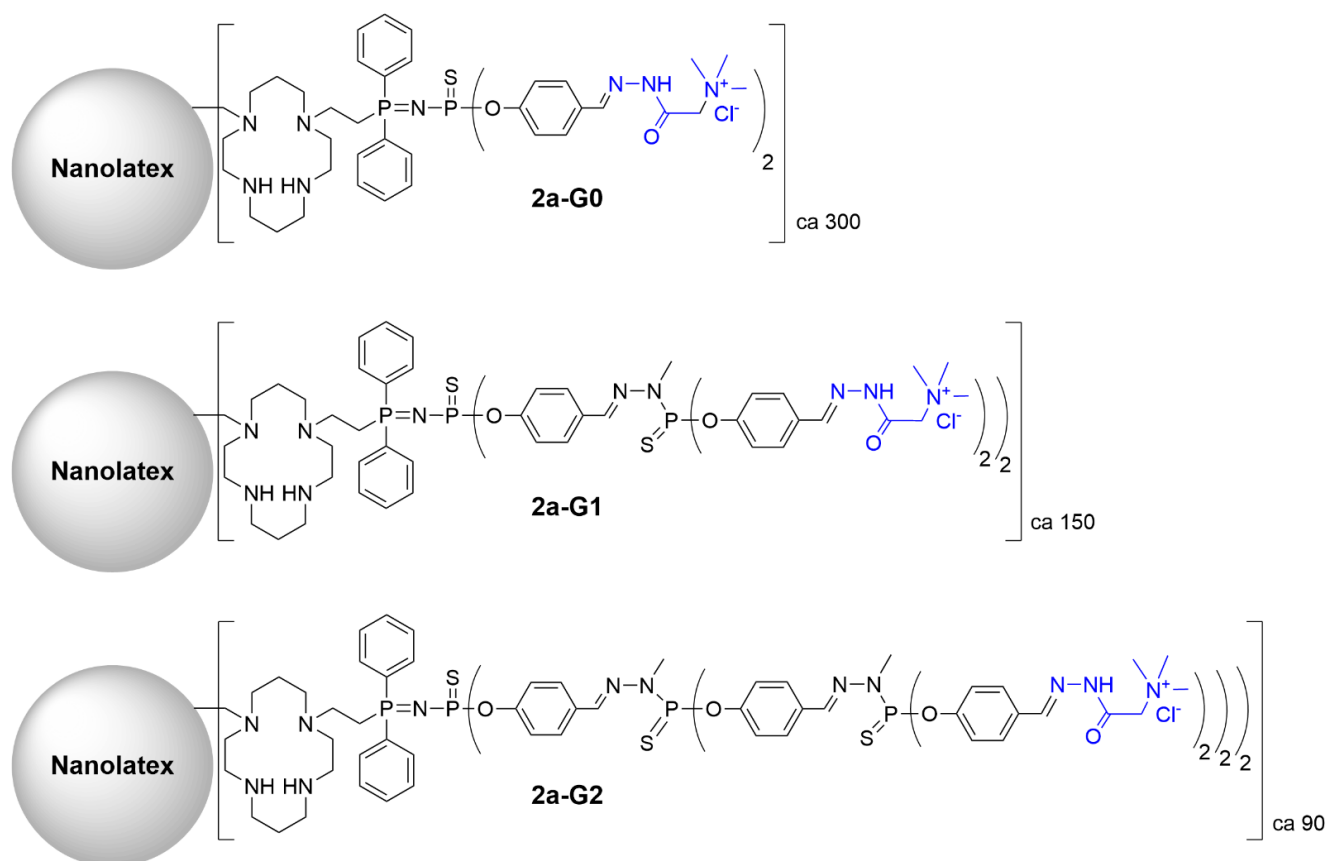


Figure 5. Nanolatex functionalized with phosphorus dendrons (generations 0 to 2) bearing the Girard T reagent as terminal functions. Cyclam moieties were suitable for the complexation of Cu^{2+} ions.

Later on, the applicability of dendrimer hydrogels for biomedical applications was explored. A series of trimethylammonium acetohydrazone-terminated or pyridinium acetohydrazone-terminated phosphorus dendrimers of generations 1, 2, and 3, based on the cyclotriphosphazene core (12, 24 or 48 surface groups, respectively), was synthesized (see Figure 6 for the full structure of dendrimer **3a-G2** and Figure 7 for the linear representation of all the dendrimers synthesized in this series). The use of such a hexafunctional core enables one to multiply by two the number of terminal functions at a given generation, compared to the trichlorothiophosphine core shown in Figure 3, and is particularly useful for the synthesis of a variety of dendritic structures [21]. The gelation properties of dendrimers **3a-Gn** and **3b-Gn** were assessed in media suitable for biological studies [22]. The gelation was carried out either in water or phosphate-buffered saline (a common solution for the handling of biomacromolecules and biological samples) in the presence of biocompatible additives (glucose, glycine or polyethyleneglycol PEG4000). The formation of light-colored gels (colorless to light yellow) was reported to depend on the concentration of the dendrimer, the dendrimer generation and the type of terminal functions, the presence of a salt, and the concentration and nature of the additive. The general conclusions supported those drawn previously [16]. However, using glucose, glycine, or polyethyleneglycol as additives generally required a longer gelation time (5–10 days), and water content in those dendrimers was lower than reported before (3300–51000 water molecules per dendrimer molecule from generation 1 to generation 3). Dendritic pyridinium salts (**3b-Gn** family) were found to be more efficient than trimethylammonium salts (**3a-Gn** family) [22], as observed previously.

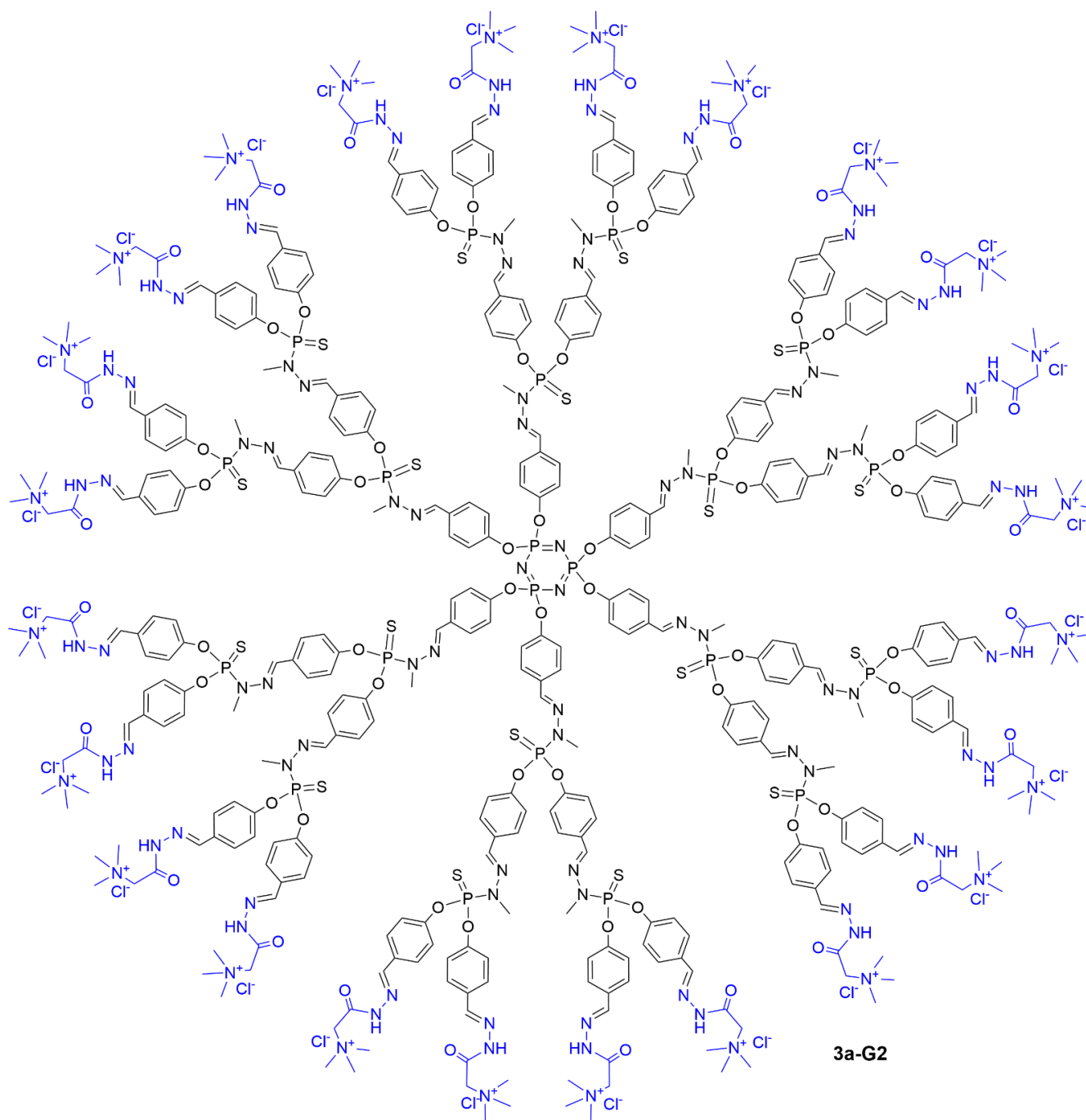


Figure 6. Full chemical structure of dendrimer 3a-G2.

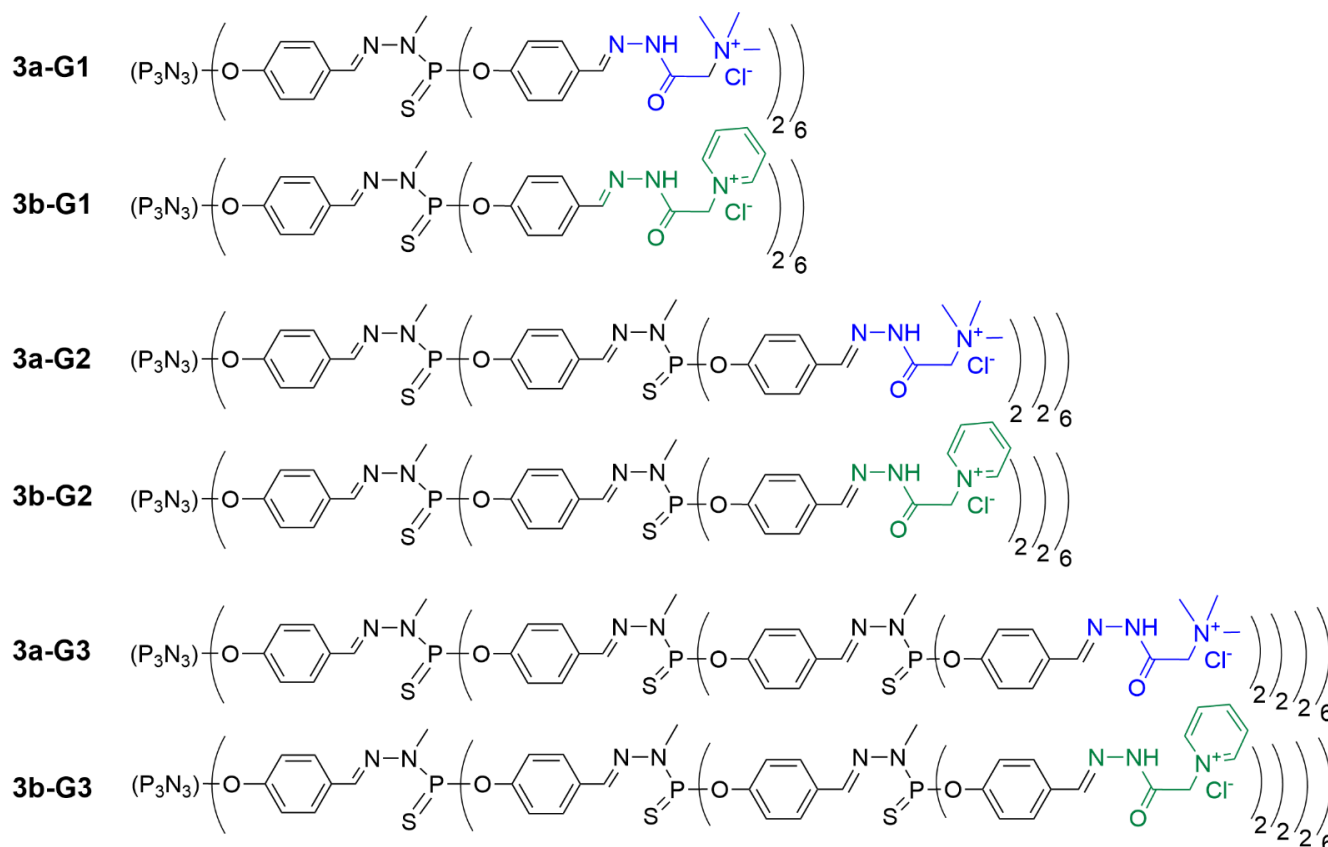


Figure 7. Linear representation of phosphorus dendrimers built from a hexafunctional core and functionalized with the Girard T reagent (in blue) or the Girard P reagent (in green) as terminal groups.

Importantly, in this work, the authors succeeded in obtaining representative TEM images of structural units of hydrogels. Dendrimer hydrogels were fixed by paraformaldehyde and cut into ultrathin sections (~70 nm thick). The TEM observation revealed random porous networks, with the network porosity and electron density of structural units correlating with the water content in hydrogels. There were two types of structural units: spherical particles and fibers co-assembled in the hydrogel network. The presence of both types of units in gels depended on the dendrimer content in the hydrogel network and on the nature of the additive [22].

Owing to the polycationic structure of aceto-hydrazone-terminated dendrimers, hydrogels efficiently bound therapeutic oligonucleotides. In general, oligonucleotide binding capacity depends rather on the nature of the additive (glucose > polyethyleneglycol > glycine) than on the nature of the cation. The loading capacity was 1.5–3 $\mu\text{mol/g}$. Once bound, oligonucleotides could be partially released from hydrogels. The release was pH-dependent; the release rate increased at $\text{pH} < 6$. Nevertheless, the overall release did not exceed 10% after 24 h [22]. This gives the idea that dendrimer hydrogels can be used as depots of therapeutic oligonucleotides for a sustained release over weeks.

Thus, phosphorus dendritic molecules present a convenient platform for obtaining functional hydrogels. By modulating dendrimer topology, generation and surface chemistry, one can produce materials with controllable properties.

2.2. Phosphorus Dendrimers in Hydrogels

A good example of a dendrimer inside a hydrogel is an agarose gel containing a polyelectrolyte dendrimer complexed with nucleic acids. In this case, dendrimers themselves are generally not involved in the formation of the hydrogel network. Such complexes, so-called dendriplexes [23], are frequently analyzed by the agarose gel electrophoresis

assay, and these studies clearly demonstrated the compatibility of polycationic phosphorus dendrimers with the agarose hydrogel scaffold. Different examples of such analyses of dendriplexes by gel electrophoresis were reported. The fluorescent dendron **4-G2** (Figure 8) was associated with the plasmid DNA coding the gene of fluorescent fusion protein BACE-GFP and also with the HygEGFP plasmid [24]. Different types of fourth-generation dendrimers bearing cyclic ammoniums as terminal functions (**5-G4**, **6-G4**, **7-G4**) were tested for their ability to interact with a [³²P]-labelled 20-mer double-stranded oligonucleotide. The pyrrolidinium derivative **5-G4** was found to be the most efficient [25]. Generations 0 to 2 of dendrimers functionalized with PTA (1,3,5-triaza-7-phosphaadamantane) complexing ruthenium were tested for their interaction with supercoiled DNA to afford relaxed DNA. Generation 0 in this series (**8-G0**) was found to be as efficient as cisplatin [26]. Generations 3 and 4 of phosphorus dendrimers bearing charged diethylethylene diamine terminal functions (**9-G3** and **9-G4** [26]) formed dendriplexes with the supercoiled form of the pUC19 plasmid, issued from *E. coli* cells. Agarose gel electrophoresis demonstrated that the dendrimers did not induce the cleavage of the plasmid [27].

Cationic phosphorus dendrimers were also used to form dendriplexes with small interfering siRNA, which were analyzed by agarose gel electrophoresis assays. Phosphorus dendrimers **9-G3** and **9-G4** were used as nanocarriers for anticancer siBcl-xl, siBcl-2, siMcl-1 siRNAs and a siScrambled sequence [28]. Phosphorus dendrimers functionalized with piperidine terminal cationic groups of the third and fourth generation (**10-G3** and **10-G4**) showed a remarkable ability to bind pro-apoptotic siRNAs [29].

Phosphorus dendrimers can also be used to bring new functionalities to hydrogels built of conventional structural blocks. The dendrimer content is thus quite low, so it can be considered a dopant enhancing the properties of the bulk, as they are placed randomly in the pores. The potential of the agarose gel to serve as a depot for the slow release of dendriplexes containing therapeutically relevant siRNA Mcl-1 was studied [30]. Third-generation polycationic phosphorus dendrimers bearing 48 cationic acetohydrazone groups (**3a-G3** and **3b-G3**) or piperidinium groups (**10-G3**) on the surface efficiently complexed fluorescein-labelled siRNA to form nanosized dendriplexes of ~100 nm diameter. Dendriplexes were cast into a hot agarose solution before gelation, and the release of siRNA-containing dendriplexes was monitored. Interestingly, the release rate appeared to strongly depend on the dendriplexes composition. Whereas dendriplexes containing a piperidinium-terminated dendrimer (**10-G3**) were released for 80% after 3 h, those containing acetohydrazone-terminated dendrimers (**3a-G3** and **3b-G3**) were released only for 20% after 24 h. This occurred most likely because of multiple hydrogen bonding between hydrazone moieties on the dendrimers' periphery and agarose scaffold. It should be reminded that this type of dendrimer was able to form hydrogels themselves [22]. Remarkably, using mixtures of dendrimers, it was possible to manipulate the dendriplexes' release rate in quite a wide range. This observation yielded the important insight that using such a kind of dendriplex anchoring in the neutral hydrogel scaffold, one can achieve a sustained local release of therapeutic oligonucleotides. This is especially important for designing local drug delivery systems and tissue engineering tools. It is also worth noting that oligonucleotides were released from a hydrogel not as individual molecules but as dendriplexes, which would facilitate their accumulation in cells of a surrounding tissue [31].

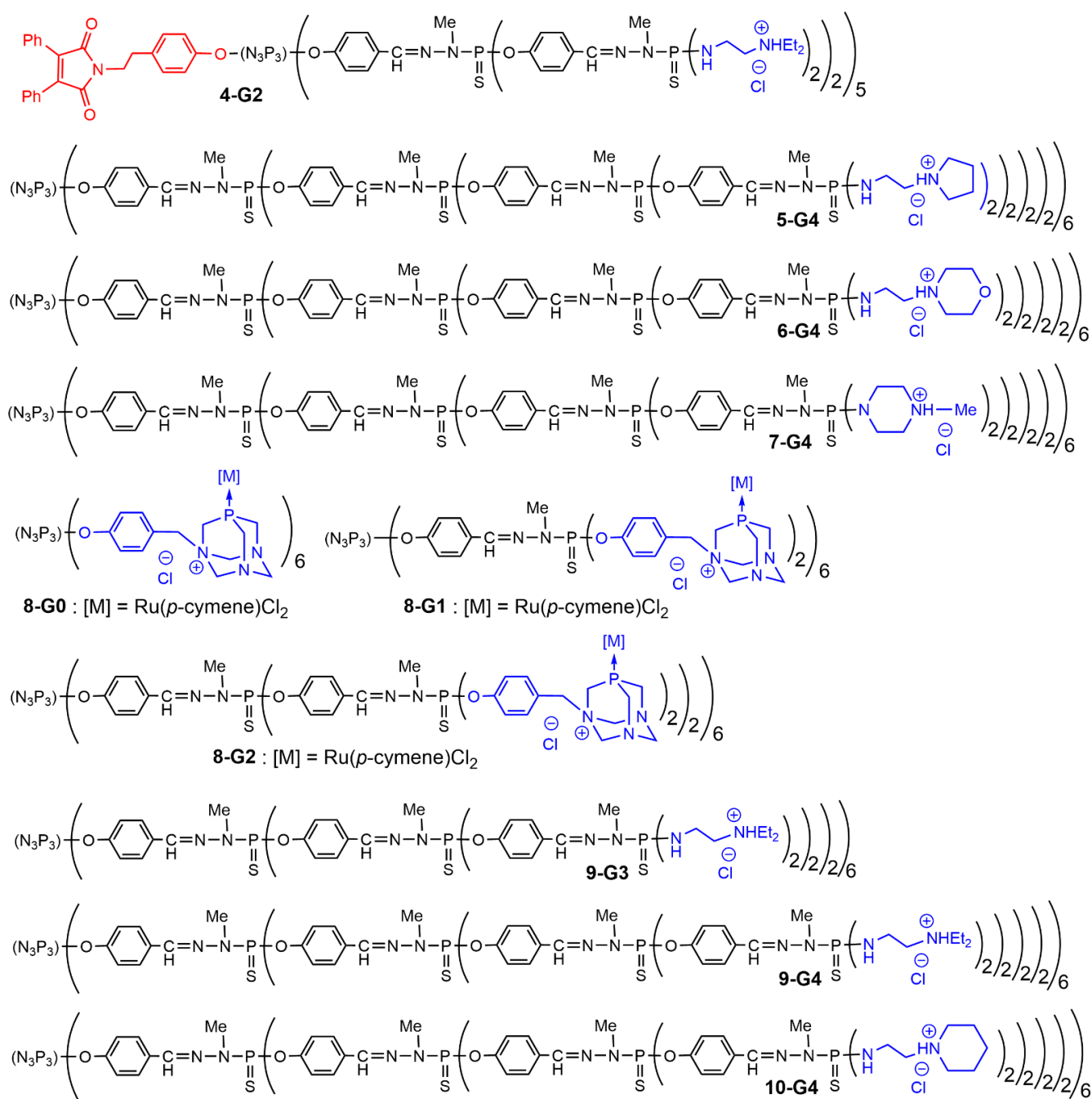


Figure 8. Structure of phosphorus dendrimers forming dendriplexes analyzed by agarose gel electrophoresis assays.

3. PAMAM Dendrimers as Physical Hydrogels and Their Properties

Poly(AMidoAMine) (PAMAM) dendrimers [32] are the most popular type of dendrimers, and they were also the first ones commercially available. They have been used as the core of star polymers, which, in some cases, were used to produce hydrogels (see, for instance, the grafting of Pluronic F127, a nonionic, surfactant polyol [33], or the grafting of a polypeptide synthesized by the ring-opening polymerization of *g*-(2-(2-methoxyethoxy)ethyl) L-glutamate (L-EG2Glu) N-carboxyanhydride [34]), but this type of poorly defined compound is out of the scope of this review, which focuses only on perfectly defined structures.

Artificial collagen-mimetic PAMAM dendrimers were synthesized by grafting different collagen peptides on their surface. The first publication concerned the grafting of the peptide proline-proline-glycine (Pro-Pro-Gly)₅ (Figure 9, compound **11a-G4**). The corresponding dendrimer formed a hydrogel, which was found suitable for the trapping and release of Rose Bengal as a model drug [35].

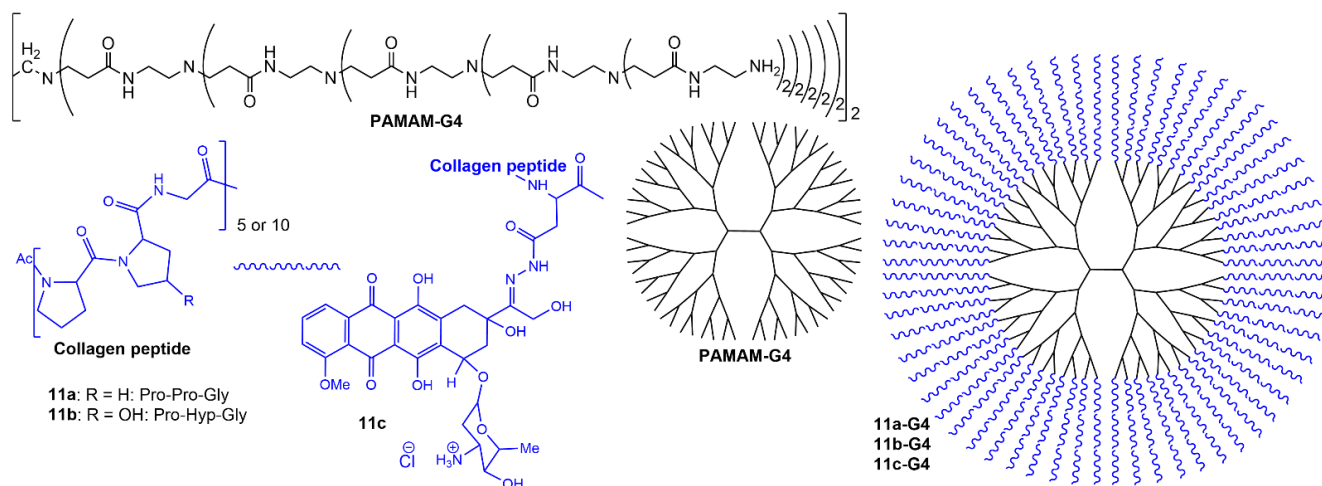


Figure 9. PAMAM dendrimers functionalized with collagen mimetics.

This work was then extended to the grafting of a longer form of the same peptidic sequence (Pro-Pro-Gly)₁₀. Using a 15 wt % aqueous solution of this dendrimer at 4 °C overnight formed a hydrogel, which could be dissolved by heating at 45 °C [36]. Another paper concerned the peptide proline-hydroxyproline-glycine (Pro-Hyp-Gly)₁₀ (**11b-G4**). The corresponding dendrimer in aqueous suspensions (15 wt%) formed hydrogels at 40 °C upon heating. The hydrogel was maintained upon heating to 80 °C, but it was dissolved by cooling to 25 °C [37]. Gel formation, stability, and reversibility were discussed in detail; then, trapping and release experiments of Rose Bengal were reported with these hydrogels [38].

A related generation 4 PAMAM dendrimer bearing both a commercially available collagen peptide (type I or type IV collagen) and doxorubicin (DOX) attached via a pH-cleavable linkage was synthesized later on (compound **11c-G4** in Figure 9). This dendrimer also afforded hydrogels in water and was used as a pro-drug against metastatic tumor cells, the highly invasive MDA-MB-231 cells. The release of DOX occurred at low pH in acidic subcellular compartments [39].

4. Janus Dendrimers as Physical Hydrogels and Their Properties

Janus dendrimers are constituted of two dendritic wedges associated by their core [40]. They are reminiscent of the bola-form dendrimers shown in Figure 1, but with two different dendritic wedges instead of two identical wedges. A series of amphiphilic Janus dendrimers was synthesized by the click chemistry between azide and alkyne in the presence of copper (**12-G₀G₂**, Figure 10). These compounds formed self-assembled fibers at a very low mass proportion (0.2 wt%) to afford supramolecular hydrogels. These hydrogels were loaded with different molecular weight bioactive compounds, such as nadolol (a low-molecular drug), gonadorelin (a decapeptide), and the enzyme horseradish peroxidase. The release rate depended both on the quantity, and the type of active ingredient encapsulated [41].

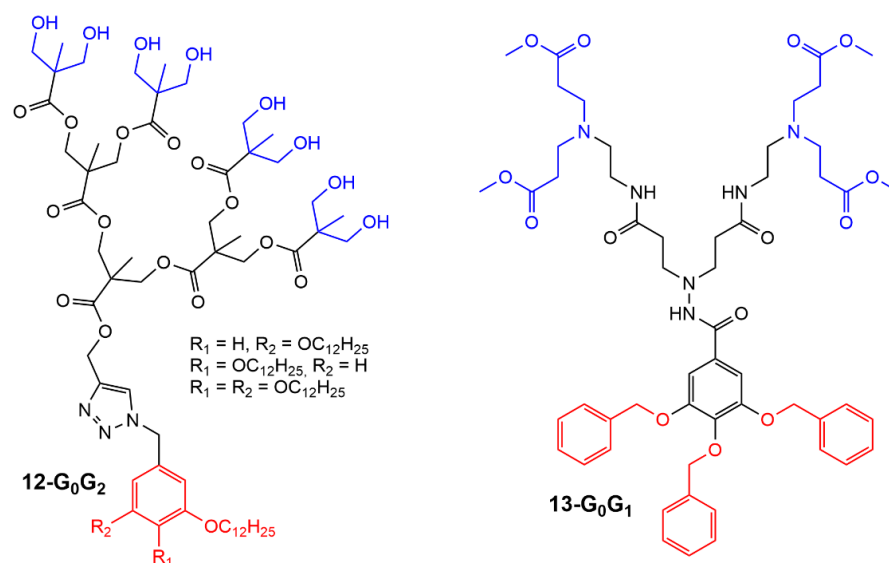


Figure 10. Structure of small amphiphilic Janus dendrimers suitable for affording hydrogels.

Another Janus amphiphilic dendrimer constituted on one side of a poly(aryl ether) dendron, and on the other side, a poly(amido amine) (PAMAM) dendron was synthesized (compound 13-G₀G₁ in Figure 10). The gelation properties of this compound were assessed in a binary solvent mixture (DMSO/water), suitable for encapsulating and releasing the Rhodamine B dye [42].

5. Dendrons as Physical Hydrogels and Their Properties

Amphiphilic dendrons are prone to self-associate in water [43]; thus, it is not surprising that numerous examples of amphiphilic dendrons possess hydrogelation properties. A series of dendrons bearing carbohydrate terminal functions and an O-allyl group at the core was synthesized using a parallel combinatorial approach, depending on the length of the alkyl linkers in the branches (values of x , y , and z in the family of compounds 14 x,y,z -G₂ shown in Figure 11). It was found that subtle differences in the dendrons' structure induced significant differences in their hydrogelation properties. Hydrogels were obtained in all cases at low concentrations in water 0.5–1.0 wt%. Gel transition (from gel to solution) depended on the structure, i.e., on the values of x , y , and z . For instance, gel transition was obtained at 15 °C with dendron 14_{5,4,3}-G₂ and at 37 °C with dendron 14_{3,4,5}-G₂, which only differed by the inversion of the x and z values [44].

The small anthryl dendron 15-G₀ (Figure 12), having gluconamides at its periphery, was shown to afford a hydrogel by heating at 60 °C in water, then cooling to room temperature. Interestingly, the presence of an anthracene at the core enabled its photo-dimerization in a quantitative yield under irradiation of the hydrogel at $\lambda > 300$ nm. Such dimerization induced physical changes from gel to solution. Such a phase transition was observed at 46 °C for the hydrogel of dendron 15-G₀ before irradiation and at 15 °C for its photo-dimerized form. This was the first example of a dendron as a photo-responsive hydrogelator. Only two forms were obtained for the dimer, the *syn* and *anti* of the head-to-tail form, whereas no head-to-head form was observed, as shown by ¹H NMR [45].

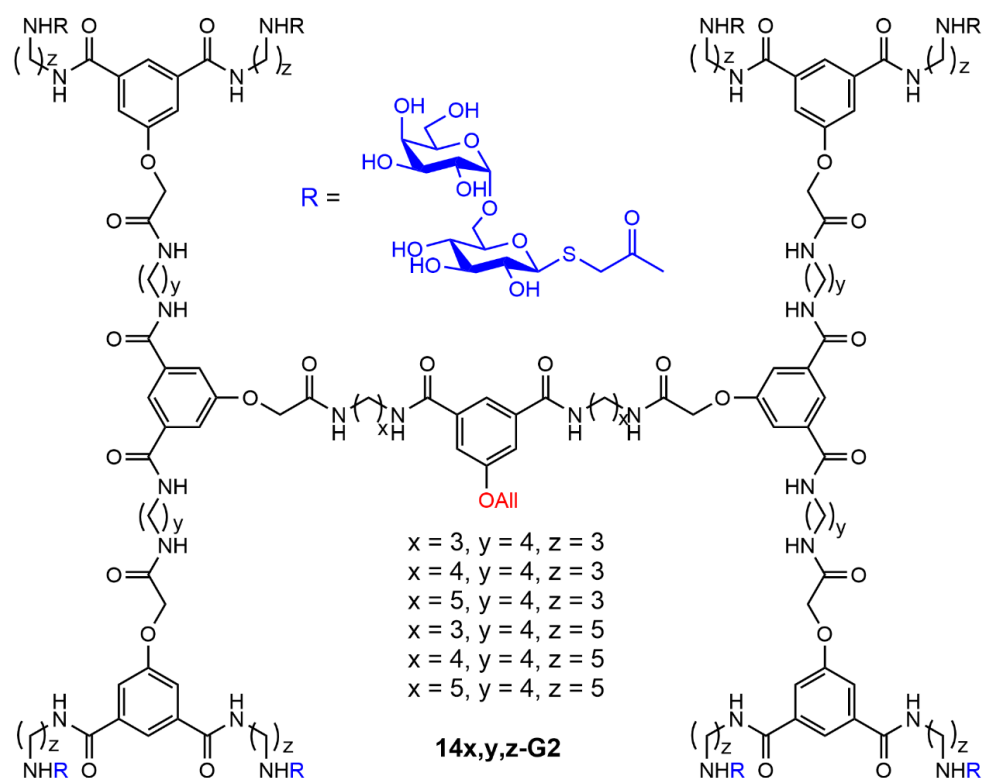


Figure 11. Structure of a large family of glycodendrons obtained by a parallel combinatorial approach and suitable for producing hydrogels at low concentration.

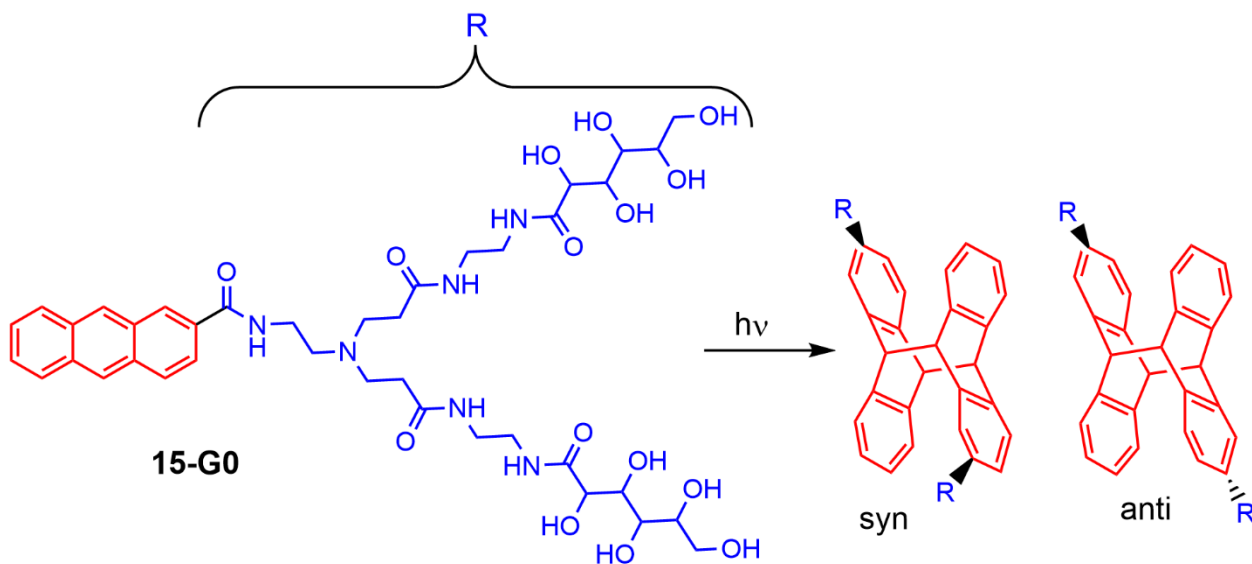


Figure 12. A small dendron having an anthracene at the core, able to dimerize under photo-irradiation.

Besides the anthracene, a series of dendrons possessing an aromatic group at the core and protected L-glutamate branches was synthesized (compounds **16a-e-G1** in Figure 13). These dendrons displayed ambidextrous properties. Indeed, they formed organogels in hexane and hydrogels in water, essentially composed in both cases of nanofibers. Gels based on naphthyl and anthryl dendrons displayed an enhanced fluorescence compared to the solutions. Strong CD (circular dichroism) values were observed for the gels, contrarily to the solution, indicating that the chirality could be observed only in the gel [46].

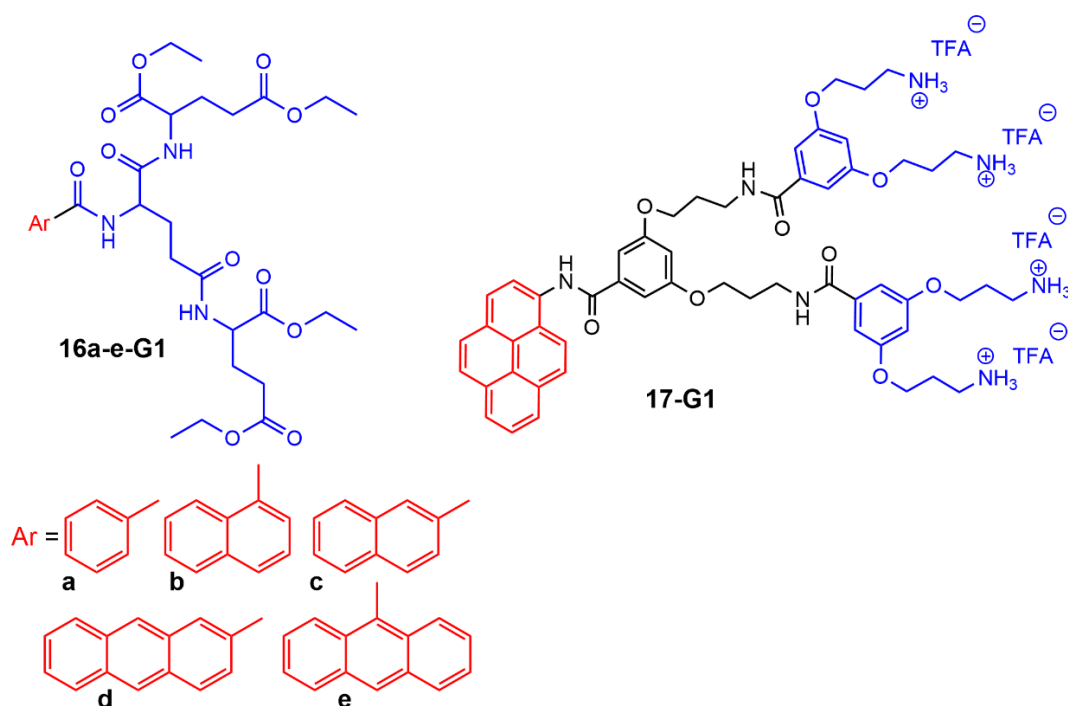


Figure 13. Examples of amphiphilic dendrons, for which the dendritic part is hydrophilic and the core is a lipophilic aromatic group.

A series of dendrons bearing a pyrene at the core and 2 to 8 ammonium terminal functions was first synthesized for DNA sensory applications [47]. The smallest dendrons of the series, such as **17-G1** (Figure 13) were then used to obtain pH-responsive hydrogels. Indeed, these dendrons formed hydrogels in basic conditions, whereas only solutions were obtained in acidic conditions [48].

Several small dendrons having an alkyl chain at the core and hydrophilic terminal functions were synthesized, and their gelation properties were studied, both in several organic solvents and in water. In the series of compounds **18a-c-G0** (Figure 14), which differed by the presence or absence of an amide group in the chain and on the chain length, compound **18c-G0** displayed the best hydrogelation ability at 0.3 mol% concentration. These hydrogels exhibited highly pH-responsive gel-sol transitions, with the hydrogels being present at high pH (pH = 9), whereas a clear solution was observed at low pH (pH = 2) [49].

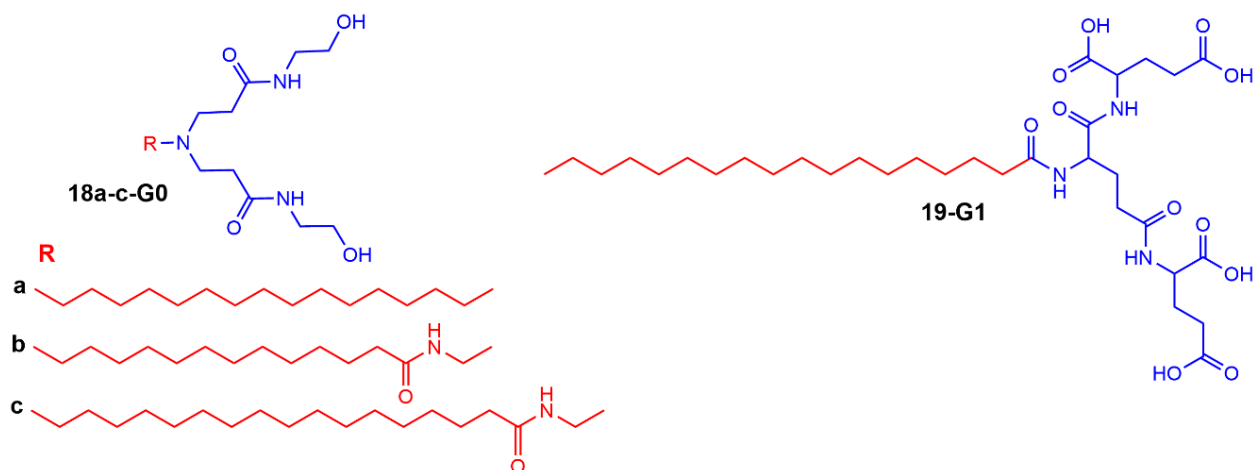


Figure 14. Amphiphilic dendrons having a long alkyl chain as their core.

The small peptide dendron **19-G1** based on L-glutamic acid and a long C17 alkyl chain at the core (Figure 14) formed hydrogels over a wide pH range (2 to 13). Interestingly, AFM images of the hydrogels at different pH values displayed different chiral structures, in particular, various types of nanotubes. At pH 3 or 4, the nanotubes were similar to a string of hollow beads. At pH 7, the nanotubes served as building blocks of a coiled superhelix. At a pH higher than 10, the ionic interactions became dominant, and dendritic-like structures were observed [50]. It was shown later on that metal ions (Ag^+ , Cu^{2+} , Zn^{2+} , Co^{2+} , Mg^{2+} , Ca^{2+} , Ni^{2+} , Cd^{2+} , Al^{3+} , Fe^{3+} , La^{3+} , Eu^{3+} , Zr^{4+}) could enhance the gelation properties, with the lowest concentration to gel water decreasing from 0.3 wt% for the dendron alone to 0.08 wt% in the presence of metal ions. Furthermore, a reversible shrinkage of the gel was observed when using divalent metal ions. Such a property was used for the controlled release of Vitamin B₁. At first, the dendron and Vitamin B₁ were heated in water, and the hydrogel, including Vitamin B₁, was obtained on cooling. The shrinkage of the gel, accompanied by the release of Vitamin B₁, was observed upon the addition of divalent metal ions, in particular Mg^{2+} [51]. Such a process with Mg^{2+} was then applied to the separation of ionic dye mixtures. The cationic dyes were methyl violet (MV), methylene blue (MB), acridine yellow (AY), and neutral red (NR), whereas the anionic dyes were methyl orange (MO) and acid red 26 (AR). The hydrogels were mixed with the same molar amounts of two different dyes (one positively and one negatively charged). It was shown that the ionic dye mixtures could be easily and spontaneously separated through hydrogel shrinkage. Indeed, the cationic dyes remained in the gel phase, whereas the anionic dyes were released into the aqueous phase. Such a process was then used for the stepwise release of two-component ionic drugs, pralidoxime iodide (PI) and phenol red (PR), being used as model drugs of small hydrophilic molecules [52].

These hydrogels based on dendron **19-G1** were also used to regulate the chiral packing of a cyanine dye, forming a helical H-aggregate. It was possible with this system to visually discriminate the presence of chiral amines ((R)-1-(4-methoxyphenyl) ethanamine and (S)-1-(4-methoxyphenyl) ethanamine) [53]. The same dendron was also used to generate hydrogels in the presence of a positively charged azobenzene derivative. The hydrogel was composed of long nanofibers and presented a dual thermal and photo-switchable reversible volume phase transition upon either heating or photo-irradiation [54].

All the previously shown dendrons are composed of a lipophilic core and hydrophilic surface. There are few examples of dendrons having, on the contrary, a hydrophilic core and a lipophilic surface composed of aromatic groups. The glucose-cored poly(aryl ether) dendron **20-G1** afforded transparent hydrogels (Figure 15). The structure of these hydrogels varied with the pH, from nanofibers to spherical aggregates. The addition of KOH (pH = 10) converted the hydrogel to a solution [55]. This hydrogel was used for enhancing resonance energy transfer from organic donors (phenanthrene, naphthalene, and pyrene) to lanthanide [Eu^{3+} and Tb^{3+}] ions. It is important to note that such a transfer was not observed in solution; it occurred solely in the hydrogel. The system has been utilized to generate cool white-light emission from the gel by incorporating an additional lanthanide ion, Tb^{3+} , along with the organic donors and Eu^{3+} [56].

Another type of amphiphilic dendron was obtained by solid phase synthesis to incorporate a single-stranded DNA at the core (compound **21-G1** in Figure 15). This dendron self-assembled in water into nanofibers, formed by the association of the hydrophobic parts of the dendrons, to produce a hydrogel. Hydrophobic species such as Nile Red entered into these nanofibers, and a bright fluorescence could be observed [57].

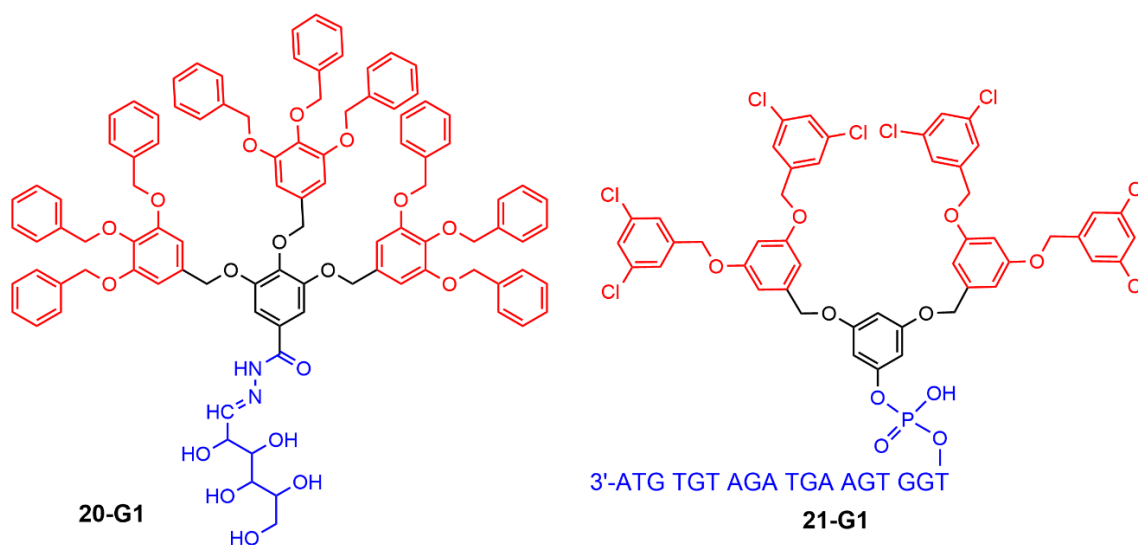


Figure 15. Structure of dendrons having a hydrophilic core and hydrophobic surface and branches.

6. Conclusions

Physical hydrogels attract the attention of researchers due to the simplicity of their preparation as well as their attractive physicochemical and mechanical properties. Dendrimers, being inherent multivalent species, are highly promising building blocks for physical hydrogels due to their high number of functional residues available for gelation. Importantly, the dendritic scaffold takes part in the gelation along with surface groups. Therefore, the use of dendritic molecules for gelation gives room for precise engineering of hydrogel properties by finding an optimal balance between the hydrophilicity/hydrophobicity of the dendritic scaffold and surface functional groups, with the choice of functional group chemistry defining the gelation mode.

Dendrimer-based hydrogels have been used as functional materials and drug-delivery vehicles, as illustrated in Figure 16. Quite limited data available to date suggests, nevertheless, that the use of dendrimers and dendrons should be developed for the adjustment of material properties. However, there are several challenges to be addressed in further explorations, namely the large-scale production of hydrogels for sustained drug release or tissue engineering. The recent success of the dendrimer-based formulation VivaGel approved by the US FDA to prevent HIV infection [58,59] and to treat bacterial vaginosis [60,61] is encouraging. Furthermore, a better understanding of the relationships between dendritic gelator structure and the following modulation of hydrogel properties can serve as key parameters to construct the next generation of therapeutic systems or biomaterials.

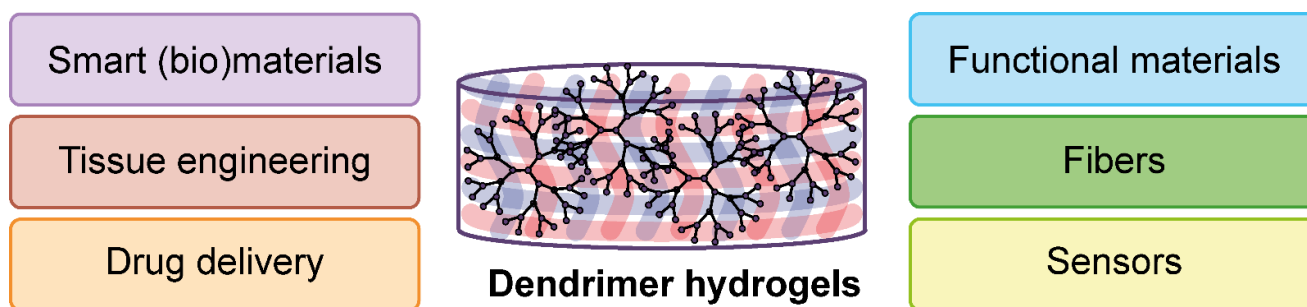


Figure 16. Already observed properties of physical hydrogels based on dendritic molecules.

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References

1. Peppas, N.A.; Bures, P.; Leobandung, W.; Ichikawa, H. Hydrogels in pharmaceutical formulations. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 27–46. [[CrossRef](#)]
2. Calo, E.; Khutoryanskiy, V.V. Biomedical applications of hydrogels: A review of patents and commercial products. *Eur. Polym. J.* **2015**, *65*, 252–267. [[CrossRef](#)]
3. Qiu, Y.; Park, K. Environment-sensitive hydrogels for drug delivery. *Adv. Drug Del. Rev.* **2012**, *64*, 49–60. [[CrossRef](#)]
4. Hoare, T.R.; Kohane, D.S. Hydrogels in drug delivery: Progress and challenges. *Polymer* **2008**, *49*, 1993–2007. [[CrossRef](#)]
5. Li, J.; Mooney, D.J. Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071. [[CrossRef](#)]
6. Narayanaswamy, R.; Torchilin, V.P. Hydrogels and Their Applications in Targeted Drug Delivery. *Molecules* **2019**, *24*, 603. [[CrossRef](#)]
7. Lee, K.Y.; Mooney, D.J. Hydrogels for Tissue Engineering. *Chem. Rev.* **2001**, *101*, 1869–1879. [[CrossRef](#)]
8. Peppas, N.A.; Hilt, J.Z.; Khademhosseini, A.; Langer, R. Hydrogels in biology and medicine: From molecular principles to bionanotechnology. *Adv. Mater.* **2006**, *18*, 1345–1360. [[CrossRef](#)]
9. Hu, W.K.; Wang, Z.J.; Xiao, Y.; Zhang, S.M.; Wang, J.L. Advances in crosslinking strategies of biomedical hydrogels. *Biomater. Sci.* **2019**, *7*, 843–855. [[CrossRef](#)]
10. Herrmann, A.; Haag, R.; Schedler, U. Hydrogels and Their Role in Biosensing Applications. *Adv. Healthc. Mater.* **2021**, *10*, 2100062. [[CrossRef](#)]
11. Kaga, S.; Arslan, M.; Sanyal, R.; Sanyal, A. Dendrimers and Dendrons as Versatile Building Blocks for the Fabrication of Functional Hydrogels. *Molecules* **2016**, *21*, 497. [[CrossRef](#)]
12. Newkome, G.R.; Baker, G.R.; Saunders, M.J.; Russo, P.S.; Gupta, V.K.; Yao, Z.Q.; Miller, J.E.; Bouillion, K. Two-directional Cascade Molecules: Synthesis and Characterization of [9]-n-[9] Arborols. *J. Chem. Soc.-Chem. Commun.* **1986**, *10*, 752–753. [[CrossRef](#)]
13. Newkome, G.R.; Baker, G.R.; Arai, S.; Saunders, M.J.; Russo, P.S.; Theriot, K.J.; Moorefield, C.N.; Rogers, L.E.; Miller, J.E.; Lieux, T.R.; et al. Synthesis and Characterization of Two-Directional Cascade Molecules and Formation of Aqueous Gels. *J. Am. Chem. Soc.* **1990**, *112*, 8458–8465. [[CrossRef](#)]
14. Newkome, G.R.; Moorefield, C.N.; Baker, G.R.; Behera, R.K.; Escamillia, G.H.; Saunders, M.J. Supramolecular Self-Assemblies of Two-Directional Cascade Molecules: Automorphogenesis. *Angew. Chem.-Int. Ed. Engl.* **1992**, *31*, 917–919. [[CrossRef](#)]
15. Jorgensen, M.; Bechgaard, K.; Bjornholm, T.; Sommerlarsen, P.; Hansen, L.G.; Schaumburg, K. Synthesis and Structural Characterization of a Bis-arborol-Tetrathiafulvalene Gel: Toward a Self-Assembling “Molecular” Wire. *J. Org. Chem.* **1994**, *59*, 5877–5882. [[CrossRef](#)]
16. Marmillon, C.; Gauffre, F.; Gulik-Krzywicki, T.; Loup, C.; Caminade, A.M.; Majoral, J.P.; Vors, J.P.; Rump, E. Organophosphorus dendrimers as new gelators for hydrogels. *Angew. Chem. Int. Ed.* **2001**, *40*, 2626–2629. [[CrossRef](#)]
17. Galliot, C.; Larre, C.; Caminade, A.M.; Majoral, J.P. Regioselective stepwise growth of dendrimer units in the internal voids of a main dendrimer. *Science* **1997**, *277*, 1981–1984. [[CrossRef](#)]
18. Caminade, A.M.; Majoral, J.P. Positively charged phosphorus dendrimers. An overview of their properties. *New J. Chem.* **2013**, *37*, 3358–3373. [[CrossRef](#)]
19. El Ghzaoui, A.; Gauffre, F.; Caminade, A.M.; Majoral, J.P.; Lannibois-Drean, H. Self-assembly of water-soluble dendrimers into thermoreversible hydrogels and macroscopic fibers. *Langmuir* **2004**, *20*, 9348–9353. [[CrossRef](#)]
20. Larpent, C.; Genies, C.; Delgado, A.P.D.; Caminade, A.M.; Majoral, J.P.; Sassi, J.F.; Leising, F. Giant dendrimer-like particles from nanolatexes. *Chem. Commun.* **2004**, *16*, 1816–1817. [[CrossRef](#)]
21. Caminade, A.-M.; Hameau, A.; Majoral, J.-P. The specific functionalization of cyclotriphosphazene for the synthesis of smart dendrimers. *Dalton Trans.* **2016**, *45*, 1810–1822. [[CrossRef](#)] [[PubMed](#)]
22. Apartsin, E.K.; Grigoryeva, A.E.; Malrin-Fournol, A.; Ryabchikova, E.I.; Venyaminova, A.G.; Mignani, S.; Caminade, A.M.; Majoral, J.P. Hydrogels of Polycationic Acetohydrazone-Modified Phosphorus Dendrimers for Biomedical Applications: Gelation Studies and Nucleic Acid Loading. *Pharmaceutics* **2018**, *10*, 120. [[CrossRef](#)] [[PubMed](#)]

23. Ramaswamy, C.; Sakthivel, T.; Wilderspin, A.F.; Florence, A.T. Dendriplexes and their characterization. *Int. J. Pharm.* **2003**, *254*, 17–21. [[CrossRef](#)] [[PubMed](#)]
24. Padie, C.; Maszewska, M.; Majchrzak, K.; Nawrot, B.; Caminade, A.M.; Majoral, J.P. Polycationic phosphorus dendrimers: Synthesis, characterization, study of cytotoxicity, complexation of DNA, and transfection experiments. *New J. Chem.* **2009**, *33*, 318–326. [[CrossRef](#)]
25. Kazmierczak-Baranska, J.; Pietkiewicz, A.; Janicka, M.; Wei, Y.Q.; Turrin, C.O.; Majoral, J.P.; Nawrot, B.; Caminade, A.M. Synthesis of a Fluorescent Cationic Phosphorus Dendrimer and Preliminary Biological Studies of Its Interaction with DNA. *Nucl. Nucl. Nucleic Acids* **2010**, *29*, 155–167. [[CrossRef](#)]
26. Servin, P.; Laurent, R.; Tristany, M.; Romerosa, A.; Peruzzini, M.; Garcia-Maroto, F.; Majoral, J.-P.; Caminade, A.-M. Dual properties of water-soluble Ru-PTA complexes of dendrimers: Catalysis and interaction with DNA. *Inorg. Chim. Acta* **2018**, *470*, 106–112. [[CrossRef](#)]
27. Loup, C.; Zanta, M.A.; Caminade, A.M.; Majoral, J.P.; Meunier, B. Preparation of water-soluble cationic phosphorus-containing dendrimers as DNA transfecting agents. *Chem.-Eur. J.* **1999**, *5*, 3644–3650. [[CrossRef](#)]
28. Gomulak, P.; Klajnert, B.; Bryszewska, M.; Majoral, J.P.; Caminade, A.M.; Blasiak, J. Cytotoxicity and Genotoxicity of Cationic Phosphorus-Containing Dendrimers. *Curr. Med. Chem.* **2012**, *19*, 6233–6240. [[CrossRef](#)]
29. Ionov, M.; Lazniewska, J.; Dzmitruk, V.; Halets, I.; Loznikova, S.; Novopashina, D.; Apartsin, E.; Krasheninina, O.; Venyaminova, A.; Milowska, K.; et al. Anticancer siRNA cocktails as a novel tool to treat cancer cells. Part (A). Mechanisms of interaction. *Int. J. Pharm.* **2015**, *485*, 261–269. [[CrossRef](#)]
30. Ihnatsyeyu-Kachan, A.; Dzmitruk, V.; Apartsin, E.; Krasheninina, O.; Ionov, M.; Loznikova, S.; Venyaminova, A.; Milowska, K.; Shcharbin, D.; Mignani, S.; et al. Multi-Target Inhibition of Cancer Cell Growth by siRNA Cocktails and 5-Fluorouracil Using Effective Piperidine-Terminated Phosphorus Dendrimers. *Colloids Interfaces* **2017**, *1*, 6. [[CrossRef](#)]
31. Apartsin, E.; Venyaminova, A.; Majoral, J.-P.; Caminade, A.-M. Dendriplex-Impregnated Hydrogels with Programmed Release Rate. *Front. Chem.* **2022**, *9*, 780608. [[CrossRef](#)] [[PubMed](#)]
32. Tomalia, D.A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. A new class of polymers—Starburst-dendritic macromolecules. *Polym. J.* **1985**, *17*, 117–132. [[CrossRef](#)]
33. Gao, C.M.; Lu, S.Y.; Liu, M.Z.; Wu, C.; Xiong, Y. CO₂-switchable fluorescence of a dendritic polymer and its applications. *Nanoscale* **2016**, *8*, 1140–1146. [[CrossRef](#)] [[PubMed](#)]
34. Shen, Y.; Zhang, S.S.; Wan, Y.M.; Fu, W.X.; Li, Z.B. Hydrogels assembled from star-shaped polypeptides with a dendrimer as the core. *Soft Matter* **2015**, *11*, 2945–2951. [[CrossRef](#)] [[PubMed](#)]
35. Kojima, C.; Tsumura, S.; Harada, A.; Kono, K. A Collagen-Mimic Dendrimer Capable of Controlled Release. *J. Am. Chem. Soc.* **2009**, *131*, 6052–6053. [[CrossRef](#)]
36. Suehiro, T.; Tada, T.; Waku, T.; Tanaka, N.; Hongo, C.; Yamamoto, S.; Nakahira, A.; Kojima, C. Temperature-Dependent Higher Order Structures of the (Pro-Pro-Gly)₁₀-Modified Dendrimer. *Biopolymers* **2011**, *95*, 270–277. [[CrossRef](#)] [[PubMed](#)]
37. Kojima, C.; Suehiro, T.; Tada, T.; Sakamoto, Y.; Waku, T.; Tanaka, N. Preparation of heat-induced artificial collagen gels based on collagen-mimetic dendrimers. *Soft Matter* **2011**, *7*, 8991–8997. [[CrossRef](#)]
38. Kojima, C.; Suehiro, T. Improvement of Temperature-responsive Drug Release from Collagen-mimic Dendrimers. *Chem. Lett.* **2011**, *40*, 1249–1251. [[CrossRef](#)]
39. Kojima, C.; Suehiro, T.; Watanabe, K.; Ogawa, M.; Fukuhara, A.; Nishisaka, E.; Harada, A.; Kono, K.; Inui, T.; Magata, Y. Doxorubicin-conjugated dendrimer/collagen hybrid gels for metastasis-associated drug delivery systems. *Acta Biomater.* **2013**, *9*, 5673–5680. [[CrossRef](#)]
40. Caminade, A.M.; Laurent, R.; Delavaux-Nicot, B.; Majoral, J.P. “Janus” dendrimers: Syntheses and properties. *New J. Chem.* **2012**, *36*, 217–226. [[CrossRef](#)]
41. Nummelin, S.; Liljestrom, V.; Saarikoski, E.; Ropponen, J.; Nykanen, A.; Linko, V.; Seppala, J.; Hirvonen, J.; Ikkala, O.; Bimbo, L.M.; et al. Self-Assembly of Amphiphilic Janus Dendrimers into Mechanically Robust Supramolecular Hydrogels for Sustained Drug Release. *Chem.-Eur. J.* **2015**, *21*, 14433–14439. [[CrossRef](#)]
42. Prabakaran, P.; Prasad, E. Janus Dendrimer from Poly(Aryl Ether) Linked PAMAM for Supergelation and Guest Release. *Chemistryselect* **2016**, *1*, 5561–5568. [[CrossRef](#)]
43. Apartsin, E.; Caminade, A. Supramolecular Self-Associations of Amphiphilic Dendrons and Their Properties. *Chem. Eur. J.* **2021**, *27*, 17976–17998. [[CrossRef](#)] [[PubMed](#)]
44. McWatt, M.; Boons, G.J. Parallel combinatorial synthesis of glycodendrimers and their hydrogelation properties. *Eur. J. Org. Chem.* **2001**, *2001*, 2535–2545. [[CrossRef](#)]
45. Sako, Y.; Takaguchi, Y. A photo-responsive hydrogelator having gluconamides at its peripheral branches. *Org. Biomol. Chem.* **2008**, *6*, 3843–3847. [[CrossRef](#)]
46. Duan, P.F.; Liu, M.H. Design and Self-Assembly of L-Glutamate-Based Aromatic Dendrons as Ambidextrous Gelators of Water and Organic Solvents. *Langmuir* **2009**, *25*, 8706–8713. [[CrossRef](#)] [[PubMed](#)]
47. Chen, C.Y.; Ito, Y.; Chiu, Y.C.; Wu, W.C.; Higashihara, T.; Ueda, M.; Chen, W.C. Design and Synthesis of New Cationic Water-Soluble Pyrene Containing Dendrons for DNA Sensory Applications. *J. Polym. Sci. Part A-Polym. Chem.* **2012**, *50*, 297–305. [[CrossRef](#)]

48. Chen, C.Y.; Ito, Y.; Chiu, Y.C.; Wu, W.C.; Higashihara, T.; Ueda, M.; Chen, W.C. pH-responsive Dendritic Gelators. *Chem. Lett.* **2012**, *41*, 92–94. [[CrossRef](#)]
49. Morita, C.; Kawai, C.; Kikuchi, A.; Imura, Y.; Kawai, T. Effect of amide moieties for hydrogelators on gelation property and heating-free pH responsive gel-sol phase transition. *J. Oleo Sci.* **2012**, *61*, 707–713. [[CrossRef](#)]
50. Duan, P.F.; Qin, L.; Zhu, X.F.; Liu, M.H. Hierarchical Self-Assembly of Amphiphilic Peptide Dendrons: Evolution of Diverse Chiral Nanostructures Through Hydrogel Formation Over a Wide pH Range. *Chem.-Eur. J.* **2011**, *17*, 6389–6395. [[CrossRef](#)]
51. Qin, L.; Duan, P.F.; Xie, F.; Zhang, L.; Liu, M.H. A metal ion triggered shrinkable supramolecular hydrogel and controlled release by an amphiphilic peptide dendron. *Chem. Commun.* **2013**, *49*, 10823–10825. [[CrossRef](#)] [[PubMed](#)]
52. Qin, L.; Xie, F.; Duan, P.F.; Liu, M.H. A Peptide Dendron-Based Shrinkable Metallo-Hydrogel for Charged Species Separation and Stepwise Release of Drugs. *Chem.-Eur. J.* **2014**, *20*, 15419–15425. [[CrossRef](#)] [[PubMed](#)]
53. Qin, L.; Xie, F.; Jin, X.; Liu, M.H. Driving Helical Packing of a Cyanine Dye on Dendron Nanofiber: Gel-Shrinkage-Triggered Chiral H-Aggregation and Enhanced Enantiodiscrimination. *Chem.-Eur. J.* **2015**, *21*, 11300–11305. [[CrossRef](#)]
54. Xie, F.; Qin, L.; Liu, M.H. A dual thermal and photo-switchable shrinking-swelling supramolecular peptide dendron gel. *Chem. Commun.* **2016**, *52*, 930–933. [[CrossRef](#)]
55. Rajamalli, P.; Sheet, P.S.; Prasad, E. Glucose-cored poly(aryl ether) dendron based low molecular weight gels: pH controlled morphology and hybrid hydrogel formation. *Chem. Commun.* **2013**, *49*, 6758–6760. [[CrossRef](#)] [[PubMed](#)]
56. Kumar, P.; Soumya, S.; Prasad, E. Enhanced Resonance Energy Transfer and White-Light Emission from Organic Fluorophores and Lanthanides in Dendron-based Hybrid Hydrogel. *ACS Appl. Mater. Interfaces* **2016**, *8*, 8068–8075. [[CrossRef](#)]
57. Wang, L.Y.; Feng, Y.; Sun, Y.W.; Li, Z.B.; Yang, Z.Q.; He, Y.M.; Fan, Q.H.; Liu, D.S. Amphiphilic DNA-dendron hybrid: A new building block for functional assemblies. *Soft Matter* **2011**, *7*, 7187–7190. [[CrossRef](#)]
58. Retention and Duration of Activity of SPL7013 (VivaGel®) after Vaginal Dosing. Available online: <https://clinicaltrials.gov/ct2/show/NCT00740584> (accessed on 5 January 2023).
59. Nandy, B.; Saurabh, S.; Sahoo, A.K.; Dixit, N.M.; Maiti, P.K. The SPL7013 dendrimer destabilizes the HIV-1 gp120–CD4 complex. *Nanoscale* **2015**, *7*, 18628–18641. [[CrossRef](#)]
60. Pellett Madan, R.; Dezzutti, C.S.; Rabe, L.; Hillier, S.L.; Marrazzo, J.; McGowan, I.; Richardson, B.A.; Herold, B.C. Soluble immune mediators and vaginal bacteria impact innate genital mucosal antimicrobial activity in young women. *Am. J. Reprod. Immunol.* **2015**, *74*, 323–332. [[CrossRef](#)]
61. Efficacy and Safety Study of SPL7013 Gel to Prevent the Recurrence of Bacterial Vaginosis (BV). Available online: <https://clinicaltrials.gov/ct2/show/NCT02237950> (accessed on 5 January 2023).

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