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Role of Dendrimers in Molecular Recognition-A Review

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Abstract

Molecular recognition refers to the interaction between molecules through without covalent bonding like hydrogen bonding, Vander Wall forces, halogen bonding, metal coordination, hydrophobic forces and, π-π interactions. Dendrimers are hyperbranched molecules which are a relatively novel class of materials with unique molecular structure and dimensions in comparison to conventional linear polymers. This review details recent notable advances in the molecular recognition in both the organic as well as inorganic components which are highly sensitive to the dendrimers. Molecular recognition has an important role in the living system such as between receptor and ligand, antigen and antibody, DNA and protein, sugar and lectin, RNA and ribosome etc. A micellar aggregate is a dynamic entity which is characterized by two distinctive layers, an inner hydrophobic core that is unsuited with the aqueous solvent, and an external hydrophilic shell. In contrast, PAMAM dendrimers are unimolecular entities, where the inner core is hydrophilic and comparatively available to the aqueous solvent.

Keywords: Molecular recognition, Dendrimers, PAMAM Dendrimers, Hydrogen bonding etc.

Contents

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1. Introduction

The term molecular recognition refers to the specific interaction between two or more molecules through noncovalent bonding such as hydrogen bonding, metal coordination, hydrophobic forces, Vander Waals forces, π-π interactions, halogen bonding, electrostatic and/or electromagnetic [1]effects. The host and guest involved in molecular recognition exhibit molecular complementarity. [2,3] Molecular recognition plays an important role in biological systems and is observed in between receptor-ligand, antigen-antibody, DNA-protein, sugar-lectin, RNA-ribosome, etc. An important example of molecular recognition is the antibiotic vancomycin that selectively binds with the peptides with terminal D-alanyl-D-alanine in bacterial cells through five hydrogen bonds. The vancomycin is lethal to the bacteria since once it has bound to these particular peptides they are unable to be used to construct the bacteria's cell wall. Molecular recognition can be subdivided into *static molecular recognition* and *dynamic molecular recognition*. Static molecular recognition is likened to the interaction between a key and a keyhole; it is a 1:1 type complexation reaction between a host molecule and a guest molecule to form a host-guest complex. To achieve advanced static molecular recognition, it is necessary to make recognition sites that are specific for guest molecules.

In the case of dynamic molecular recognition the binding of the first guest to the first binding site of a host affects the association constant of a second guest with a second binding site.[4] In the case of positive allosteric systems the binding of the first guest increases the association constant of the second guest. While for negative allosteric systems the binding of the first guest decreases the association constant with the second. The dynamic nature of this type of molecular recognition is particularly important since it provides a mechanism to regulate binding in biological systems. Dynamic molecular recognition may enhance the ability to discriminate between several competing targets via the conformational proofreading mechanism. Dynamic molecular recognition is also being studied for application in highly functional chemical sensors and molecular devices. A recent study based on molecular simulations and compliance constants describes molecular recognition as a phenomenon of organisation. Even for small molecules like carbohydrates, the recognition process can not be predicted or designed even assuming that each individual hydrogen bond's strength is exactly known.[5]

1. Molecular Recognition in Organic Molecules

Newkome et al. investigated the micellar properties of hydrocarbon surge molecules terminated with carboxylic functionalies (Fig.1)[6]. The carboxylic acid groups were rehabilitated into the corresponding tetramethyl ammonium salts, and the physical behaviour of the dendritic _particles_ was investigated by electron microscopy (EM). The studies exposed uniform particles (30AA±5 AA) without any evidence of macromolecular aggregation. Further experiments passed out in the presence of molecular probes such as diphenylhexatriene, chlortetracycline, phenol blue, pinacyanol chloride (PC) and naphthalene added evidence of molecular inclusion of the guest molecules within the lipophilic interior of the dendrimers, and in particular, when PC was used as a guest molecule, a 1:1 complex was evident. Soon after this initial study, Tomalia et al., having established that the occupation of the microspace inside the dendrimer was the direct function of dendrimer size, shape, and functionality, carried out a similar investigation upon a series of PAMAM dendrimers[7].

Molecular modelling and hydrodynamic diameter measurements on carboxylic acid or amine terminated PAMAM demonstrated that the dendritic structures mimic the topology and the aggregation pattern of multimolecular micellar assemblies. In particular, the carboxylic acid salts of the half-generation PAMAM dendrimers revealed a close correlation to the anionic micelle systems formed by anionic surfactants. In a similar study to that described by Newkome and coworkers, the two dendrimer species were observed directly using EM techniques [8]. Although the superficial similarities of dendrimers and micelles, they differ in many aspects. A micellar aggregate is a dynamic entity where the monomeric surfactant chains assemble together and are in swift substitute with the surrounding environment. They are characterized by two distinctive layers, an inner hydrophobic core that is unsuited with the aqueous solvent, and an external hydrophilic shell. In contrast, PAMAM dendrimers are unimolecular entities, where the inner core is hydrophilic and relatively accessible to the aqueous solvent [9]. The structural similarities in solution have, however, triggered further investigations of the overall shape adopted by dendrimers and their ability to host, assemble and modify the chemical reactivity of small guest molecules. Initial molecular mechanics simulations were approved on b-alanine based dendrimers using the AMBER force field with the POLYGRAF simulation program [10].

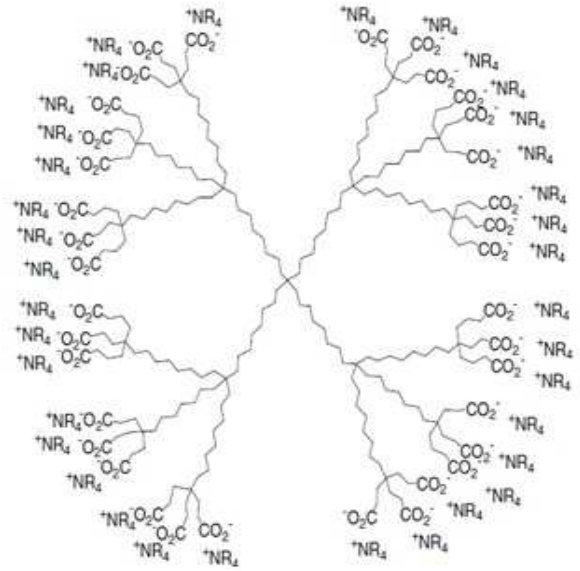


Fig 1. **The micellar analogue cascade dendrimer developed by Newkome et al. [6**].

These studies exposed a transition in the molecular shape at generation four with lower generations presenting very open conformations. Higher generations exhibited more compactly packed near spherical topologies, with hollows connected by channels running through the three-dimensional structure. The presence of void volumes _isolated_ from the external environment also recommended the possibility of guest molecule encapsulation. NMR spectroscopic studies of guest molecules, such as 2,4-dichlorophenoxyacetic acid and acetylsalicylic acid, in solutions with carboxymethyl-terminated b-alanine dendrimers confirmed the ability of the dendrimer to encapsulate guest molecules when a shape transition has the internal structure of PAMAM dendrimers resembles strongly proteins and enzymes, an understanding of their ability to form ion complexes might prove to be of great biological relevance. In the light of the chemical and architectural resemblance of anionic surfactant micelles to high generation anionic PAMAM dendrimers, the physical and chemical behaviour of the surfaces were investigated. A cooperative association of the surface groups on dendrimers above generation 3.5 was evident from these preliminary studies, carried out by probing the surface of the dendrimers with photophysical and photochemical techniques [11]. Such behaviour is consistent with surfactant solutions above their critical micelle concentration (CMC). Further photophysical investigations involved the use of the electron transfer quenching of photoexcited Ru (bpy) 2þ 3 by methyl viologen and indicated similar behaviour of dendrimers and micelles. It was demonstrated that in the presence of early generation dendrimers as well as small micelles, the quenching of the fluorescent probe occurred in the proximity of the dendritic/micelle surface, as the probe is free to move from the surface to the outside and vice versa, thus indicating a very _loose_, open structure. In contrast, in then presence of high generation dendrimers as well as micelles above the CMC value, the quenching occurred in an intramolecular fashion as the diffusion of the probes outside the systems was much slower. These results indicate that the positively charged probe molecules were present within both the high generation dendrimers and large micelles, decreasing the ability of the probes to diffuse towards the external environment. In reality, although these studies provide an important comparison of the anionic dendrimers and micelles and the different conformations adopted by different generation dendrimers, an accurate description of the ability of the dendrimers to interact specifically with molecules and ions was not determined**.** Ottaviani et al. investigated the complex equilibria of Cu (II) species with PAMAM dendrimers in solution using electron paramagnetic resonance (EPR) [12] at high and low temperature. The recorded spectra at low-temperature showed, two different signals were visible and attributed to the presence of two different Cu(II) complexes, in which the Cu species were synchronized to two oxygen atoms from carboxylate groups and two nitrogen atoms from the dendritic core; the second complex was formed by synchronization of Cu(II) by three or four nitrogen ligands from the core of the dendritic structure. A third complex was only observed at low pH in which the Cu(II) species was bound to two oxygen atoms of the carboxylate groups at the external crossing point of the dendrimer (see in Fig. 2).

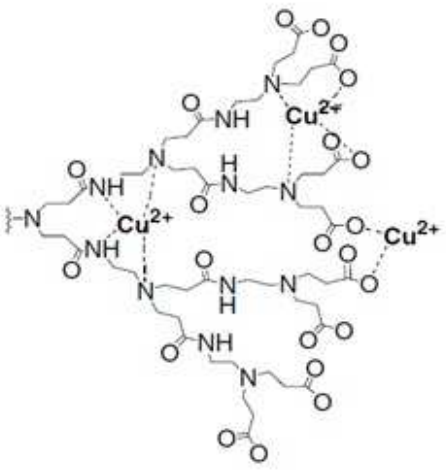


Fig. 2. **Representation of the Cu (II)–PAMAM complex determined by EPR spectroscopic studies [12]**

Ottaviani et al also studied and conducted the structural properties of PAMAM dendrimers and their interaction with radical sources. [13]. The ability of the carboxylate groups to interact with positively charged nitroxide probes at different protonation states and charge density was studied. Other aspects of the investigation incorporated the formation of both hydrophilic and hydrophobic interactions with nitroxide radicals of different chain lengths and the effect of temperature variation on the interactions of the nitroxides with the surface binding sites. Using EPR, it was possible to determine that the nitroxide radicals were localized at the dendrimer/water interface, where both electrostatic and hydrophilic interactions could occur. Entrapment of the radicals on the dendritic surface was observed as the generation number of the dendrimer and the chain length were increased. Hydrophobic interactions also occurred between radicals with long chains and hydrophobic sites within the dendrimers and were attributed to

partial penetration of the probe into the dendritic interior predominantly driven by electrostatic interactions between the positively charged probes and carboxylic functionality. Following the accurate characterization of the shape and the micelle like behaviour of PAMAM dendrimers (vide supra), several studies have investigated the possibility of using dendrimers for the encapsulation of guest molecules. PAMAM dendrimers have been shown to transport CuSO4 from water into toluene, by encapsulating the copper ions into the hydrophilic dendritic structure [14]. The ability of dendrimers with piperazine sub-units to form coloured complexes with Cu(II) and Pd(II) was reported by Newkome et al.[15]. In order to compress the dendritic gallows around the metal centre the piperazine ring had to adopt a boat conformation thus maximising the interaction **(see in Fig. 3).** NMR spectroscopic relaxation measurements have been used to estimate the diffusion of aspirin into the core of PAMAM dendrimers [10] and the guest molecule was found to be free to diffuse in and out of the dendritic structures. The _host_ ability of dendritic macromolecules has also found interesting application in extraction methodologies, for example, the use of _inverted unimolecular dendritic micelles_ for the extraction of a series of anionic xanthene dye molecules from water was investigated by Meijer and coworkers [16]. The dendrimers were based on the polar poly (propylene imine) dendrimer customized at the surface with palmitoyl chloride. Once protonated, the internal tertiary amine groups of the dendrimer were expected to form ionic complexes with the negatively charged dye molecules, occurred [10].

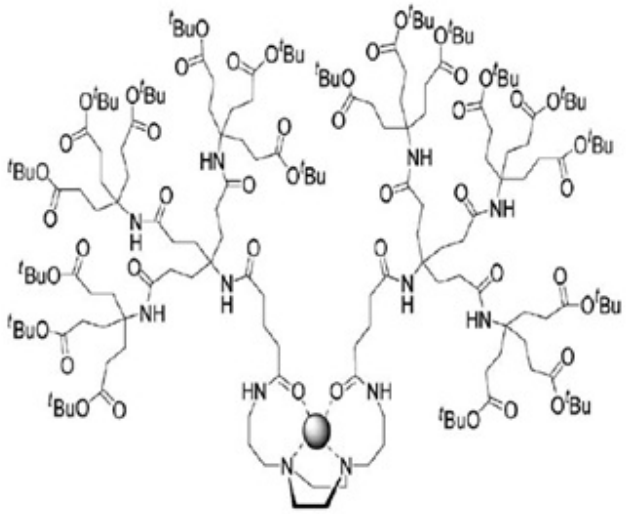
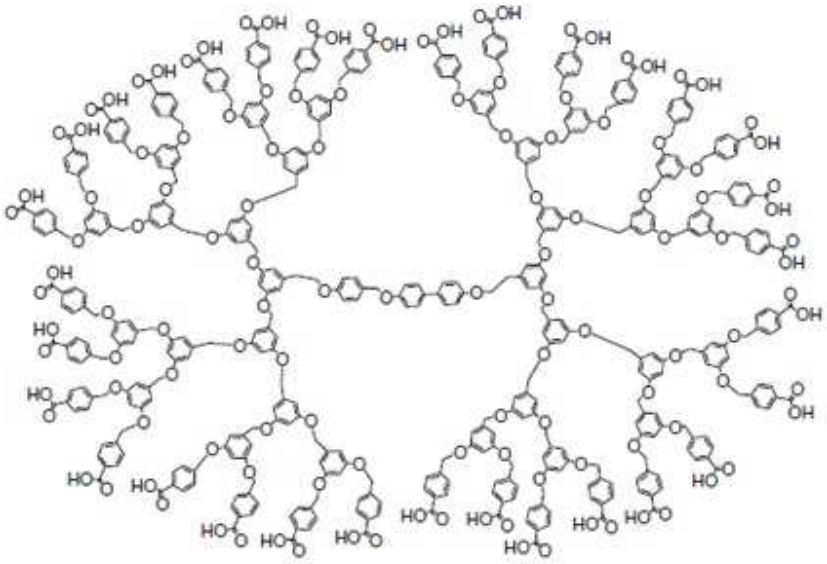


Fig. 3. Representation of the metal binding with a dendrimer containing a piperazine core [15].

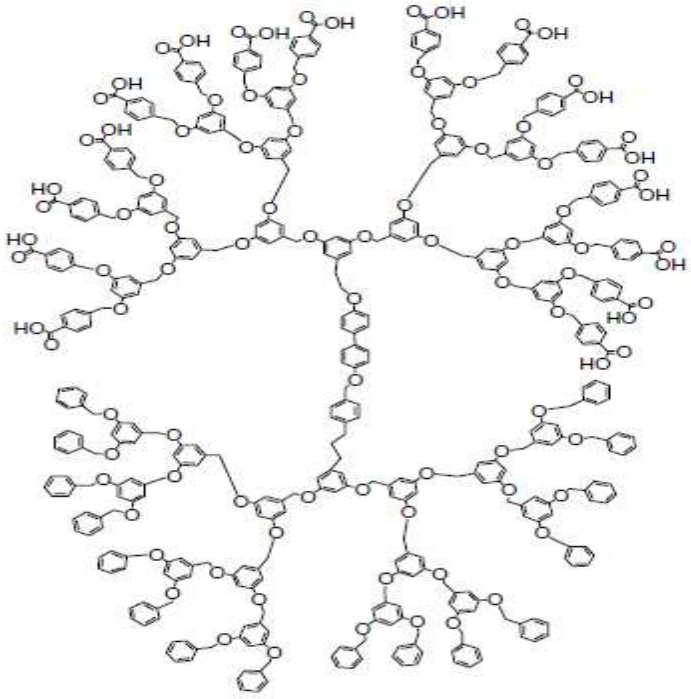
Therefore promoting extraction from the aqueous phase. The dendritic extraction ability was found to be a function of the pH, as all the dyes were extracted successfully at low pH, whereas at high pH only Rose Bengal was successful. It was concluded that in all cases, the interactions between solute and dendrimer were determined by their acid-base properties, although the high hydrophobicity of Rose Bengal was responsible for the pH independent extraction yield. A remarkable example of the use of dendrimers in the extraction of hydrophilic compounds from water into supercritical carbon dioxide (scCO2) presented by Cooper et al.[17]. CO2 has become a popular solvent system as it represents a cost effective, environmentally friendly media that reduces the use of expensive organic solvents that are used each year in synthetic, extraction and cleaning procedures. Unfortunately, a large number of polymers have shown rather limited solubility in scCO2 and there has been a considerable effort in the development of fluorinated surface active agents which may be able to stabilize the dispersions in supercritical fluids. The solubilising properties of poly (propylene imine) dendrimers with a hexafluoropropylene oxide surface modification were investigated using ultraviolet–visible (UV–vis) spectrophotometric analysis. In the absence of agitation, the polar dye molecules were transferred rapidly from the aqueous layer into scCO2 as indicated visibly by a colour loss of the water phase and an increase in colour of the scCO2. During depressurisation, the dye loaded dendrimers were deposited as a yellow film. Studies of the progressive increase of the UV absorption of the dye in the scCO2 phase at different dye/ dendrimer ratios suggest that only one dye molecule could be extracted per dendrimer.

Hawker et al. have synthesized a novel class of carboxylate terminated polyether dendrimers with micelle like behaviour as recyclable systems to solubilise and extract hydrophobic molecules and have exploited the synthesis of hybrid macromolecules comprising hydrophobic and hydrophilic moieties (see (1) and (2) in Fig. 4)[18]. The solubilising ability of the hybrids was assessed using UV–vis spectrophotometry and showed a remarkable increase in the concentration of the model compound (pyrene) in the aqueous phase compared to a saturated aqueous solution or in the presence of a surface active agent. A further increase in concentration was also observed when sodium chloride was dissolved in the water, attributed to a decrease in the water content within the dendritic structure caused

by the higher ionic strength of the medium, thereby favouring the interaction between the dendrimer and the apolar guest molecule. Precipitation of the pyrene containing dendrimer in acidic media followed by re-dissolving the complex in organic solvent and final extraction of the dendritic macromolecule with aqueous base afforded a pyrene solution and the intact dendritic scaffold ready to be used in a new extraction cycle. Meijer and coworkers were the first to entrap guest molecules physically in a dendritic molecule, coined the dendritic box [19, 20].



(1) Polyether unimolecular micelle



(2) Hibrid dendrimer

Fig. 4. Frechet-type unimolecular dendritic micelles [18]

In this dendritic system, guest molecules such as Rose Bengal and p-nitrobenzoic acid were entrapped and then released into the desired environment by chemical modification of the dendrimer surface. The dendritic box was formed by a flexible poly(propylene imine) dendrimer and an outer rigid shell of FMOC-protected amino acids. Detailed spectroscopic studies exposed that an average of four Rose Bengal molecules were entrapped within the cavities of each dendrimer (after construction of the rigid shell after diffusion of the aromatic guests into the structure).

In the case of entrapped poly(propylene imine) dendrimer/ p-nitrobenzoic acid complexes, subsequent removal of the protecting groups from the surface amino acid moieties triggered the release of the small molecules of p-nitrobenzoic acid. In contrast, the bigger Rose Bengal guest molecules could not be liberated in this manner and further degradation of the outer shell (with hydrochloric acid 12 N) was required to the release the dye. Molecular dynamic simulations also predicted the entrapment of guest molecules and the maximum number of guest that the dendrimer could host with very high efficiency, demonstrating that this type of computational calculations could be used to design and optimise encapsulation devices [21]. The Meijer research group have studied the host:guest properties of a series of poly(propylene imine) dendrimers modified with 3,4,5-tris(tetraethyleneoxy) benzoyl units **(see in Fig. 5)** in aqueous media using two water-soluble guest molecules: 4,5,6,7-tetrachlorofluorescein and Rose Bengal [22]. The results obtained indicated a stronger binding affinity of the dendrimer towards Rose Bengal, and also the presence of dye–dye interactions. The association between host and guest was attributed to strong electrostatic interactions, although in the case of Rose Bengal, the strong complexation may arise as a consequence of the hydrophobicity of the dye.

Pistolis et al investigated about the PPI dendrimers as pH-sensitive controlled-release systems [23]. Changing of pH in the dendrimer microenvironment varied through protonation of the tertiary amines of the dendritic scaffold, therefore triggering either encapsulation or release of the guest molecules. In particular, pyrene incorporation was observed at basic pH, when the hydrophobic dendritic microenvironment was suitable to host the guest molecules. In contrast, at acidic pH values the inner dendritic core was protonated and the increased polarity ejected the pyrene into the surrounding aqueous phase. A dendritic host–guest system, in which the recognition of guest molecules occurred at a specific binding unit within the dendritic structure was developed by Diederich and coworkers [24,25]. The device contains a cyclophane group linked to four water-soluble arborol-type dendrons (**see in Fig. 6**) for the selective complexation of steroids [26] or flat arenes [27].

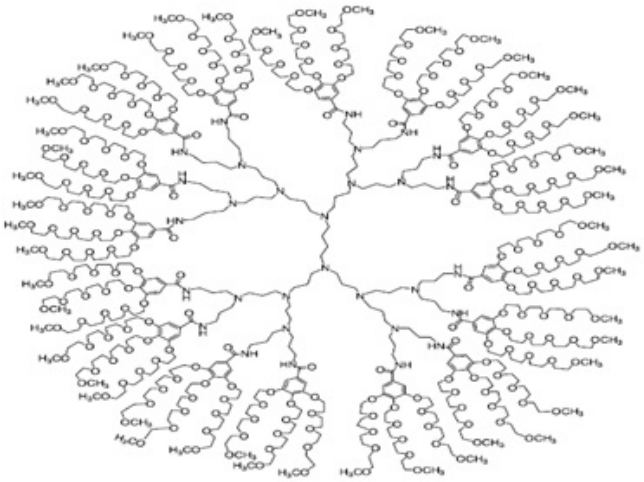


Fig. 5. OligoPEG-functionalised poly (propylene imine) dendrimer [22]

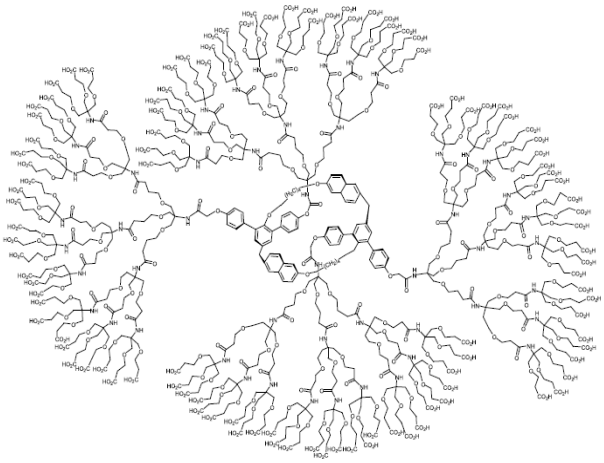


Fig. 6. **The dendrophane receptor reported by Diederich and coworkers [26, 27]**

Using spectrofluorimetric or 1H NMR spectroscopic titrations with different substrates, the complexation of the guest molecule was found to occur essentially inside the cyclophane moiety, mimicking the apolar binding sites buried in proteins. The host–guest association constants (Ka) obtained by fluorescence titrations were in good agreement with those obtained by 1H NMR spectroscopic studies. Furthermore, the host-guest exchange kinetics observed for all dendrophanes were incredibly fast (Kdecompl > 102–103 s_1) and the cyclophane recognition sites proved to remain accessible and effective at all dendritic generations studied. Zimmerman et al. [28] demonstrated the formation of host/guest complexes between two classes of dendrimers 25, 26 and amidinium guests 27, 28, based upon specific hydrogen bonding with the dendritic core **(Fig. 7**). Complex formation was studied by 1H NMR spectroscopy, which revealed the formation of highly stable complexes independent of the dendrimer size and nature. The use of dendrimers as multi-site guests for chemical interaction and chemical amplification was investigated by Kaifer and coworkers [29]. Dendritic macromolecules were synthesized bearing ferrocene moieties at the peripheral surface for the inclusion within b-cyclodextrins, to facilitate the formation of large supramolecular complexes **(see in Fig. 8**). The presence of these complexes resulted in an increase in aqueous solubility over the _bare_ dendrimer. Ferrocene-modified dendrimers was synthesized and designed by Astruc and coworkers **(see in Fig. 9)** as supramolecular redox sensors for the recognition of small inorganic anions such as H2PO4, HSO4, Cl , Br, and NO_3 [30]. The complexation of ferrocene dendrimers with the different anions was monitored 1H NMR spectroscopy and by cyclic voltammetry. In the presence of H2PO_4 , a new reversible wave was observed at less positive potential than that of the Fe(II)/Fe(III) couple, with the progressive disappearance of the original wave. This observation was rationalized as a consequence of the electrostatic interactions between the ferricinium moieties and the anions. In the presence of HSO4, Cl, and NO3, this new electrochemical cycle was not observed but a progressive cathodic shift of the original wave arose. All the waves were electrochemically reversible, indicating that the binding process was fast and reversible on the electrochemical time scale. Cyclic voltammetry and NMR spectroscopic analyses of the dendritic complexes also revealed that complex formation was attributable to a synergic combination of electrostatic interactions (involving the ferricinium cation and the anion) and hydrogen-bonding interactions between the amide functionalities of the dendritic moiety and the anion.

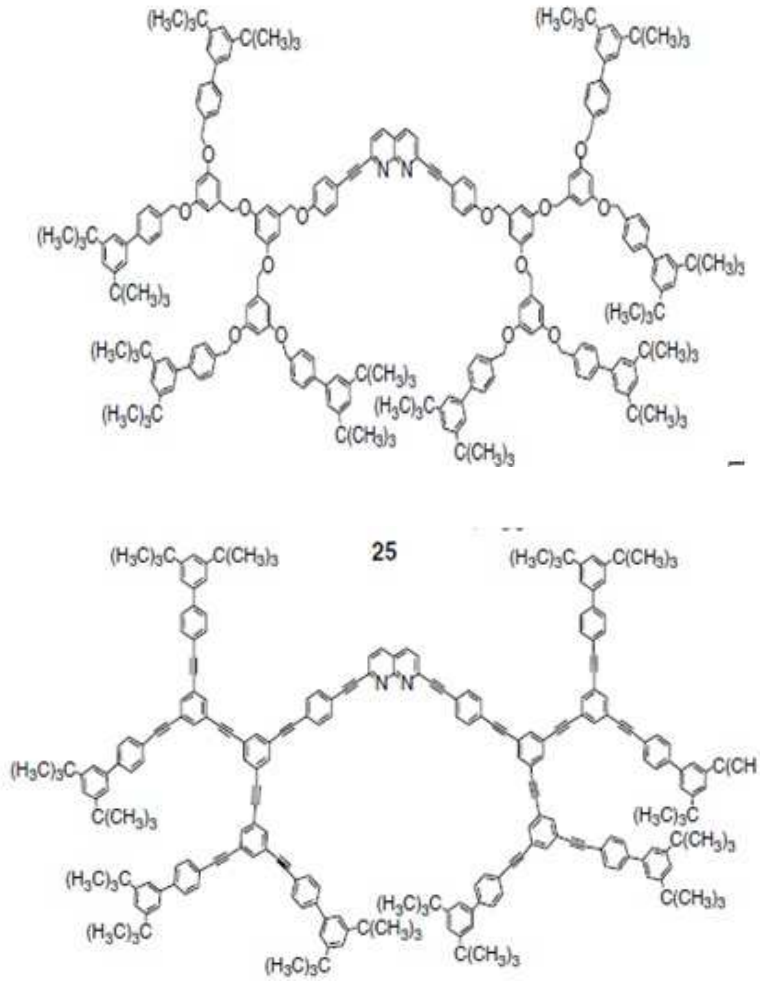


Fig. 7. Dendritic hosts with benzamidinium guests molecules developed by Zimmerman et al. [28]

The highest overall binding affinity was observed in the case of the second generation dendrimer - steric surface saturation was observed in the case of the third generation dendrimer, thereby limiting the penetration of the anion through the ferrocene surface. Ferrocene end-capped carbosiloxane dendrimers were synthesized by Kim et al. as CO gas sensing devices [31]. The system was deposited on a silicon wafer by spin coating and the gas sensing abilities were evaluated by electrical measurements where detection of CO was due to coordination with the ferrocene leading to increased electron mobility. Multivalent receptors have been developed on the outer shell of poly(propylene imine) dendrimers. In this initial study, urea–glycine guests interacted with the urea and thiourea-modified dendrimer via urea–urea and thiourea–urea hydrogen bonding and by the electrostatic interaction between carboxyl functionalities on the guest and the tertiary amine groups on the host molecule as determined by 1D- and NOESY NMR spectroscopic experiments [32]. Based upon the same principle, the use of the same urea/thiourea-modified dendrimers as multivalent carriers of seven different tripeptides was also investigated (Scheme 1) [33]. N-terminal tert-butoxycarbonyl protected tripeptides were chosen as substrates in order to avoid aggregation of the peptides in apolar solvents and the nature of the interactions between host and guest were investigated by infrared spectroscopy. The complexation appeared to originate from the expected hydrogen bonding interactions although the steric repulsion between the dendrimer and the peptide side chain seemed to disfavour hydrogen bonding and limit the interaction. Spin–lattice relaxation (T1) and spin– spin relaxation (T2) measurements were carried out to investigate the variation in mobility of the peptide in the complex. The general trend was a decrease in mobility upon complexation compared to the unbound state Higashi et al. have synthesised a novel water-soluble PAMAM dendrimer surface functionalized with ahelices of poly(L-glutamic acid) as a receptor for the enantioselective encapsulation of a-amino acids [34].

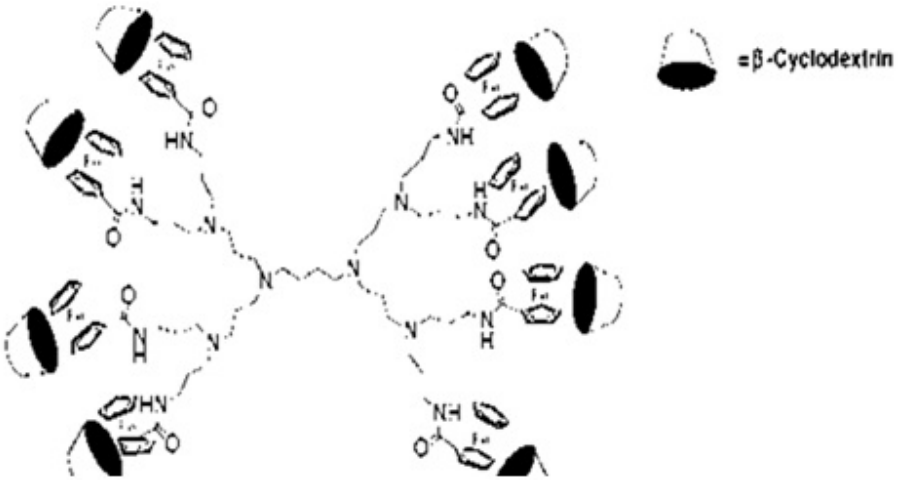


Figure 8. b-Cyclodextrin–ferrocene dendrimer complex [29]

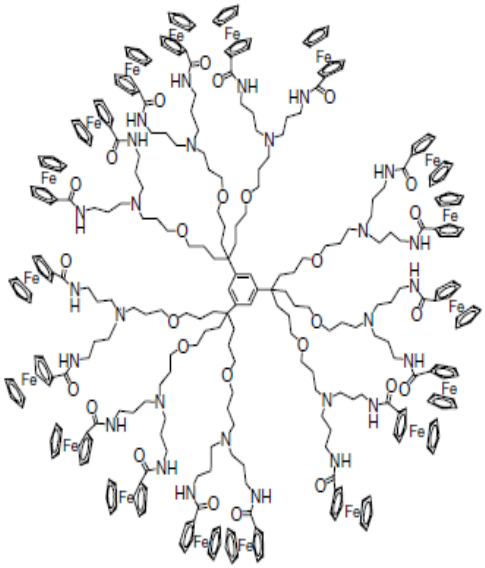
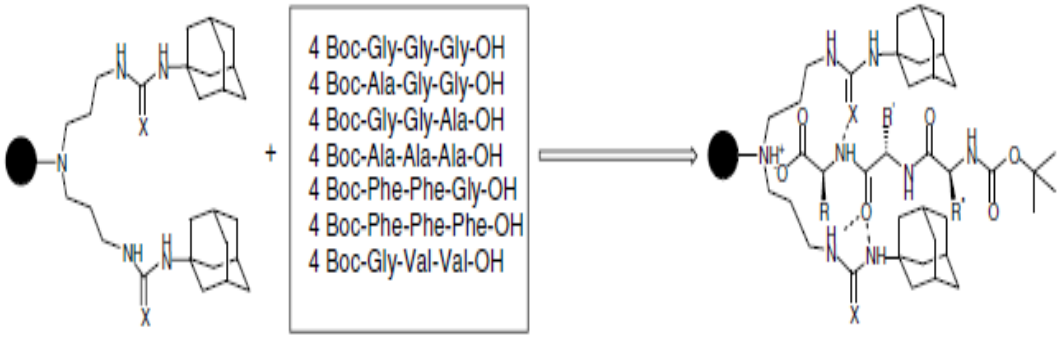
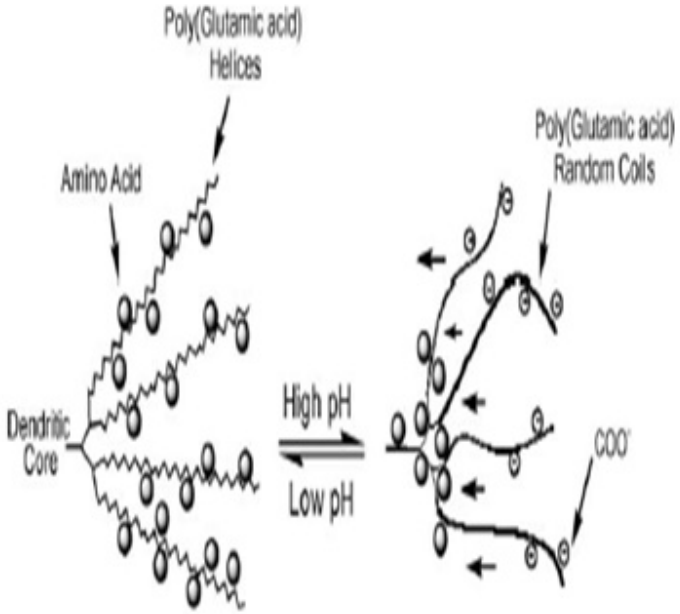


Figure9. A ferrocene dendrimer as a redox sensor for small anions [30]



Scheme 1. Formation of multiple peptide–dendrimer complexes [33]



Scheme 2. **Schematic representation of a peptide shell PAMAM dendrimer interacting with D-amino acids at varying pH [34]**

Conformational analysis of the dendrimer in aqueous solution using circular dichroism showed that the peptide shell adopted a right handed helix at pH¼3.9, which changed progressively to random coil structures when the pH was increased to 8.9. Furthermore, the helical conformation was stabilized by the chain inter-actions induced by the attachment of the peptide chains onto the dendritic branches. The binding study was repeated on different D- and L-amino acids at different pH and showed specific, consistent and preferential binding for the D-amino acids, probably as a consequence of the characteristic helical conformation which assumed a radial alignment on the surface of the dendritic core. It was also noted that at higher pH when the carboxylate groups of the poly(glutamic acids) were deprotonated, the encapsulated amino acids were not released into the aqueous environment but were transferred to the more hydrophobic core of the dendrimer (Scheme 2). Coordination of anionic organic molecules was achieved with novel types of polycationic dendrimers developed by van Koten and coworkers [35]. The first type reported was formed by polyaryl (di) amine molecules at the core that, once protonated, generated a ionic interior surrounded by a less polar outer shell of Frechet type dendrons. The second type was constructed from large carbosilane core, followed by an ionic layer and an apolar outer shell (see **in Fig. 10**).

Extraction of methyl orange and other anionic compounds from water was achieved successfully due to the strong electrostatic interactions with the quaternary ammonium units. The formation of complexes was shown to be reversible with the displacement of the methyl orange being achieved with the addition of bromide. Shinkai and coworkers were the first to design and synthesize a new class of dendritic macromolecules, coined _crowned arborols_ (**see in Fig. 11)** that were able to form stable complexes with metal ions [36]. The metal binding study was carried out in a biphasic system, and each diaza-18-crown-6 moiety was shown to form 1:1 complexes with Naþ

and Kþ atoms. These macromolecules were also used as dissolution aids for myoglobin in organic solvents. Myoglobin is a protein with polyanionic groups distributed on the surface and it was predicted that the complexation of the cations by the crown ethers would facilitate solubilisation in organic media.

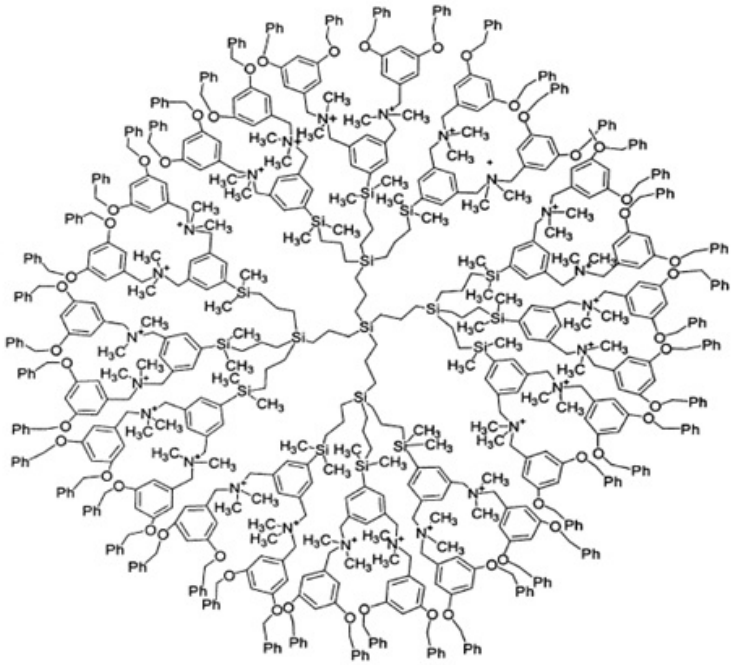


Figure 10. Polycationic dendrimer developed by van Koten and coworkers [35]

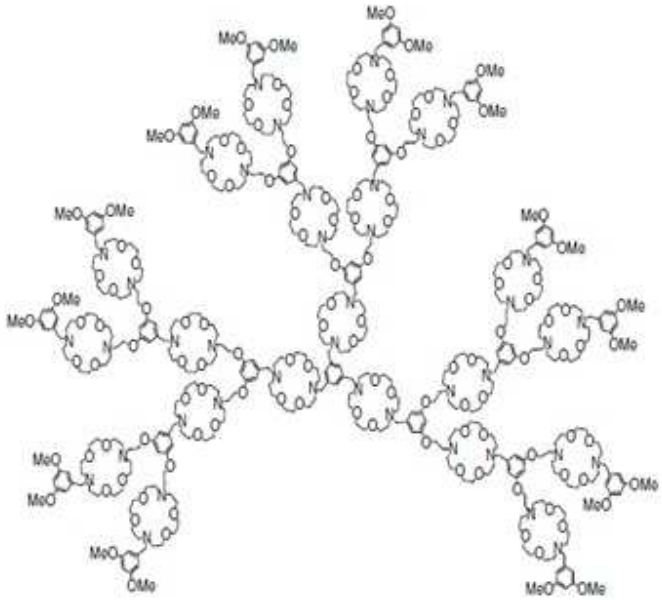


Fig. 11. The third generation Crowned Arborol described by Nagasaki et al. [36].

Only the first generation dendrimers were able to improve the myoglobin solubility, probably as a consequence of the increased size at higher generations preventing the required interaction with the protein surface. Multi-crown dendrimers based on the surface modification of polypropylene amine (POPAM) dendrimers with benzo [15]-crown-5 units have been developed [37] by Stephan et al. for the simultaneous binding of anions and cations **(see in Fig. 12**). The host–guest properties of the systems were investigated using sodium pertechnetate (a contaminant of nuclear waste), and mercury (II) chloride (pollutant of chloride containing effluents of incineration processes) as guest molecules, and the ability of the dendrimers to extract these molecules from aqueous solution. It was observed that the extraction efficiency was a function of pertechnetate concentration and dendrimer generation. Sodium uptake was poor at pH lower than 12, although increased efficiency was observed at higher generation of

dendrimers. The dendrimers were also able to extract Hg (II) from chlorinated aqueous solutions either in the neutral form (HgCl2) or as the anionic species (HgCl_ 3 and HgCl2_4). Metal coordination has also been achieved by Beer and Gao [38], using dendrimers based on the 1, 4, 7- triazacyclononane ligand [39] **(see in Fig. 13).** The metal coordination of Cu (II) species was studied using UV–vis spectrophotometric titrations and showed the ability of this dendrimer to complex the metal at each recognition site. Although electrostatic interactions play a crucial role in the metal binding properties of a wide variety of dendrimers, Shinkai and coworkers investigated a new dendritic sensor for saccharides [40]. The system was based on the selective interaction between diboronic acids and saccharide molecules that was reported by the same authors in a related study [41]. The dendrimers **(see in Fig. 14),** obtained by derivatisation of PAMAM dendrimers with boronic acids, were able to form stable intramolecular 2:1 boron-saccharide complexes with higher affinity towards D-galactose and D-glucose than their deoxy-, deoxymethyl-, and partially protected derivatives. Recently the use of poly (Lysine) dendrons functionalised at the focal point with 18-crown-6 for the binding of Kþ and benzylammonium cations was reported by Dykes et al. [42]. The binding ability was investigated by 1H NMR spectroscopy, and a progressive decrease in the binding constant from the [G-1] to the [G-3] dendrons were observed, possibly as a consequence of non-selective binding within the dendritic branches.

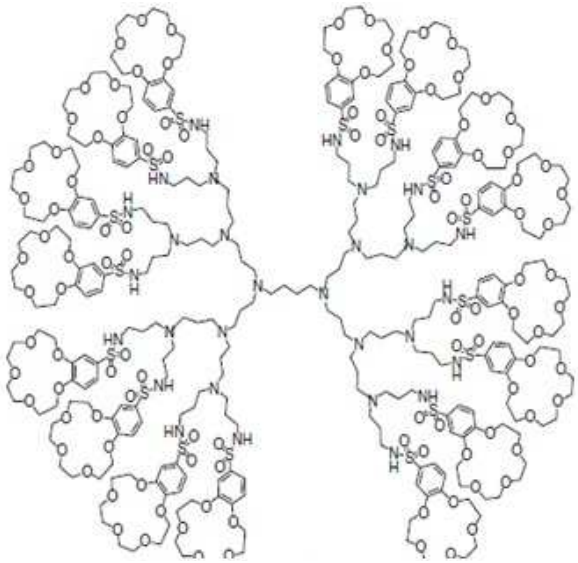


Figure 12. Multi-crown POPAM dendrimer developed by Stephan et al. [37]

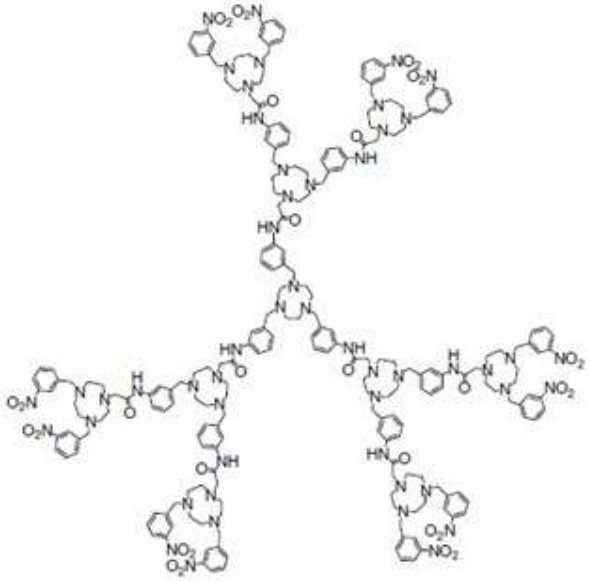


Fig. 13. The [G-2]-dendrimer based upon 1,4,7-triazacyclononane developed by Beer and Gao [38].

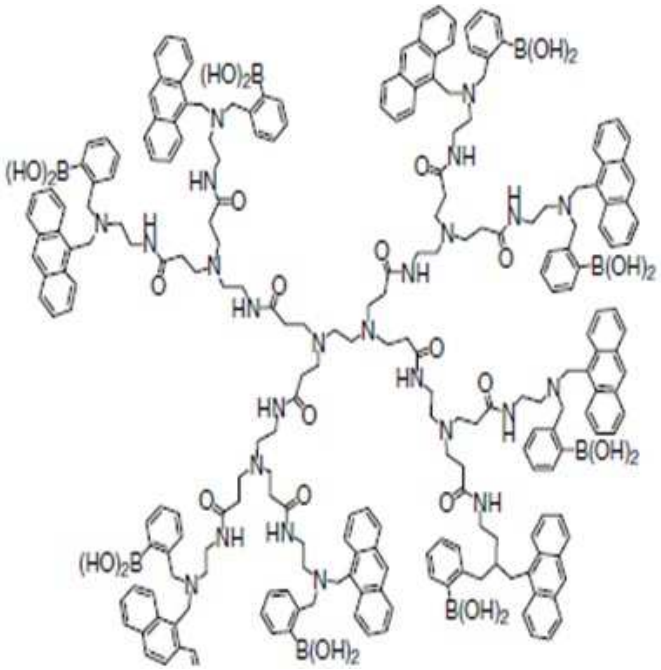


Fig. 14. PAMAM dendrimer functionalized with boronic acids for the selective binding of sugars [40]

2. Recognition of Inorganic Anions

The area of anion recognition, pionierred by Lehn [43-46], is of particular importance for its biological implications. Various types of sensors are known, including redox sensors with macrocycles and tripods [47-52]. The anion receptors designed so far are endo-receptors [53-57]. On the other hand, dendrimers with redox sensors at the extremities of the branches could function as exo-receptors, especially if the surface covered with redox sensors is not too far from steric saturation. At this point, it could mimic the surface of micro-organisms such as viruses. The ferrocene unit has long been used as a redox sensor since both Fe(I1) and Fe(II1) forms are stable enough for electrochemical scanning without loss of reversibility. The principle is that the redox potential of the Fe(IIIII1) redox system of the ferrocene unit is not the same in the presence and absence of substrate whose recognition is looked for. In the meantime, the binding constant of the substrate with the host bearing the ferrocene unit close to the receptor is not the same in the neutral Fe(I1) redox form of ferrocene and in its Fe(II1) cationic form. These thermodynamic values are related by the following thermodynamic cycle.

The amidoferrocene fragment also has the benefit of the acidic amide hydrogen atom which can form a hydrogen bond with an oxygen atom of 0x0-anions. Amidoferrocenes have indeed been used as redox sensors in tripodal units (68, 69). We have compared the 9-Fc and 18-Fc dendrimers with mono- and tripodal amidoferrocenes of closely related structure in order to investigate dendritic effects. Recognition studies have been carried out by cyclic voltammetry and by 1H **NMR.** In each case, titrations of the ferrocene dendrimers were effected by n-BqN+ salts of H2PO4-, HSO4-, C1- and NO3-. By far, the most informative results were obtained by cyclic voltammetry by scanning the Fe(II/III) wave. Before any titration, the cyclic volammograms or the 9-Fc and 18-Fc dendrimers show a unique wave at 0.59 V vs. SCE in CH2C12 corresponding to the oxidation of the 9 redox centers, which indicates that, as expected, the 9 or **18** redox centers are electrochemically equivalent, thus independant (when for instance two equivalent redox centers are not so far away from each other, two waves are observed at two distinct potentials, even if there is no electronic connection, because of the electrostatic effect).

Upon addition of the anion, two situations can arise **[58].** In the case of H2P04, a new wave starts appearing at less positive potentials and correlatively, the intensity of the initial wave starts decreasing. When one equivalent of anion per dendrimer branch has been added, the initial wave has disappeared and, upon addition of the anion, the intensity of the new wave does not increase any longer. In the case of the other anions, no new wave appears but the initial wave is progressively shifted to less positive potentials upon titration until1 one equivalent of anion has been added per dendrimer branch. The shifts *AE'* of potentials observed after addition of one equiv. anion per dendrimer branch are given in table 1 for the four anions. It clearly appears that the ***AEo*** value considerably increases in the series: 1-Fc ---> 3-Fc ---> 9-Fc ---> 18 Fc, which shows a dramatic dendritic effect represented for the B titration with the HSO4- anion. The magnitude of interaction with the anion increases as follows both situations upon titration -

appearance of a new wave and shift of the initial wave have already been analyzed from the thermodynamic standpoint [58].

Table 1. Titration of the Fc Ds by Varlous n.Bu,N' Salts Monltored by the Variation *AF* (mV lor 1 Equivaleni of Anion per Branch) of the Standard *Redox* Polentlal *F* of the Redox Couple In Cyclic Vollammelry'

Anions	1-Fc	3-Fc	9-Fc	18-Fc
$H2PO4^-$	45	110	220	315
$HSO4^-$		30	65	130
Cl^-	ϵ	ϵ	20	45
$NO3^-$	ϵ	ϵ	ϵ	30

'In the case of **HSO;,** the variation A F along the illations **is** represented for the various dendrimers. The uncertainties of **the *AEO*** values are estimated to be 20 **mV.** Thus, lower shifts are indicated **by c.**

Table 2. Apparent Association Constants *K(+)* Determined in CH,CI, by *CV* (or the FcD Sorles from the Shill of the CV Wave using Eqs 1 and 2.

Anions	1-Fc	9-Fc	18-Fc
$H2PO4^-$	9390	216900	b
$HSO4^-$	544	8530	61400
Cl^-	c	417	2120
$NO3^-$	c	C	403

(K (+) determined for the 9.Fc dendrimer from Ihe combination **01 *K (0)*** determined by 'H NMR In CD,CI, and the ***K(t)IK(O)*** ratio determined by CV In CH,CI, using eq 1. For 1 8-Fc, the *K(+)IK(O)* ratio was found to be 219000. The uncertainties on K values are estimated to 10%. 'Since the **AP** values are much smaller than the uncertainties (Table l) , calculation of the small K values would be meaningless.)

In the first situation in which H2P04- is concerned, equation (1) applies: Measurement of *AE"* leads to K(+)/ K(0). The determination of K(+) requires the determination of K(O), the binding constant between the neutral ferrocene form of the dendrimer and H2PO4-, in the present case by 1H NMR using Hynes' EQ ***NMR*** program [59]. Indeed the shift of the amide proton also shows that the equivalence point is reached after addition of one equiv. H2PO4- per dendrimer branch (from ***6*** = 6.82 ppm before titration to 6.65 ppm after this addition). In the second situation concerning the other anions, this binding constant K(0) between the neutral ferrocene dendrimer and the anionic substrate is very small **(>1)** and does not intervene in the expression of *AE"* (equation (2)):

AE" (V) = 0.059 log [K (+)/ K (O)] at 25°C **(1)**
AEo (V) = 0.059 log [cK (+)] at 25°C **(2)**

Where c is the concentration of added anion. Thus, K (+) is directly accessible by measurement of *AE"* only. These apparent association constants K (+) between the femcinium form of the dendrimer and the anionic substrate are gathered in table 2.

The "MR monitoring of the titrations is not as useful in the case of the other anions as in the case of H2PO4- because, as indicated above, the ineraction is weak. Indeed, equivalent points are very variable and very far from corresponding to one equiv. anion per branch, whereas they do so for the ferricinium form which more strongly binds the different anions. In general, the ferricinium form of the tripod or dendrimer binds the anions relatively strongly because of the synergy of the electrostatic attraction with the intermolecular hydrogen bond formed between the acidic amide H atom and the anionic substrate through an oxygen atom of an oxoanion or the halogen anion. Both factors are important and, if one of them is absent, the interaction becomes loose and cannot be used for sensing (except in the case of H2PO4- for the dendrimers). This effect has previously been recognized and used [56,57]. Of special interest here is the dramatic dendritic effect observed for all the anions. Even when the synergy between the electrostatic and H-bonding is fulfilled, the AE" value is unobservable or small when the amido-ferrocene used is monometallic (1-Fc) or trimetallic (3-Fc).

The shape selectivity designed in the dendrimer is crucial and its effect is much more marked for 18-Fc than for 9-Fc as the ferrocene termini are closer to each other when the dendritic generation increases. This dendntic effect is thus maximum for the generation (1 8-Fc) which precedes steric saturation by ferrocene groups on the dendrimer surface (36-Fc). It can be understood in the course of the dendntic synthesis as the insolubility of sterically saturated ferrocene dendrimers is complete in all the solvents. In the amido-ferrocene dendrimers, the amide H atom is located on the branch behind the ferrocene unit which provide the surface bulk. Thus the anion has to reach the inside of the

micro cavity formed by the amido-ferrocene units at the surface of the dendrimer. These conditions become optimal for redox sensing and recognition by the close ferrocene units at the 18-Fc generation, since the channels allowing the entry of the anions into the surface micro cavity to reach the amide H atom are **as** narrow as possible. In conclusion, after having synthesized organo metallic dendrimers, we have now been able to demonstrate a dendritic effect in molecular recoption. Other effects are expected with polycationic organometallic dendrimers and molecular recognition studies are presently in progress in our laboratories along this line. We thank E. Leize and A. van Dorsselaer from the Universite Louis Pasteur (Strasbourg) for electrospray mass spectra, **M.J.** Hynes for providing and discussing his EQ NMR program [59]**,** the Institut Universities de France (D.A.), the Universite Bordeaux I, the **CNRS,** the Region Aquitaine and Rh6ne-Poulenc for financial support, the Ministere de la Recherche et de la Technology for a thesis grant to C.V., and the Ministerio de Education **y** Ciencia (Spain) for a postdoctoral grant to E.A.

4. Conclusion

Molecular recognition is an important process for the complexation of the various type of the molecules without using covalent bonds. Dendrimers are the most important macromolecules which take part in the complexation of the materials and it has also various applications in drug delivery system. Molecular recognition has also help in the aggregation of the molecules. This review article focused on the details of the role of dendrimers in the molecular recognition.

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