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Stimuli Sensitive Amphiphilic Dendrimers

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Abstract

In the past decade, there has been an increasing interest in supramolecular systems that can undergo physical or chemical transformations upon encountering a specific stimulus. Micelle-forming amphiphilic systems based on polymers and dendrimers are particularly preferred over small molecule amphiphiles, due to their ability to sequester and release a vast library of hydrophobic guest molecules at micromolar polymer or dendrimer concentrations. Here we review a relatively underexplored, yet rapidly advancing, field of amphiphilic systems based on dendritic architecture that exhibit stimuli sensitive behaviour. In particular, we will be focusing on stimuli such as temperature, pH, enzymatic and non-enzymatic proteins. These stimuli-responsive systems offer a unique opportunity in the field of drug delivery and sensing.

Introduction

Amphiphilic molecules are primarily interesting due to the self-assembled structures^{1–10} they exhibit both in solution (micelles,^{11–15} vesicles^{16–19}) and in thin films.^{20,21} The fundamental driving force for the formation of these assemblies is to maintain a favorable hydrophilic-lipophilic balance (HLB) between the hydrophilic and the lipophilic functional group components of the amphiphile. In solution, these molecules self-assemble only above a certain concentration of the amphiphile, known as critical aggregation concentration (CAC). Amphiphilic macromolecules have garnered significant interest, because their CACs are substantially lower than their small molecule counterparts. For example, assemblies achieved from macromolecules, such as amphiphilic block copolymers, have CACs in micro or nanomolar range, compared to the millimolar CAC for small molecule surfactants.^{22,23} Other polymeric systems like amphiphilic homopolymers were also explored for their self-assembling properties.²⁴ Although polymers offer advantages over their small molecule counterparts such as reduced CACs and increased stability, the inherent non-uniform nature (polydispersity) associated with them presents a challenge of reproducibility when studied for drug delivery and sensing applications.²⁵ This calls for molecules, which possess salient features such as lower CACs and higher stability, while being structurally uniform (monodisperse).

Dendrimers are particularly interesting among amphiphilic macromolecules, because of their unique branched structures, uniform structure, and ease of functionalization.²⁶ Multivalency is another desired feature of dendrimers, where an increase in generation of dendrimer corresponds to an increase in the number of terminal functional groups, providing a unique opportunity to decorate them with ligands or spectroscopic labels for therapeutic and imaging applications respectively.²⁷ These structural modifications can be performed without compromising their monodisperse nature, hence minimizing the experimental variability when used for biological studies.²⁵

Further, it was recognized that dendrimers assume globular structure at higher generations. Newkome et al.^{28,29} reported amphiphilic dendrimers, where only the peripheral moieties are hydrophilic. Since the peripheral functionalities in a globular macromolecule are primarily in contact with the bulk media, these dendrimers were water-soluble. By rendering the backbone of the dendrimer hydrophobic, it was possible to achieve unimolecular micelles from these dendrimers; similar systems have been reported by other groups (Figure 1a).^{30, 31}

We will begin this perspective by describing, in general terms, the molecular design of amphiphilic dendrimers that form micelle-like nanostructures upon aggregation. Then we will discuss how the introduction of specific functional groups on these dendrimers renders them responsive to stimuli such as temperature,^{32,33} light,³⁴ pH,³⁵ or biological stimuli such as proteins³⁶ and enzymes.³⁷

Molecular design of amphiphilic dendrimers

Micelle-forming amphiphilic dendrimers are composed of two segments: a hydrophilic and a lipophilic (hydrophobic) component. Driven by non-covalent forces such as hydrophobic interactions, van der Waals forces, electrostatic interactions, π - π interactions and hydrogen bonding, these molecules self-assemble above their CAC, when dispersed in aqueous media.^{26,27} The hydrophilic components, such as carboxylates, phosphates and quaternary ammonium groups, render these dendrimers water soluble. However, the non-specific interactions of these charged species with biomolecules often limit their use in biological applications. To address this issue, non-ionic hydrophilic molecules such as poly(ethylene glycol)s (PEG) have been used.³⁸ Hydrophobic components, on the other hand, dictate parameters such as stability, loading capacity, and the release profile of the loaded hydrophobic guest molecules. A variety of functional groups, such as propylene glycol,³⁹ trimethylene carbonate,⁴⁰ ϵ -caprolactone,^{41,42} and long alkyl chains, have been explored as hydrophobic components.

Fréchet and coworkers also reported on amphiphilic dendrimer systems, which form unimolecular micelles in solution.³⁰ The amphiphilic components of these Fréchet-type dendrimers comprise of hydrophilic periphery such as carboxylate or PEG moieties, and a hydrophobic polyether core. Similarly, Newkome et al.,²⁹ and Meijer et al.,³¹ have also reported unimolecular micelles based on poly(amidoamine) (PAMAM) and poly(propylene imine) (PPI) cores respectively.

Our group has reported on a unique class of amphiphilic dendrimers, based on a biaryl AB₂ monomer (Figure 1b).⁴³ The orthogonal placement of hydrophilic and hydrophobic components assisted by an inherent biaryl twist and solvophobic interactions, render these dendrimers facially amphiphilic. In contrast to the well known unimolecular dendrimer micelles, these biaryl dendrimers form micelle-like aggregates from several amphiphilic dendrimers and hence, have an associated CAC.⁴⁴ Above the CAC, the equilibrium between the amphiphilic dendrimers and the micellar aggregates opens up an opportunity to incorporate stimuli-responsive characteristics as shown in Figure 2.

Thermoresponsive dendrimers

Macromolecules that undergo temperature-dependent solubility changes are highly attractive molecular systems for the development of functional thermoresponsive materials. These materials could be utilized for biomedical applications, such as programmed drug delivery, because the temperature at the target site in the body can be affected by “thermotherapy”.⁴⁵ Several polymers that undergo phase transition through temperature change have been developed. Among them poly(*N*-isopropylacrylamide) (poly(NiPAM)) and PEG based systems have been extensively studied.⁴⁶

Kimura et al developed temperature-sensitive dendrimers, by decorating amine end groups of PPI dendrimers with poly(NiPAM) chains (Figure 3a).⁴⁷ These dendrimers are shown to encapsulate catalytic guest molecules, whose catalytic activity is controlled by the change in temperature. Here, it was demonstrated the catalytic oxidation of mercaptoethanol to the corresponding disulfide by metal catalyst (Cobalt(II)Phthalocyanine), in the interior micro-environment of dendrimers. These thermo-sensitive dendritic polymers with narrow transition temperatures could have implications in drug delivery and sensing.^{48–50}

From the preliminary studies on thermosensitive dendritic polymers, it was inferred that temperature sensitivity is influenced by the overall HLB of the system,^{48–50} which leads to a new design and synthesis of thermosensitive dendrimers. Alternatively, temperature sensitive dendrimers were synthesized, by controllably decorating them with hydrophilic small molecules, to introduce varying degrees of amphiphilicity. For example, Kono et al reported the temperature sensitive PAMAM and PPI dendrimers decorated with functional groups such as isobutyramide (IBAM) on their surface (Figure 3b).^{33, 51} The temperature sensitivity of these dendrimers was directly dependent on their generation and change in pH, since these factors affect the HLB of the system. Similarly, dendrimers decorated with various amino acids and peptides were also developed to have sharp phase change or cloud point temperature.⁵²

Dai et al developed a new class of amphiphilic dendrimers consisting of hydrophobic oligo (*p*-phenylene vinylene) core and hydrophilic oligo(ethyleneoxide) terminal groups (Figure 4a).⁵³ These dendrimers formed micellar assemblies and exhibited lower critical solution temperature (LCST) behavior to form assemblies with thermosensitive properties. Thermosensitivity in these dendrimers was found to be dependent on both the generation and nature of terminal groups. Similarly, Li et al reported dendrimers based on three-fold branched oligoethylene glycol dendrons as terminal groups (Figure 4b).⁵⁴

Recently, we developed a new class of amphiphilic dendrimers that can self-assemble to form nanostructures with temperature-sensitive properties (Figure 4c).³² These dendrimers are composed of hydrophilic PEG and hydrophobic decyl chains in every repeat unit. The resultant dendrimers exhibited generation-dependent temperature sensitivity, with higher generations showing lower LCST. Similar studies with corresponding amphiphilic homopolymer did not exhibit LCST behavior; the reason for such a dendritic effect is not clear. Dynamic light scattering (DLS) and dye encapsulation studies confirmed the formation of nanostructures with container properties, while high tension voltage measurements confirmed the LCST behavior of these dendrimers.

Photosensitive dendrimers

Photodynamic therapy (PDT) is a relatively new clinical treatment developed for biomedical applications.⁵⁵ PDT has evolved as a possible site-specific and non-invasive treatment for diseases such as cancer, in recent years. PDT is typically achieved through photochemical generation of reactive single oxygen ($^1\text{O}_2$) species in a specific disease site. Dendrimers have been developed to either covalently incorporate or non-covalently encapsulate photosensitizers for PDT. For example, Kataoka's group has reported dendritic polymers possessing hydrophobic photosensitizer core moieties and hydrophilic PEG groups with efficient photosensitive properties both in vitro and in vivo.^{56, 57} This effect was achieved through the generation of $^1\text{O}_2$ oxygen species by the photosensitive protoporphyrin IX core. Similarly, Battah and co-workers conjugated dendrimers with protoporphyrin IX through ester bonds, and demonstrated the cytotoxicity of these conjugates after photo-induced cleavage of ester bonds and hence releasing the contents.^{58,59} On the other hand, Kojima et al demonstrated the photosensitive properties of PEG-decorated PPI and PAMAM

dendrimers, by non-covalent encapsulation of photosensitizers. Oar et al further improved on this concept by using a two-photon system to excite the photosensitizer.⁶⁰

Photodegradable dendrimers constitute another important class of light-sensitive systems. Shabat et al have developed light-triggered self-immolative dendrimers consisting of a photolabile dendrimer core, self-immolative building blocks, and terminal reporter molecules (aminomethylpyrene).⁶¹ When the core moiety is photo-activated, the dendrimer collapses and releases the reporter molecules (Figure 5a). Similarly, Smith et al reported a new class of degradable dendrimers decorated with cationic spermine groups on their surfaces via photo labile linker (o-nitrobenzyl group) (Figure 5b).⁶² These dendrimers form complexes with DNA using multivalent interactions. Upon UV-irradiation, the surface spermine groups will cleave, switching off the multivalent interactions and leading to DNA release. These studies have implications in developing systems for controlled DNA binding and release. Kim et al developed amide dendrimers with photoresponsive functionalities at the focal point, such as o-nitrobenzyl and diazobenzene groups (Figure 5c).⁶³ These dendrimers are shown to form vesicular assemblies and undergo morphological transformations from vesicles to fibrillar structures upon photo irradiation, which in turn controls the release of encapsulated guest molecules (Nile red).

Our group reported photodegradable amphiphilic dendrimers (Figure 6), composed of hydrophilic PEG groups and hydrophobic alkyl chains with photodegradable linkers.³⁴ These dendrimers encapsulate hydrophobic guest molecules like Nile red, as confirmed by UV-Vis and fluorescence studies. Irradiation of these dendrimers triggers the release of the encapsulated dye molecules (Figure 7). This is because the photo-assisted cleavage of the nitrobenzyl ether causes the hydrophobic alkyl chain to be removed from the dendrimers causing a significant loss of hydrophobicity. Moreover, the carboxylate by-product of the reaction makes the originally hydrophobic part of the dendrimer hydrophilic, hence, causing the dendrimer aggregates to lose their container property resulting in guest molecule release.

Change in pH

It is well known that the micro-environments of tumors, as well as the lysosomal and endosomal components of the cell, are acidic in nature. Therefore, delivery vehicles that could respond to variations in pH are highly desired. Dendrimers have been designed with a variety of functional groups, where a pH- dependent release was accomplished by disrupting the amphiphilicity of the system.⁶⁴ This change in amphiphilicity could either be obtained by cleavage of key covalent bonds or by altering the charge on the dendrimer. Haag et al have reported a hyperbranched polymer system based on polyglycerol (PG) and polyethyleneimine (PEI) units; acid-sensitive linkers like acetals/ketals and imines (Figure 8a) were incorporated onto these polymers respectively. These hyperbranched polymers encapsulated polar guest molecules and released them at mildly acidic pH due to the cleavage of acetal or imine functionalities (pH 5–7).^{65, 66}

Paleos and coworkers reported on PPI based dendrimers (DAB-32, DAB-64) functionalized with quaternary ammonium groups, incorporating pyrene as a guest molecule (Figure 8b).⁶⁷ When these dendrimers were subjected to acidic pH, the resultant protonation of internal secondary and tertiary amines, rendered the dendrimer more hydrophilic. This change in amphiphilicity of dendrimers resulted in the release of the encapsulated pyrene.⁶⁸ Similarly, carboxylic acid functionalities were incorporated onto the dendrimers to introduce pH sensitive behavior.^{69, 70}

Hydrazide functional groups were also used as pH sensitive components. For example, Kono et al have reported on PAMAM dendrimers conjugated with PEG groups through a glutamic acid residue. The free acid functionality on glutamic acid was attached to

Adriamycin through a hydrazide linker. (Figure 9).⁷¹ These drug-conjugated dendrimers were stable under physiological conditions, only releasing Adriamycin in acidic environments (pH 5.5). Similar work has also been reported with *cis*-aconityl group as a pH-sensitive linkage.⁷² pH-responsive amphiphilic dendrimers were also used for cell transfection applications. For example, Diederich et al reported on cationic amphiphilic dendrimers, based on diphenylacetylene (tolane) core for cell transfection applications. These dendrimers self-assemble to form complexes with DNA showing optimum transfection activity at rather low molecular weights ($M_w = 1500$ – 2700) compared to classical dendrimers ($M_w = 116000$). Transfection activity of these complexes was presumably due to a “proton sponge” effect.^{73,74}

Protein sensitive amphiphilic dendrimers

In addition to the various stimuli- responsive systems presented earlier, it would be interesting to have dendrimers, which could respond to stimuli that are pathologically relevant. Diseases are often due to imbalances in protein concentrations or enzymatic activities at the diseased site.^{75–77} Therefore, having delivery vehicles that could specifically respond to such stimuli would be advantageous. Recently, there have been interesting reports on enzyme-sensitive systems based on non-covalent supramolecular assemblies. Here, modification of the enzyme sensitive component will change the associated supramolecular interactions, resulting in a suitable response.^{78–82} Several works have been reported based on liposomes and polymeric assemblies,^{83,84} but the use of dendrimers is relatively limited. Recently, Shabat and coworkers have reported a unique enzyme sensitive system based on a dendrimer architecture named “cascade release dendrimers”.⁸⁵ These dendrimers, upon a single activation, for example by the enzyme Penicillin-G-amidase, undergo sequential 1,6-quinone methide rearrangement and decarboxylation reactions to release multiple drug molecules into the solution (Figure 10).

In this section, however, we emphasize on protein responsive amphiphilic assemblies, where the guest molecule release is induced either by covalent or non-covalent modifications to the amphiphiles. In both these scenarios, the guest release is actuated by the change in the HLB imparted by their specific interactions with enzymes or proteins.

Change in HLB based on covalent modification by enzymes

One way of affecting the HLB of an amphiphilic system is to increase the hydrophilicity through cleavage of the hydrophobic segment. This can be achieved with an enzyme through appropriate placement of an enzymatic substrate on the hydrophobic segment. For example, Zhang et al have reported on a phosphatase-responsive system using a super-amphiphile concept.⁷⁹ In this case, when a double hydrophilic block copolymer methoxy-poly(ethyleneglycol)₁₁₄-*block*-poly(L-lysine hydrochloride)₂₀₀ was mixed with the hydrophobic ATP, a so-called superamphiphile is formed. These superamphiphiles self-assemble and non-covalently encapsulate hydrophobic guest molecules. When an enzyme, Calf intestinal alkaline phosphatase, selective to the substrate ATP was added to the superamphiphile solution, disassembly followed by guest molecule release was observed. Recently, we have reported the concept of enzyme-triggered disassembly based on our amphiphilic dendrimer system.³⁷ The molecular design of this enzyme-sensitive dendrimer is shown in Figure 11. Here the substrate is placed as a linker between the hydrophobic component and the dendrimer core. Cleavage of this linker prompts a significant loss of hydrophobic tail from the dendrimer backbone and also, introduces hydrophilic carboxylic acid functionality to that end, resulting in disassembly of the aggregates. When G1 dendrimer and G1 control solutions (Figure 11) were subjected to the enzyme Porcine liver esterase, a systematic decrease in size of the assemblies with time was observed only for G1 dendrimer, suggesting an enzyme-specific disassembly. It was also observed that the rate of

guest release decreases with increase in dendrimer generation. Although, there was a generation-dependent guest molecule release, the control exercised through such variation is rather limited. Accordingly, our group has recently explored an enzyme sensitive dendrimer design where such control is imparted through photochemical crosslinking reactions. Here, we have also found that monomer-aggregate equilibrium plays an important role on the enzymatic cleavage and the ensued guest molecule release.⁸⁶ Currently studies are underway in our laboratory to discern alternate pathways, if any, involved to affect the non-covalent guest molecule release from these nanocontainers.

Change in HLB based on non-covalent binding interactions

While enzymatic reaction-based cleavage is feasible with the strategies mentioned above, there exists an even larger family of proteins that are pathologically relevant. This involves non-enzymatic proteins, which do not have catalytic cleavage reaction, but can bind to complementary ligands. Non-covalent binding interactions of specific ligands with proteins are abundant in nature. Such interactions are often utilized to bring about associated physiological responses. These binding interactions have been exploited in the field of imaging and sensing where fluorophores are conjugated with protein specific ligands in small amphiphiles. For example, we have reported on a binding induced disassembly of a polymer-surfactant complex in response to a protein binding event.^{87,88} Similarly, Hamachi and coworkers have reported self-assembling surfactant systems, where binding of a ligand with the protein was monitored through a change in the emission characteristics of the fluorophore or ¹⁹F-MRI/NMR signal.^{89,90} Our group has recently reported on binding induced disassembly based on amphiphilic dendrimer systems, where a ligand **R** (covalently tethered onto the hydrophilic face of the dendrimer) binds to a specific protein (Figure 12).³⁶ Since the water-soluble globular protein (receptor for ligand **R**) contains a hydrophilic surface, the amphiphilicity of the resultant dendrimer-protein complex is significantly different compared to the dendrimer itself. This change in HLB causes the micelles to disassemble and release the encapsulated guest molecules. These dendrimers were synthesized with decyl groups as lipophilic components, and PEG units as hydrophilic components. Biotin, which is known for its strong binding affinity with Avidin, was attached to the dendrimer through “click” chemistry. These dendrimers self-assemble in aqueous solution and encapsulate hydrophobic guest molecules (pyrene). Upon subjecting these dendrimeric solutions to Avidin, a decrease in emission intensity of pyrene was observed suggesting its release from micellar interiors. Monitoring the size of the assembly with DLS further confirmed that these micelle type aggregates disassemble upon interaction with Avidin. Selectivity studies with other non-specific proteins neither led to disassembly nor guest molecule release. Note that in this molecular design the ligand functionality is placed on the hydrophilic component of the dendrimer, hence disassembly can occur through the direct binding of the ligand on the surface of the aggregate. However, when the ligands are hydrophobic, the ligand moieties would be buried within the assembly interior. In this system, a pathway still exists, where the possible equilibrium between the monomeric state of the dendrimer and micelle-type aggregate provides access to the ligands for binding in the monomeric state. Studies with ligand on the hydrophobic side of the dendrimer also resulted in protein-induced disassembly, highlighting the role that the dendrimer-aggregate equilibrium can play in the disassembly process.⁹¹

Summary and Perspective

In the last quarter of the century, the dendrimer field has grown into an active research area, which could be attributed to their unique properties such as uniform structure, easily functionalizable peripheral groups, and opportunity to carry out molecular-level structure-property relationship studies for macromolecules. When amphiphilicity is incorporated into

dendrimers, they self-assemble to form supramolecular aggregates like micelles and vesicles. Significant work has been done, where stimuli-responsive characteristics were introduced into these amphiphilic dendrimers for various applications, especially drug delivery and sensing. Temperature and pH-responsive systems have been relatively extensively studied. However, stimuli-sensitive systems responsive to the primary biological imbalances, such as protein overexpression and enzymatic hyperactivity, remain relatively underexplored - hence providing a new avenue for research. In our group we have developed a new class of amphiphilic dendrimers that are responsive to both enzymatic and non-enzymatic proteins. These dendrimers serve as model systems for a novel category of stimuli-sensitive drug delivery vehicles. Development of reproducible methods for large scale syntheses of highly versatile dendrimers, without compromising their fidelity for a targeted application, is a remaining challenge for the field to make a large scale impact in downstream biological applications.

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Figure 1.

a) Fréchet type unimolecular dendrimer micelle; b) Biaryl dendrimers with AB₂-type building block forming self-assembled aggregates

Figure 2.
Triggered disassembly through various stimuli based on monomer-aggregate equilibrium

Figure 3.

a) PPI dendrimer decorated with temperature sensitive poly(NiPAM) groups; b) Schematic representation of PAMAM G4 dendrimer decorated with temperature sensitive small molecule, IBAM

Figure 4.
Different types of temperature-sensitive amphiphilic dendrimers with a) Phenylene vinylene core; b) 1,1,1-tris(4-hydroxyphenyl)ethane core; c) Biaryl core.

Figure 5.

a) Schematic representation of triggered release in self-immolative dendrimers; b) Structure of photolabile spermine dendrimer; c) Structure of photosensitive amide dendrimer

Figure 6.
Structures of photo-cleavable G1 and G2 dendrons

Figure 7.
Cartoon representation of light-induced disassembly of dendrimer micellar assemblies

Figure 8.

a) Amphiphilic core-shell architectures (PG and PEI) functionalized with acetal/ketal or imines; b) Functionalization of polypropylenimine dendrimers (DAB- 32 and 64) with quaternary ammonium salts

Figure 9. Synthetic route for PEG-Glu(ADR) and PEG-Glu(NHN-ADR) dendrimers. ADR = Adriamycin

Figure 10.
Second-generation cascade release dendrimer, before and after undergoing enzymatic reaction

Figure 11.
Structures of enzyme sensitive biaryl dendrimers

Figure 12.
Structures of protein responsive dendrimers