

Electron-transfer processes in dendrimers and their implication in biology, catalysis, sensing and nanotechnology

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The extraordinary development of the design and synthesis of dendrimers has allowed scientists to locate redox sites at precise positions (core, focal points, branching points, termini, cavities) of these perfectly defined macromolecules, which have generation-controlled sizes and topologies matching those of biomolecules. Redox-dendrimer engineering has led to fine modelling studies of electron-transfer metalloproteins, in which the branches of the dendrimers hinder access to the active site in a manner reminiscent of that of the protein. It has also enabled the construction of remarkable catalysts, sensors and printboards, including by sophisticated design of the interface between redox dendrimers and solid-state devices — for example by functionalizing electrodes and other surfaces. Electron-transfer processes between dendrimers and a variety of other molecules hold promising applications in diverse areas that range from bio-engineering to sensing, catalysis and energy materials.

Electron-transfer processes in molecular assemblies on the nanoscale are of prime importance for fundamental biological processes, as shown by insightful studies from bioinorganic chemists¹ — respiration, for example, involves 15 such processes. They are also key for applications in nanotechnology, such as the construction of functional devices on surfaces², and have served to engineer supramolecular redox sensors³ and to modify surfaces, for example in the preparation of derivatized electrodes. Finally, the inner-sphere components in electron-transfer processes can operate biomimetic catalytic steps involved in numerous oxidation reactions.

Dendrimers are precise cauliflower-shaped macromolecules constructed from the central core, in either a divergent or a convergent way. The number of their branches is usually multiplied by 2 (1 → 2 connectivity) or 3 (1 → 3 connectivity) each time it increases by a generation (Fig. 1 shows a generic representation of dendrimers, as well as two examples of dendritic branches). After several generations, the sizes of dendrimers match those of biological components. Their topology allows a perfect location of active sites, for example redox sites, and this combination makes them a powerful tool for fine studies of electron-transfer kinetic and thermodynamic parameters^{4,5} in biosystems.

Newkome showed in his seminal report that dendrimers behave as water-soluble molecular micelles if their core is hydrophobic and their periphery hydrophilic⁶. This property led to applications in nanomedicine, initially developed by the groups of Tomalia and Fréchet, for the encapsulation of water-insoluble drugs⁷. The multiple possibilities of catalyst attachment (periphery, core, branching points, cavities, focal point — that is, a group through which dendrons are linked to construct a dendrimer) also offers choices for catalyst engineering involving inner-sphere redox processes that take into account mechanistic features⁸. There are thus multiple directions that take advantage of the dendrimer size, structure, topology and conformation for beneficial use of electron-transfer processes in biomimetic studies, surface functionalization, and nanomaterials design, including sensors and catalysts.

Dendrimers have been the subject of an extraordinary synthetic development in the inorganic^{9,10}, organometallic^{8,11}, biochemical^{7,12,13}

and energy materials communities¹⁴. This large variety in structures and engineered functionalities^{4,11,15} has endowed dendrimers with electron-transfer processes that have far-reaching implications, for both fundamental studies and practical applications.

Dendrimers mimicking redox enzymes

Transition-metal-cored dendrimers are efficient models of metalloproteins in which a redox-active metal centre is deeply buried, and indeed, relevant studies have shed light on this biomimeticism since the early days of metallodendrimer chemistry^{4,5,7,10,16} (Fig. 2).

Porphyrins are naturally occurring macrocycles — the active centre of haem proteins, for example haemoglobin, consists of a porphyrin macrocycle with an iron atom coordinated in its central cavity (Fig. 2a). Dendrimers centred around iron-porphyrin cores have been designed in seminal studies by the teams of Diederich and Gross as models of haemoglobin, and derivatives bearing a chloro ligand in axial position on the iron-porphyrin centre have been studied as a cytochrome model^{16–19}.

A better understanding of the haem proteins has been gained using dendrimer models. For example, the oxidation potential of the iron centre of cytochrome *c* — a small haem protein — is known to be much more positive (300 to 400 mV higher) than that of haem model systems based on dendrimers, even though they show similar metal ion ligation²⁰. When the redox potentials of the iron centre were recorded for two dendritic models (one a first generation (G_1) and the other a second (G_2)) in water, the G_2 dendrimer (as shown in Fig. 2a) exhibited a potential in water that was more positive than that found with its first-generation counterpart by 420 mV. The large difference between these potentials was attributed to differences in solvation of the redox-active iron core: the open dendritic branches in the dendrimer G_1 did not inhibit access of bulk solvent to the central redox site, whereas the densely packed dendritic bulk of the dendrimer G_2 reduced contact between the haem and external solvent, which in turn destabilized the more charged Fe(III) state^{19–22} (Figs 2a,c). This situation mimics and explains the above comparison between cytochrome *c* and a less crowded model¹⁶.

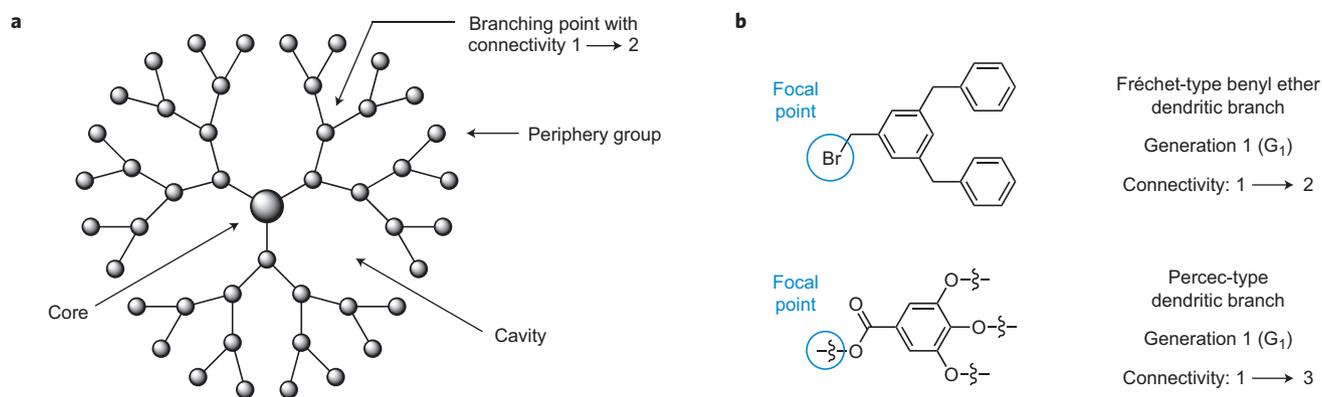


Figure 1 | Schematic representation of the general structure of dendrimers. **a**, Scheme showing the location of the core, branching points, termini (at the periphery) and inner cavities of a dendrimer, here represented with a connectivity 1 → 2. **b**, dendritic branches of a Fréchet- and a Percec-type dendrimer, here both first-generation (G_1). Circled: focal point, which serves as a chemically addressable group used to attach dendritic branches together to construct a dendron or a dendrimer.

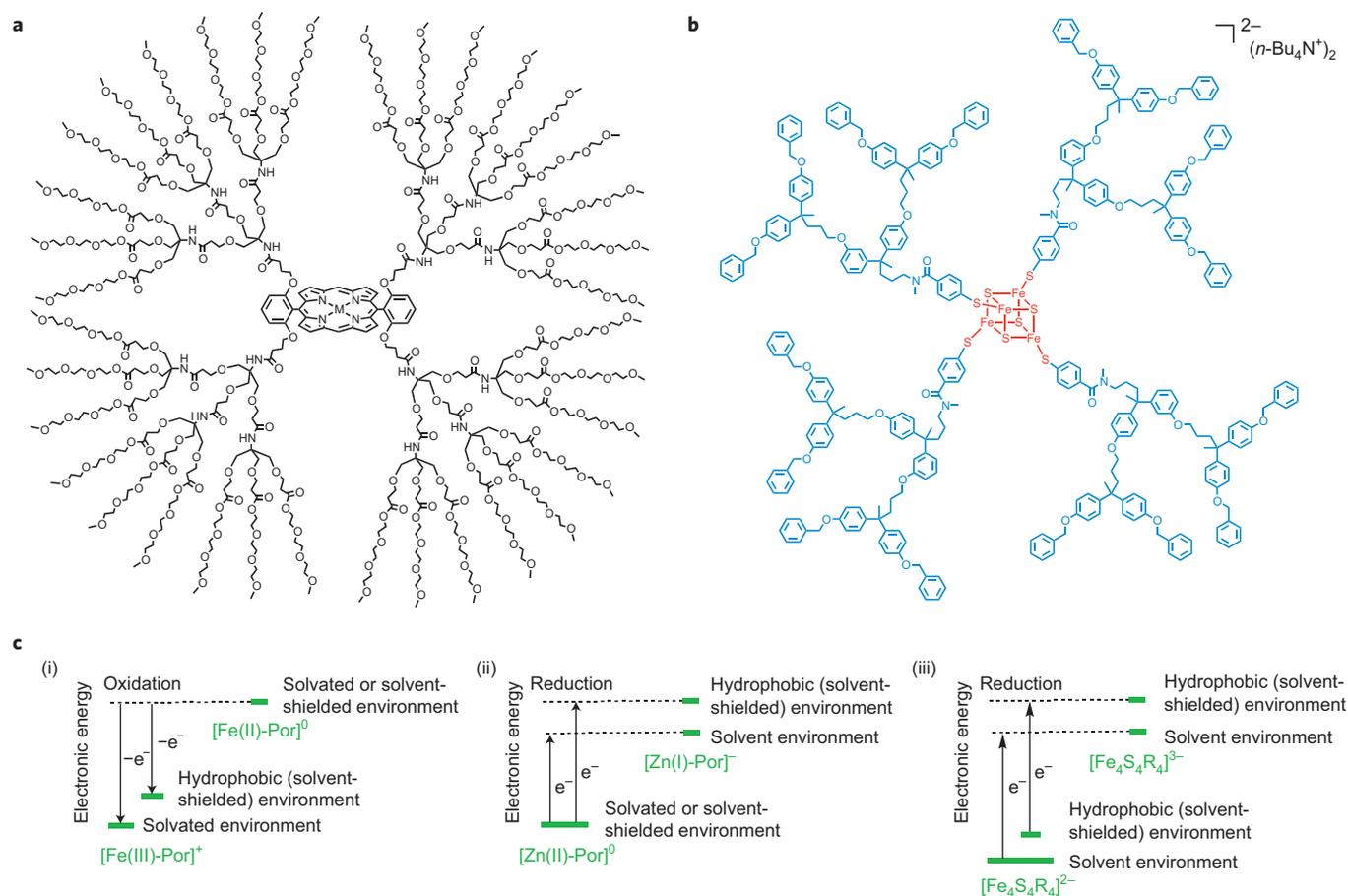


Figure 2 | Metal-centred dendrimers modelling electron-transfer metalloproteins. **a**, Dendritic iron porphyrin models of cytochrome *c* ($M = \text{Fe}(\text{III})\text{Cl}$)^{16–19}. Reprinted with permission from ref. 15, © 1995 Wiley. **b**, Example of a series of dendritic $\text{Fe}_4\text{S}_4\text{R}_4$ clusters synthesized and studied by Gorman's group^{22–24} as models of Fe_4S_4 -cored electron-transfer proteins. **c**, Gorman's 'charge destabilization' model for redox centres buried inside metallodendrimers or redox-cored electron-transfer proteins. (i) monoelectronic reduction of $\text{Fe}(\text{III})$ -porphyrin cored dendrimers; (ii) monoelectronic reduction of $\text{Zn}(\text{II})$ -porphyrin-cored dendrimers; (iii) monoelectronic reduction of Fe_4S_4 -cored dendrimers²³ (Gorman's group). A redox change involving a change between a charged and a neutral species results in a significant potential shift, whereas one involving a change between two charge species does not.

Similar studies carried out by the Abruña and Fréchet groups showed that reduction of the monocationic $\text{Fe}(\text{III})$ - to the neutral $\text{Fe}(\text{II})$ -porphyrin centre of dendrimers at a cathode electrode became easier (occurred at more positive potentials) with increasing molecular weight of the surrounding dendritic branches — that

is, with increasing dendrimer generation. In contrast, a shift to more negative potentials was observed for the monoelectronic reduction of neutral $\text{Zn}(\text{II})$ -porphyrin dendrimers to mono-anionic $\text{Zn}(\text{I})$ -porphyrin dendrimers with increasing generation. In both cases, however, the potential shift could be accounted for

by the destabilization of the charge on increasing the dendrimer generation, that is, when the access of the solvent to the redox core was restricted²¹. All of the results discussed above fit this charge-destabilization model, although the lack of shift in anodic oxidation potential observed on increasing the generation of the Zn-porphyrin-dendrimer remains unexplained²¹.

Iron-sulfur proteins can also be modelled by dendritic systems, this time featuring $\{\text{Fe}_4\text{S}_4\}$ clusters as cores (Fig. 2b), as investigated by Gorman and co-workers^{22–24}. Electron-transfer studies revealed that, in contrast to the metalloporphyrin studies, the redox potentials were invariant with dendrimer generation, whereas $[\text{Fe}_4\text{S}_4]$ peptide models showed redox potential shifts of 360 mV in response to changes in peptide sequence²⁵. Since the redox change involves the -2 and -3 charges of the dendrimers in this model case, the destabilization was also about the same for both multiply charged species. These results rationalize the lack of redox potential variation according to the charge model of Fig. 2c²² — only a redox change involving a change between a charged and a neutral species results in a significant potential shift.

Another crucial biomimetic aspect of transition-metal-cored dendrimers appeared in the investigation of electron-transfer rates, with electrodes or other redox substrates: such studies mimic electron-transfer rates and mechanisms occurring in redox proteins — a very challenging field developed for metalloproteins themselves in particular by the group of Harry Gray^{1,26}. Indeed, the decrease of the electron-transfer rate with an increasing distance between the substrate and the active centre has been well established in metalloproteins and cytochrome c ^{1,25,26}. It was suspected that protein conformation played a key role around the redox core of the biological systems^{27,28}.

To investigate this, the Gorman group compared heterogeneous electron-transfer rates for the mono-electronic cathodic reduction of various iron-cluster-cored dendrimers $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$, where R is a dendron containing either flexible or rigid tethers^{22–24}. For comparable tether lengths, rigid dendrimers indeed exhibited slower electron transfer than flexible ones. This is because the rigid dendrons maintain a large cage around the redox centre, forcing electrons to travel along a larger distance than in their flexible counterparts, for which the tether termini fold back closer to the $[\text{Fe}_4\text{S}_4]$ cluster at the core. A remarkable additional result was that comparing dendrimers of analogous radii revealed that electron transfer proceeded faster across rigid branches than across flexible ones²². Gorman's group also recently found a slower rate of heterogeneous electron transfer with water-soluble Fe_4S_4 -cluster-cored dendrimers, compared with non-amphiphilic analogues. This behaviour correlates with the larger size of the water-soluble systems, and thus a larger effective distance of electron transfer²⁹.

These kinds of study are delicate, because burying metal centres inside dendrimers results in weakened, irreversible waves in cyclic voltammetry (CV) that are difficult to analyse. At the early stage of metal dendrimer chemistry, several research groups recorded redox potentials of redox-active metal-cored dendrimers^{29–32}. For instance, in an early study, the group of Newkome designed dendrimers with a ruthenium bis(terpyridine) complex $[\text{Ru-bis(terpy)}]^{2+}$ as core, linked to dendritic branches through its terpy ligands³⁰ (Fig. 3). This concept for constructing dendrimers continuously proved to be remarkably powerful in engineering dendritic macro-supramolecular assemblies³¹. It allows for the construction of dendrons with a more approachable core, and also permits the synthesis of asymmetric dendrons. Kinetic studies of the Ru-bis(terpy)-cored dendrimer by the Newkome, Echegoyen³⁰ and Gorman groups^{33,34} showed that heterogeneous electron-transfer rates decreased as the dendron generation increased. Gorman *et al.* used an NMR line-broadening technique to determine the self-exchange kinetics between oxidized and reduced metal-tris(bipyridine)-cored dendrimers and observed that, as the generation of the dendrimer

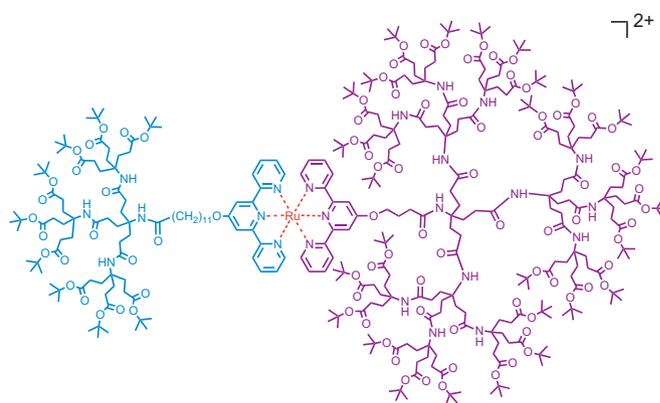


Figure 3 | A bis-dendronic terpy-ruthenium complex. Newkome's group synthesized bis-dendronic terpy-ruthenium complexes by successive reactions of RuCl_3 with two distinct dendrons. The study by CV of the kinetics of the heterogeneous electron transfers shows a quasi-reversible metal-centred mono-electronic oxidation that becomes more and more irreversible (larger $E_{\text{p,anode}} - E_{\text{p,cathode}}$ values) as the purple dendron become larger (higher generation), as expected. On the cathodic side, two terpy-centred reduction waves are observed, because the microenvironments of the two terpy ligands are different³⁰.

increased, the rate of self-exchange decreased as expected and in line with the other results (as discussed above)³⁴.

Kaifer and his group synthesized three Newkome-type dendrons⁶ of increasing generations possessing a $1 \rightarrow 3$ connectivity^{6,11} with an amido-ferrocenyl unit linked to the dendron focal point through the amido link³⁵ (Fig. 4a). These compounds were studied as models of redox proteins containing an asymmetrically positioned redox active group — a property relevant to the control of the electron-transfer reactions of these proteins. The oxidation potential of these compounds in a solution of dichloromethane became less positive on increasing the generation. This trend first seems counter-intuitive, and was initially difficult to rationalize, but followed the same trend as the porphyrin-cored species discussed above, for which the heterogeneous electron-transfer rates were found to decrease with increasing generation^{36–38}.

Subsequent studies of the Kaifer group with a variety of redox sites (ferrocene^{35,36}, cobalticinium³⁷ and viologen^{37–39}) at the dendron focal point systematically also resulted in a similar cathodic shift of redox potential and decreased electron-transfer rates on increasing generations. The redox-site microenvironment was shown to be influential; for instance growth of the Newkome dendron with $1 \rightarrow 3$ connectivity had a more pronounced effect on the half-wave potential for the oxidation of the ferrocenyl group than growth of the Fréchet dendron with $1 \rightarrow 2$ connectivity³⁵.

Kaifer *et al.* also compared heterogeneous electron-transfer rates between gold electrodes derivatized with ammonium groups and dendronized ferrocenes terminated by carboxy group as a function of the pH (Fig. 4b). In acidic medium, the electron transfer of the dendrimers was faster than at neutral pH, because the dendrimers were uncharged and thus free to rotate. In neutral medium, however, the carboxylate dendrimers formed electrostatic bonds with the ammonium groups of the modified electrode, in turn inhibiting the approach of the ferrocenyl group to the electrode. These now well-established electrochemical properties of ferrocenyl species and other redox systems encapsulated in dendrimers have since been used to localize redox sites at specific positions in the interior of peptide dendrimers⁴⁰.

Another very different biological aspect concerns neuronal science. It is well known that neurons have dendritic networks, but a fundamental question concerns the mechanism of how neurites, thin extensions from a neuronal body of dendrites that receive

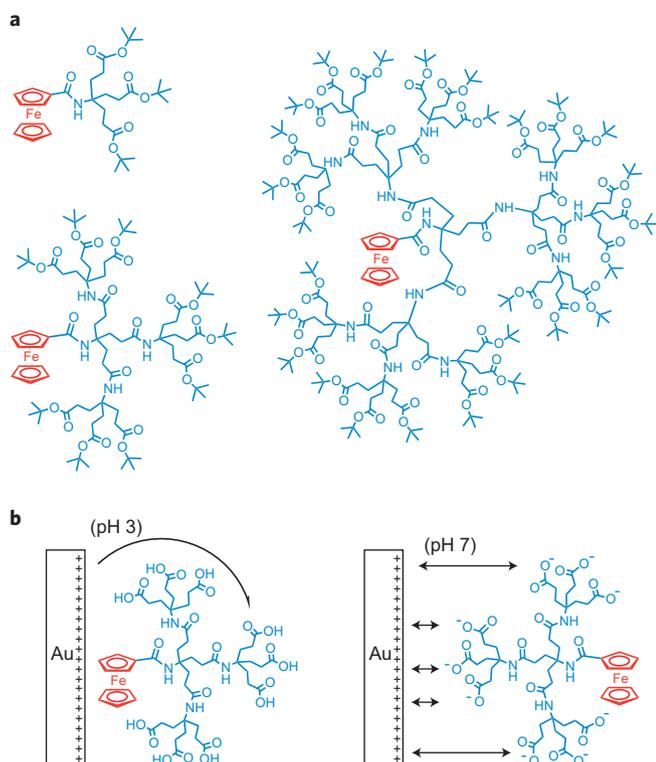


Figure 4 | Electron-transfer reactions of ferrocenyl redox sites attached to the focal point of Newkome dendrons. **a**, Kaifer's group investigated Newkome-type dendrons of G_1 , G_2 and G_3 . The rate constant for heterogeneous electron transfer using CV in dichloromethane decreased and the $E_{1/2}$ value of the ferrocenyl redox centre was shifted to less positive potentials as the dendron generation increased³⁷. **b**, Behaviour of Kaifer's dendronized ferrocene (G_2) on a gold electrode derivatized with ammonium groups of cystamines schematized by positive charges. At pH 3 (left), the carboxylic dendrimer groups are protonated. The ferrocenyl dendrimer freely rotates in solution showing a reversible (fast) anodic oxidation wave, because the free ferrocenyl redox group can come close to the Au electrode surface ($8 \times 10^{-3} \text{ cm}^2$). At pH 7 (right), the charged carboxylate moieties are electrostatically bound to the positively charged ammonium groups of the ammonium-derivatized electrodes, forcing the ferrocenyl group to remain away from the electrode. Heterogeneous electron transfer is thus slower at pH 7 ($1.5 \times 10^{-5} \text{ cm}^2$) than at pH 3 (ref. 37).

inputs from other neurons, process signals physiologically and electrically. How such neurotransmitters and electrical signals are used to process information in a neuron is so far very poorly understood⁴¹. When such a fascinating area is further understood, it is probable that fundamental aspects of biomimetic electron-transfer processes in synthetic dendrimers will find even further interest.

Metallo-dendritic electron reservoirs and molecular batteries

To construct molecular batteries, it is desirable that the redox centres be stable, and even preferably robust, at least under two stable oxidation states⁴² — late transition-metal sandwich or first-row transition-metal cluster structures seem ideal. To possess these characteristics, the redox systems need to be electron reservoirs⁴³ that assemble into molecular systems with degenerate orbitals and low-lying singly occupied molecular orbitals (SOMOs). The molecular electronic characteristics of these metallo-dendrimers that feature well-defined electron-transfer properties are modulated by the intra- and inter-dendrimer processes. Mechanisms of electron transfer in such nanomaterials involve the interplay between redox-active metallo-dendrimers and surfaces, metallic nanoparticles and other solid-state devices. Such studies were

initiated in the early 1990s^{6,43}, still at the early stage of metallo-dendrimer chemistry^{4,7}.

Among redox-stable late-transition-metal sandwiches, iron-sandwich complexes derived from ferrocenes⁶ and cyclopentadienyl iron arene⁴⁴ structures gave the best results in terms of robustness of two or several oxidation states. Ferrocenes are oxidized to the ferricinium salts that are modestly stable, especially in solution⁴², but they are considerably stabilized on using pentamethylcyclopentadienyl instead of parent cyclopentadienyl for one of the ligands, whereas the other cyclopentadienyl bears the functional link to the dendrimer core. In this way, up to 14,000 pentamethylferrocenyl units could be branched to the periphery of dendrimers⁴³ constructed in a divergent manner from a 1,3,5-trisubstituted arene core⁴⁵ according to a $1 \rightarrow 3$ connectivity (Fig. 5 shows a G_2 dendrimer constructed in this way that bears 81 terminal ferrocenyl moieties)^{5,6,11}.

Noteworthy observations are made on recording the cyclic voltammograms. In these metallo-dendrimers, the redox centres are sufficiently separated from one another to give rise to extremely small, unobservable electrostatic effects. The redox potentials of all the ferrocenyl units are theoretically all different from one another^{45–47}. For the dendrimer bearing 14,000 ferrocenyl sites, however, the electrostatic effect is sufficiently tiny so that only a single CV wave is observed for all these redox centres⁴³. Despite the fact that 14,000 electrons from a single dendritic molecule are exchanged with the electrode, the CV wave resembles a mono-electronic wave. In small rigid dendrimers, the situation can be different: strong electrostatic effects between ferrocenyl moieties can be selectively isolated, that is, if the fixed inter-site distance between the terminal groups is short and there is no significant intramolecular conjugation — such as in the example of Fig. 6 where the redox sites are located in meta position of the arene^{48,49}. With small rigid dendrimers the electrostatic effect splits the CV wave representing equivalent redox sites into several waves. Such enhancement of electrostatic effects are large with tetra(aryl)borate salts. These are used as supporting electrolytes, because in the salts formed with tetra(aryl)borate anions the strength of ion pairing is minimized, as shown in seminal studies by the Geiger group^{50,51}, which in turn maximizes the electrostatic effects.

Remarkably, giant redox-robust dendrimers show electrochemically reversible redox waves by CV, although adsorption is more and more apparent as the dendrimer generation increases (as characterized by the reduced value of the difference between the peak potentials, $E_{p,\text{anode}} - E_{p,\text{cathode}}$). This means that the heterogeneous electron transfer reflected in these cyclic voltammograms is relatively fast between the dendrimer redox sites and the electrode — faster than the timescale of the electrochemical experiment (typically 0.1 V s^{-1}) — even for the largest ferrocenyl dendrimers⁴³. Two mechanisms can be invoked to account for such a fast electron transfer, even with so many redox sites: the first one involves rotation of the metallo-dendrimer faster than the electrochemical timescale⁵², and the second deals with hopping from one ferrocenyl site to the next given the flexibility of movement of the chain termini that can bring two redox sites at the ideal relative distance and orientation^{53,54}. In a study by the Amatore and Abruña groups investigating the second mechanism, the nanoscale size of dendrimers was fully taken into account. Ultramicroelectrodes are used at very fast scan rates; this decreases the thickness of the diffusion layer below the dendrimer diameter, which in turn enables investigation of the dynamics of electron transfer at the periphery of dendrimers that bear multiple identical metal centres⁵⁵. The former mechanism — rotation of the metallo-dendrimer faster than the electrochemical timescale — is no longer viable when dendrimer-modified electrodes are used, that is, in the solid state. To test these hypotheses, Wang *et al.* used ultramicroelectrodes to determine inter-dendrimer electron transfers on electrodes that had been coated with ferrocenyl dendrimers. They

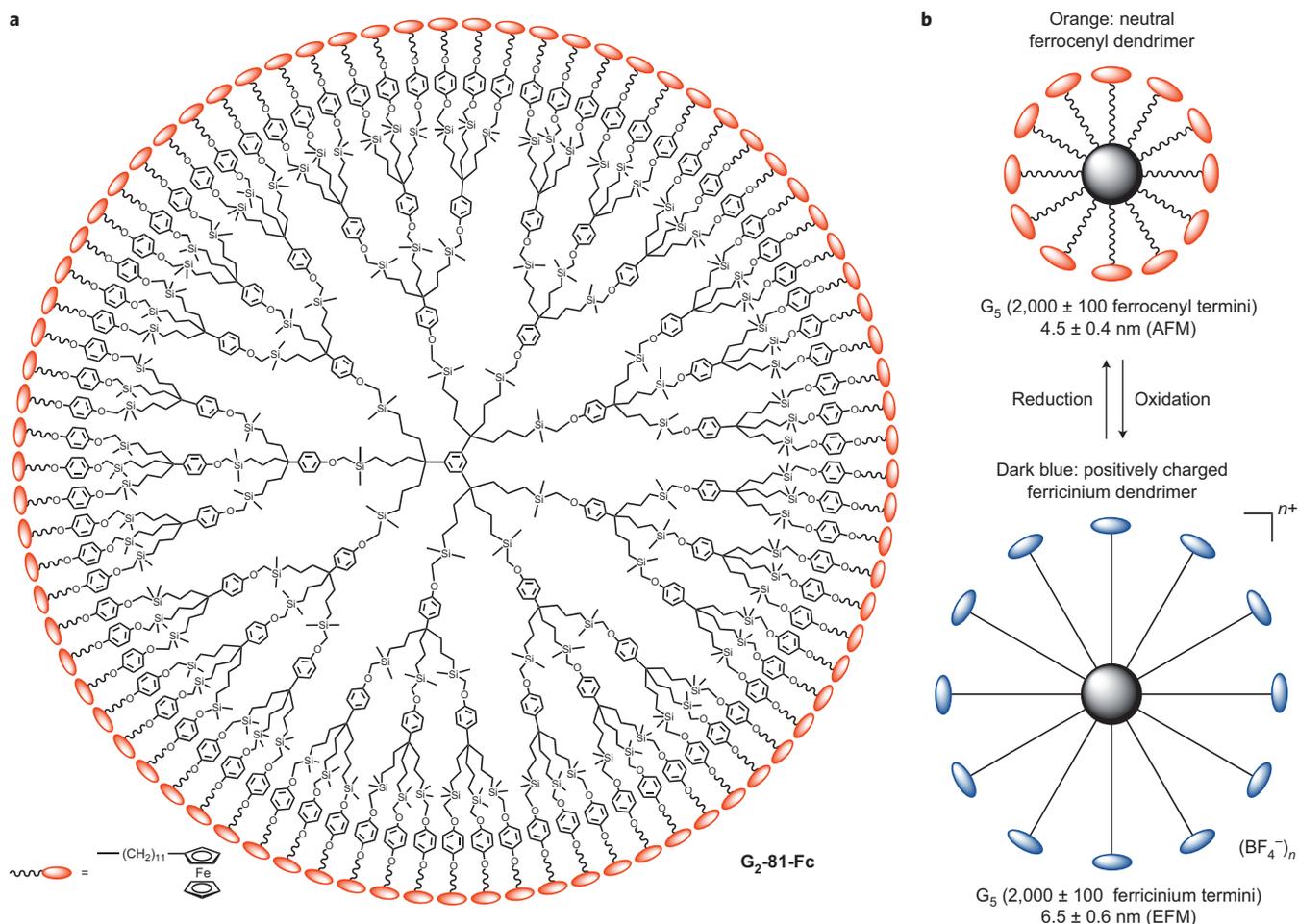


Figure 5 | Giant ferrocenyl- and pentamethylferrocenyl dendrimers as electrochromic molecular batteries. **a**, Example of a second-generation (G_2) arene-centred ferrocenyl dendrimer with extended tethers. Its synthesis involves CpFe^+ -induced nona-allylation of mesitylene followed by a reaction sequence consisting of hydrosilylation of the nona-allyl core with chloromethyldimethylsilane, nucleophilic substitution with sodium iodide, and Williamson reaction with a *p*-phenoltriallyl dendron. The ferrocenyl termini (bottom left) were introduced using such a Williamson reaction. These ferrocenyl dendrimers were synthesized using iteration of this sequence until G_7 (effective number of terminal ferrocenyl groups about 15 000), and cyclic voltammetry in dichloromethane using $[\text{N}(n\text{-Bu})_4][\text{PF}_6]$ 0.1 N as the electrolyte showed a simple reversible wave as for ferrocene itself until the last generation. **b**, Representation of the reversible 'breathing mechanism' of giant ferrocenyl dendrimers on redox switching between the neutral Fe(II) form (in orange) and the cationic Fe(III) form (in blue)⁴³.

observed that the heterogeneous electron-transfer rate is somewhat slowed down on increasing the dendrimer generation⁵⁵. In any case, the unexpectedly fast heterogeneous electron transfers that are observed between electrodes and giant dendrimers in spite of the large distance between the electrode and the remote redox sites is remarkable, and indicate that these giant redox dendrimers are candidates as conducting nanodevices.

On oxidation by varying the redox potential of the electrode, the giant ferrocenyl dendrimers significantly increase in size, as observed by atomic force microscopy. The dendrimers can be reversibly extended or shrunk on back-and-forth variation of the electrode potential around the ferrocenyl redox potential (Fig. 5b). This is because oxidation creates a very large number of positive charges. The formation of charged groups causes electrostatic repulsion forces between the termini, in turn inducing an increase of the dendritic molecular size. In a low-dielectric-constant solvent, each charged terminal redox moiety becomes associated with a counter anion of the electrolyte, forming tight ion pairs. With standard electrolyte counter anions such as hexafluorophosphate, this tight ion pairing actually masks the electrostatic effects between termini — that is, an ion pair acts as a covalent entity, with regard to the other terminal groups. These rather fast electron-transfer processes with

redox-robust metallodendrimers give the opportunity to consider the metallodendritic systems as molecular batteries. Similar redox-robust ferrocenyl and pentamethylferrocenyl dendrimers have also been constructed with other cores, such as gold nanoparticles, inorganic hexamolybdenum clusters and silica. The redox potential of ferrocenes ($\text{Fe(III)}/\text{Fe(II)}$) are located in the positive region of the redox scale, therefore electron-rich metallodendrimers have also been designed with late transition-metal sandwich complexes having negative redox potentials so that their reduced forms are strong reductants and act as efficient electron-reservoirs^{56–58}.

The cobalticinium/cobaltocene $\text{Co(III)}/\text{Co(II)}$ redox system is also fully chemically and electrochemically reversible^{56–58}. The reduced cobaltocene form is a Co(II) , d^7 19-electron complex, although the SOMO orbital of the nineteenth electron, of e_1^* symmetry, is 50% delocalized onto the ligands (that is, the complex could be called a '18.5-electron' one)⁵⁸. The redox potential of this system is -0.85 V versus decamethylferricinium/decamethylferrocene system — a reliable reference independent of the medium⁵⁷ — thus moderately negative. Pentamethylcobaltocene derivatives containing one monofunctional cyclopentadienyl ligand have a redox potential that is shifted cathodically (more negative) by 0.2 to 0.3 V when compared with the parent cobaltocene analogues, and

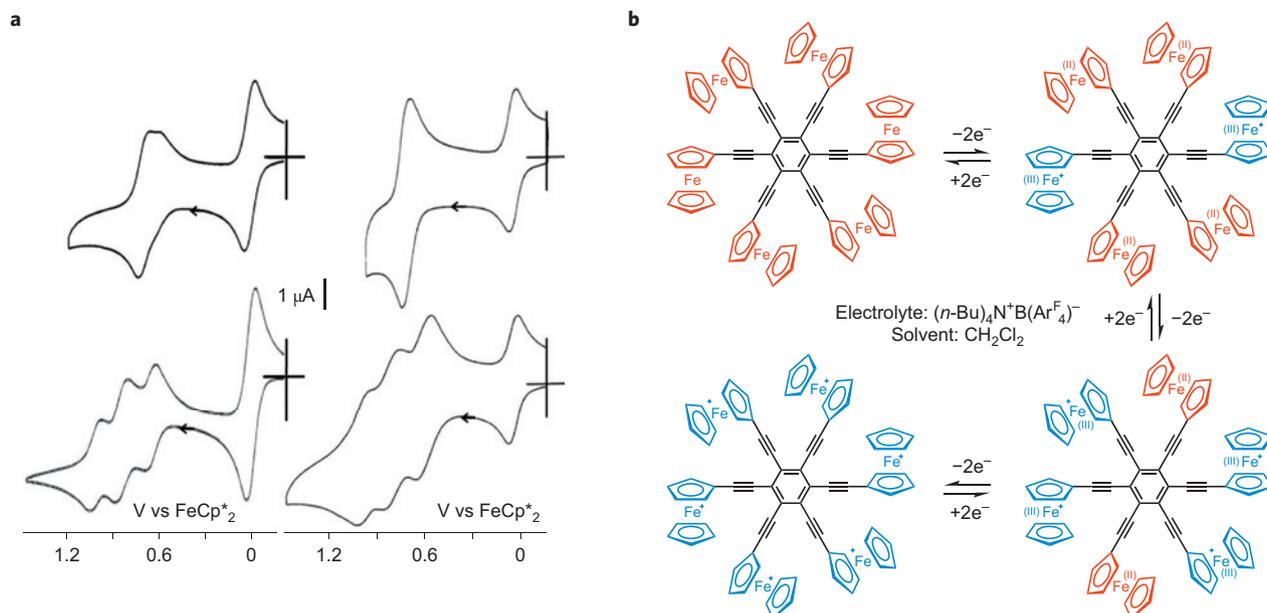
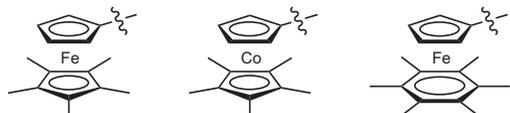


Figure 6 | Selective electrostatic effects in multi-ferrocenyl systems. **a**, Compared cyclic voltammograms of 1,3,5-tris(ferrocenylethynyl)benzene (left) and hexakis-(ferrocenylethynyl)benzene (right) in CH_2Cl_2 with $[N(n\text{-Bu})_4][PF_6]$ (top) and $[N(n\text{-Bu})_4][BAR^f_4]$ (bottom, $Ar^f = 3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2$). **b**, Mechanism of the oxidation of hexakis-(ferrocenylethynyl)benzene in the presence of $[N(n\text{-Bu})_4][BAR^f_4]$ 0.1 N with $Ar^f = 3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2$, in CH_2Cl_2 , a cascade of three two-electron oxidation steps shown in **a** with the CV (right, bottom). The ferrocenylethynyl groups are represented in red whereas the ferriciniummethynyl groups are in blue^{48,49}.

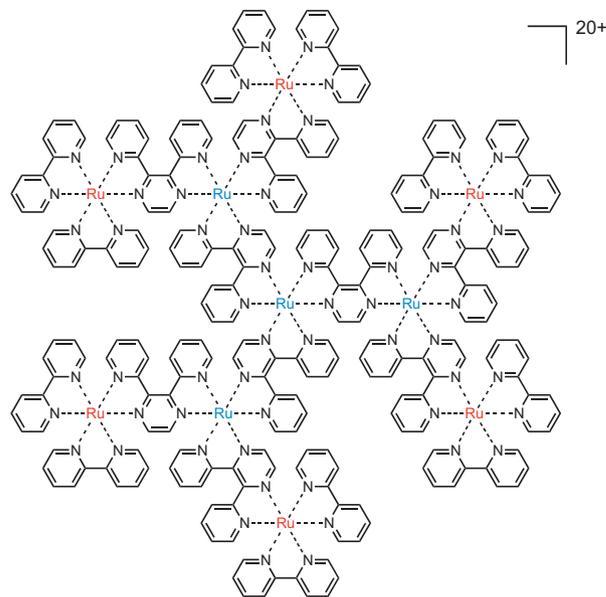
their reduced form is rendered more robust on ring permethylation. These groups have been grafted onto the termini of giant dendrimers mentioned above (featuring up to 14,000 branches) through the monofunctional cyclopentadienyl (C_5H_4R) ligand of pentamethylcobalticinium derivatives. Their CV also shows reversible waves with some electrostatic effects⁵⁸.



Iron sandwich complexes that are non-ferrocenic are also useful. For instance, the bis(hexamethylbenzene)iron sandwich complexes are stable under three oxidation states ($Fe(II)$, d^6 , 18-electron; $Fe(I)$, d^7 , 19-electron, $Fe(0)$, 20-electron)^{59,60}. Such bis(arene)iron complexes are useful for electron-transfer-mediated arene functionalization⁶⁰, and thus may be utilized for dendrimer branching, although no attempt has been made yet.

The most well-known non-ferrocenic iron sandwich complexes belong to the rich cyclopentadienyl-iron-arene series, for which hundreds of complexes have been reported, including the stable 17- to 19-electron complexes $[Fe(\eta^5C_5R_5)(\eta^6-C_6Me_6)]^{n+}$ ($n = 0-2$; $R = H$ or Me)⁶¹⁻⁶⁴. The $Fe(I)$ complexes and their binuclear homologues are genuine 19-electron complexes, because the orbital of the nineteenth electron is mostly metal-based^{65,66}. Indeed, these complexes have very negative redox potentials (down to -2 V versus $FeCp_2^{+/0}$)⁶⁴⁻⁶⁷. They are still the most electron-rich neutral compounds known, based on their extremely low ionization potential values, as disclosed by $He(I)$ photoelectron spectroscopy⁶⁷. Recently, it has been possible to branch the 18-electron cationic form of these electron-reservoir complexes to large dendrimers and to observe the chemical and electrochemical reversibilities of their CV waves. Moreover, the ability of a single molecular dendrimer (19-electron form) to reduce a large number of C_{60} molecules to the radical anion $C_{60}^{\cdot-}$ (one fullerene per dendritic branch) has been shown, indicating their potential function as molecular batteries⁴³ (Fig. 7).

An entirely different approach to the construction of dendrimers led to polymetallic species. Balzani and his group reported^{10,68-70} polypyridine dendrimers containing $Ru(II)$ and $Os(II)$ centres. A dendritic decarthenium complex synthesized by Balzani's group features bipyridine (bpy) and 2,3-dipyridyl-pyrazine as terminal and bridging ligands respectively. Oxidation of the six equivalent peripheral Ru^{2+} centres (in red in the structure below) to Ru^{3+} generates a species containing 26 positive charges. The electrostatic effect of these charges inhibits further oxidation of the inner Ru^{2+} centres (in blue) within the electrochemical window¹¹.



These types of assembly based on the multimetallic complexation of bridging bis(2,3-pyridyl)pyrazine ligands and ancillary bipy termini, can attain large sizes; for example, the largest dendrimer of this kind contained 1,090 atoms — of which 22 were metal centres¹⁰

— had an estimated size of 5 nm and a total charge of +44 (+2 per metal centre). Besides the 22 metal atoms, this dendrimer was composed of 24 terminal ligands and 21 bridging ligands¹⁰. Owing to their multi-metallic nature, these dendrimers provide polyredox properties and were also the first dendrimers to be recognized as light-harvesting species.

These ordered, dendritic ensembles of Ru(II) or Os(II)-based polypyridines⁶⁹ exhibit (i) intense ligand-centred (LC) absorption bands in the UV region and moderately intense metal-to-ligand charge-transfer (MLCT) bands in the visible region, (ii) a relatively long-lived luminescence in the red spectral region, due to the lowest MLCT level, (iii) single reversible one-electron oxidation of each metal ion — (Os(II) is oxidized at a much less positive potential than Ru(II)), and (iv) reversible one-electron reductions of each ligand.

These dendrimers were subjected to variable electronic interaction between neighbouring mononuclear units (for example, for the deca-ruthenium complex shown above, the ruthenium–bipyridine components), which depend on their relative proximity. The absorption spectrum and the electrochemical properties of each dendrimer were often found to be the addition of the spectra and redox patterns of its constituent units, modulated by mutual interactions. The rich cyclic voltammograms of these dendrimers therefore showed cascades of polyelectron transfers, corresponding for the most part to complexes spanning along the oxidation and reduction scales. For instance, in the deca-ruthenium complex, oxidation of the six peripheral Ru(II) ions in a six-electron wave was observed at 1.53 V versus a saturated calomel electrode (SCE) using pulse voltammetry. The electronic connections between these peripheral redox centres is negligible⁶⁹, and this

six-Ru(II)-centred oxidation reaction thus generates a mixed-valence species that bears 18 positive charges. The oxidation of the four remaining inner Ru(II) centres was not observed within this electrochemical window, obviously because of the enormous electrostatic factor that caused a large anodic shift for the oxidation of these centres. When these four inner Ru(II) were replaced by much more easily oxidizable Os(II) centres, a shoulder was observed at 1.35 V versus SCE⁶⁹.

Nanoparticle catalysis

Since the early 1950s it has been known that relatively monodisperse metal nanoparticles can be formed by reduction of transition-metal cation complexes (using NaBH₄) using polymers containing heteroatom ligands as scaffolds⁷¹. In 1998, this concept was extended to dendrimers containing polyamidoamine groups (PAMAM) by Crooks⁷², shortly followed by others^{73–75}. The transition-metal complexes first coordinate to the nitrogen atoms of the PAMAM groups throughout the dendrimer. This holds them in place during the reduction by NaBH₄, and the metal(0) formed then aggregates within the dendrimer, whose growth is therefore limited by steric hindrance caused by the branches, giving monodisperse metal nanoparticles (Fig. 8a). Such nanoparticles (NPs) were called dendrimer-encapsulated NPs (DENs). Palladium DENs stabilized in this way were shown to be catalytically active, and the encapsulating dendrimers — when they were large enough, that is, in generations 4 to 6 of PAMAMs — were also used as a selective filter for the substrates (as discussed below)^{75–82}. Crooks also demonstrated that PAMAM dendrimers bearing hydroxyl or protonated amine termini, can complex metal ions such as Cu²⁺, Pd²⁺, Pt²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Au³⁺ and Ru³⁺. Complexation occurs inside the dendrimers

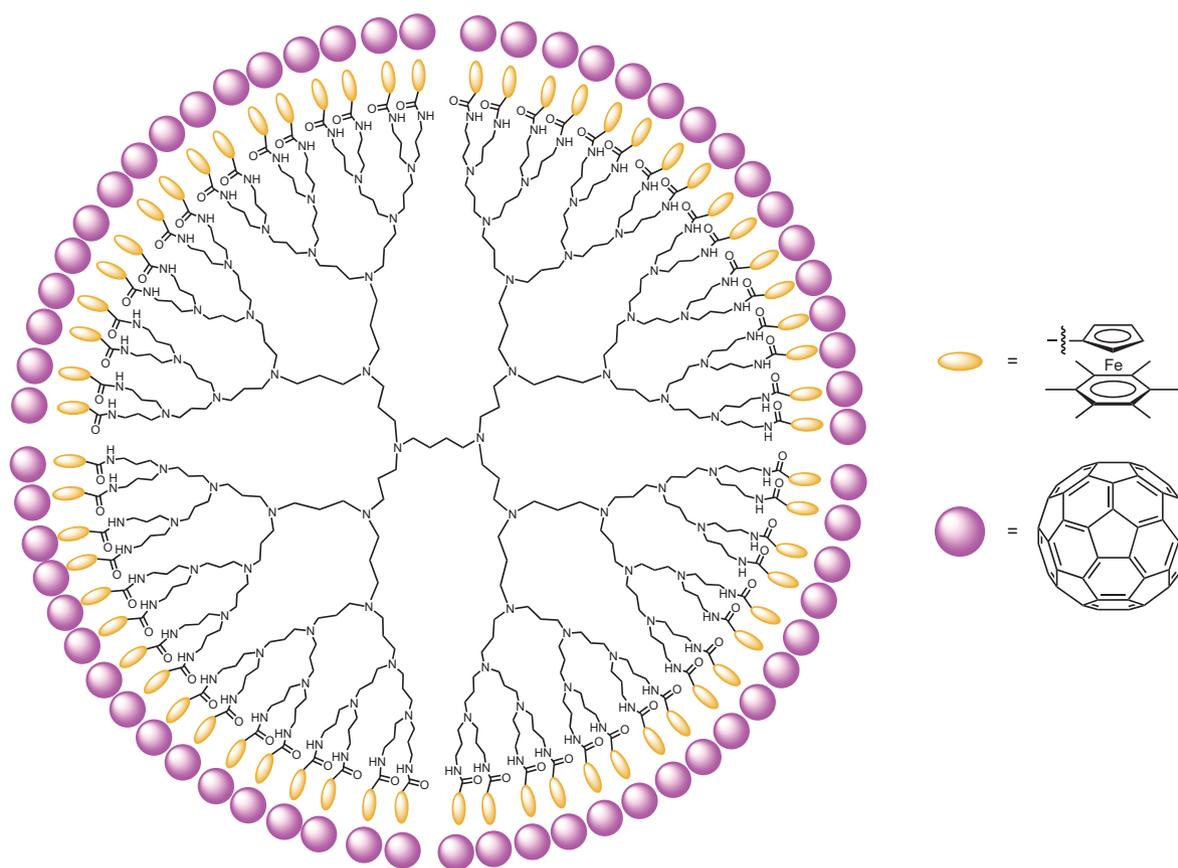


Figure 7 | Dendritic molecular battery for the reduction of C₆₀. In a 64-electron-transfer reaction the G₅-propyleneimine dendrimer — functionalized with 64 19-electron complexes CpFe(η⁵-C₆Me₆) as termini (orange) — reduces 64 equivalents of C₆₀ (purple) in MeCN/toluene to their mono-ionic form, resulting in a 64-NHCO-CpFe(C₆Me₆)⁶⁴⁺, 64 C₆₀^{•-} dendrimer.

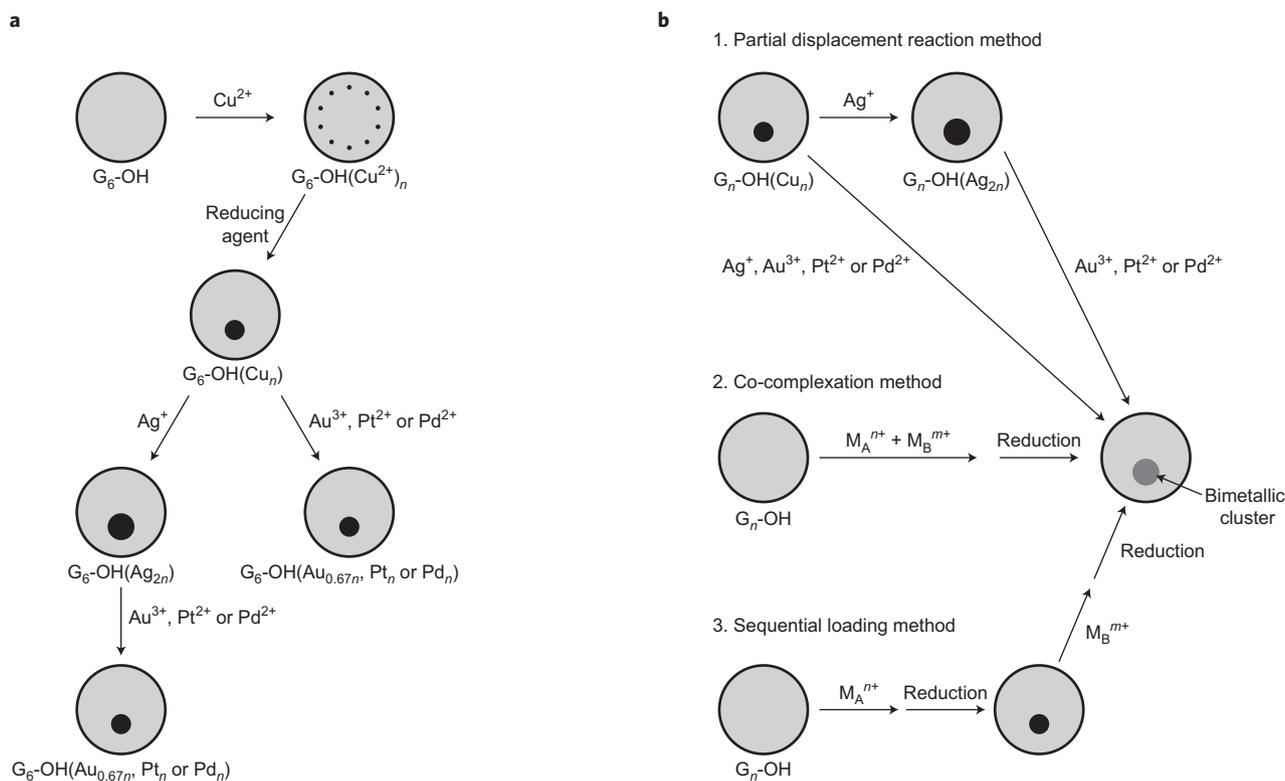


Figure 8 | Crooks's concept of synthesis of DENs with catalytic and materials applications. **a**, Direct reduction of transition-metal complexes of dendritic ligands and galvanic displacement for the synthesis of a variety of DENs (black spheres), here shown schematically for a six-generation PAMAM dendron (grey spheres) bearing hydroxyl groups as termini. **b**, Three different strategies enable the synthesis of heterobimetallic core-shell DENs. The dendrimers are represented as greyed large spheres, the nanoparticles as small black spheres, for clarity purposes. Reproduced with permission from ref. 78. © 2001 ACS.

only, because the ammonium or hydroxyl groups located at the dendrimer periphery cannot bind these transition-metal cations. Subsequent reduction by NaBH_4 of Cu^{2+} and Pt^{2+} incorporated within various PAMAM dendrimers led to DENs⁷⁶.

For several ions for which the complexation between metal centres and the dendrimers was not strong enough, such as Ag^+ , it was astutely demonstrated that dendrimer-encapsulated monodisperse NPs can still be produced, using a 'supporting' redox reaction from Cu-encapsulated PAMAM dendrimers, for instance according to: $\text{Cu} + 2 \text{Ag}^+ \rightarrow \text{Cu}^{2+} + 2 \text{Ag}$. This so-called galvanic redox displacement also enabled the formation of DENs with Au^{3+} , Pt^{2+} and Pd^{2+} , because the standard reduction potentials (E°) of these ions are more positive than that of Cu^{2+}/Cu . Remarkably, this method was also extended to the synthesis of heterobimetallic DENs when a sub-stoichiometric amount of oxidizing ions such as Pd^{2+} , Pt^{2+} , Au^{3+} or Ag^+ was used with a sixth-generation PAMAM dendrimer bearing hydroxyl groups at its periphery, yielding PdCuNPs, PtCuNPs, AuCuNPs or AgCuNP DENs respectively^{75,76} (Fig. 8a).

Catalysis with DENs was pioneered by Crooks in 1999 with Pd and Pt DENs complexed to OH-terminated PAMAM dendrimers (G_4 to G_8) for the hydrogenation of allylic alcohol and *N*-isopropylacrylamide in water. The $G_4\text{-OH Pd}_{40}\text{NP}$ was found to be much more efficient than the G_6 and G_8 DENs, because the latter serve as nanofilters, inhibiting to some extent the penetration of the *N*-isopropylacrylamide substrates inside the dendrimer in which the catalytically active NP is located. On the other hand, linear alkenes penetrate more easily, resulting in a much smaller decrease in activity⁷⁷. This catalytic area extended to nitroarene reduction and PdNP-catalysed cross carbon-carbon coupling reactions such as the Miyaura-Suzuki and Heck reactions in various media such as perfluorinated solvents and supercritical CO_2 ,

A remarkable sophistication involved the use of heterobimetallic core@shell DENs such as Au@Pd NPs. Figure 8b shows three different strategies devised to construct such hetero-bimetallic DENs, which were subsequently found to be more efficient than mononuclear Pd DEN catalysts due to synergistic electronic effects^{75,76,79}.

Dendrimers have been constructed by 'click' chemistry — a fast, convenient Cu(I)-catalysed cycloaddition between an azide and an alkyne moiety that forms a five-membered 1,2,3-triazole ring. The dendritic branches thus feature a layer of triazole rings for each generation, including at their periphery. The dendrimers can coordinate metal ions at each 1,2,3-triazolyl layer, and ferrocenyl termini can also be grafted at the periphery through covalent bonding to the peripheral triazole groups. Such click metallodendrimers bearing ferrocenyl termini have been shown to electrochemically sense both anions (for example oxo anion ATP^{2-}) and metal cations (such as Cu^+ , Cu^{2+} , Pd^{2+} and Pt^{2+}) using the {triazole-ferrocenyl} recognition site^{83,84}.

Such palladium 'click' metallodendrimers, for example, have also been reduced to yield DENs (with G_1 and G_2) or, when the dendrimer is too small (G_0) to encapsulate the nanoparticles, dendrimer-stabilized palladium NPs. Reduction of transition-metal-cation-dendrimer complexes by NaBH_4 to Pd DENs is straightforward, but the resulting catalytic activity is limited by the side reaction of boride formation, which inhibits the surface reactivity of the PdNPs. Indeed, it was observed that reduction of click-dendrimer-stabilized Pd^{2+} complexes by methanol instead provided much more catalytically active PdNPs for olefin hydrogenation and Miyaura-Suzuki cross-coupling reactions⁸⁴⁻⁸⁶. Likewise, the reduction of Au^{3+} complexes of click dendrimers terminated by triethylene glycol fragments by the electron-reservoir complexes $[\text{Fe}(\eta^5\text{-C}_5\text{Me}_5)_2]$ and $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\eta^6\text{-C}_6\text{Me}_6)]$ yielded monodisperse AuNPs for which the size was

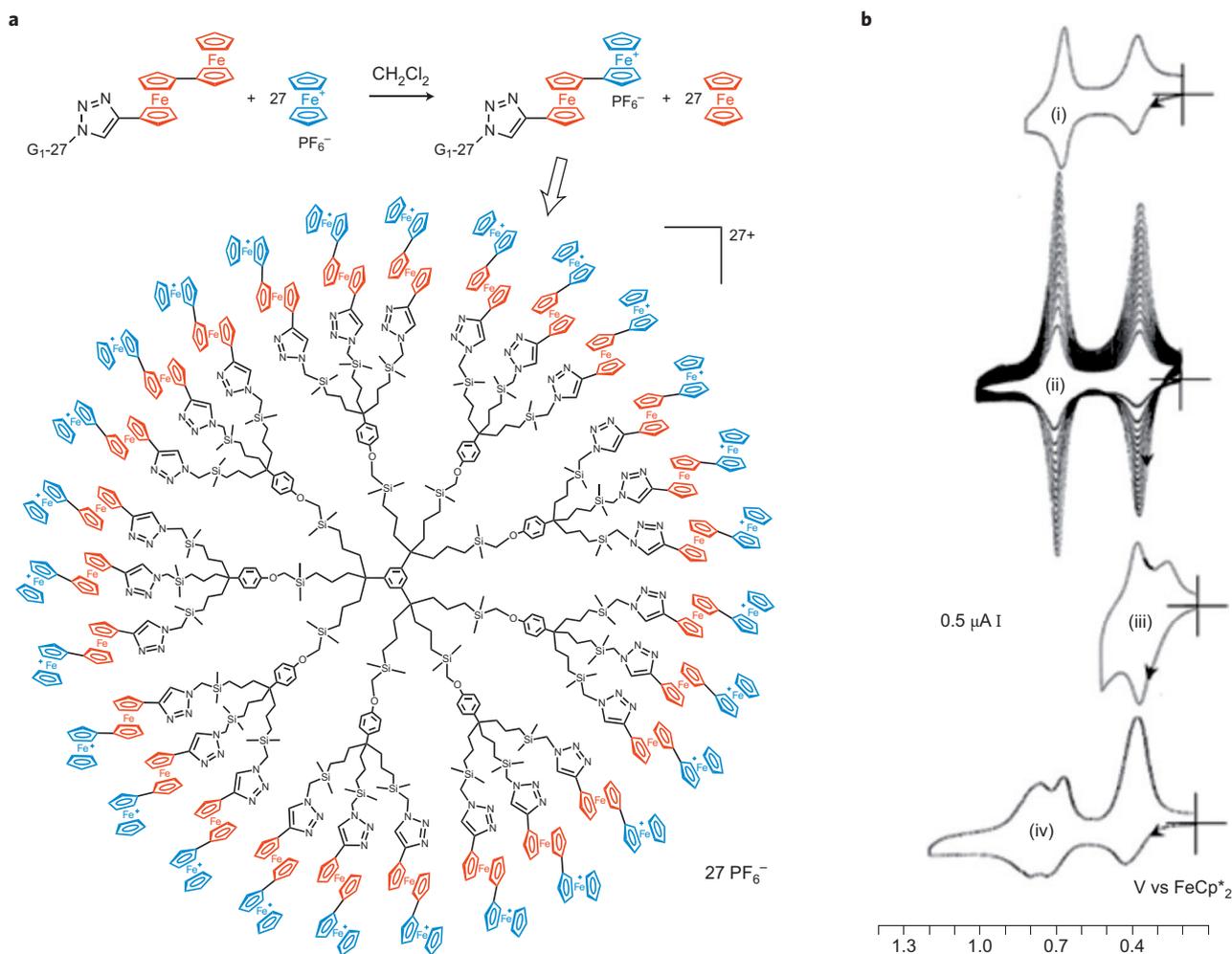


Figure 9 | Biferrocenyl dendritic redox sensors for both metal cations and oxo-anions. **a**, Selective oxidation of the outer ferrocenyl groups of the G_1 dendrimer using ferricinium. Ferrocenyl groups are represented in red and ferricinium groups in blue⁹². **b**, Cyclic voltammograms of the G_2 -81 biferrocenyl dendrimer and specific roles of the outer and inner ferrocenyl groups in transition-metal cation- and oxo-anion redox sensing: (i) CV in dichloromethane, $[N(n\text{-Bu})_4][PF_6]$ 0.1 M; (ii) progressive adsorption upon scanning around the potential of the biferrocenyl area; (iii) splitting of the outer-ferrocenyl CV wave at 0.4 V on addition of oxo anion ATP; (iv) addition of $Pd(OAc)_2$ provoking the splitting of the inner-ferrocenyl wave at 0.7 V.

controlled by the reduction potential of the electron-reservoir complex. When the terminal triethyleneglycol groups were integrated in Percec-type (Fig. 1b) tripodal dendrons⁸⁷, reduction in water could even proceed in the absence of external reductant.

This is due to the fact that the Au^{3+} ions complexed by such dendrons were strong enough oxidants in themselves to oxidize the polyethers of the dendrons, and thus form stabilized monodispersed gold nanoparticles⁸⁸. Thus, this method of reduction with electron-reservoir complexes may be usefully applied to the clean synthesis of gold nanoparticles of medicinal or catalytic use.

Assemblies of DENs can also be deposited physically or chemically on electrodes to serve as electrocatalysts. Electrocatalysis is indeed a promising property of surfaces modified with redox-active dendrimers⁸⁹. For instance, Au DENs were immobilized on a glassy carbon electrode. An atom-thick shell of copper was first added to the gold core by electrochemical underpotential deposition, and subsequently replaced with platinum by galvanic exchange. The resulting Au@Pt electrocatalyst was also more efficient for oxygen reduction than its monometallic analogues⁸⁹.

Dendrimer catalysis is a very broad field involving a variety of approaches that are not discussed here⁵, but, for instance, redox-active dendrimers functionalized with heteropolyanions for catalytic oxidation of substrates were pioneered by Newkome's group⁹⁰.

In another example, surface properties of multilayer films based on a Ru^{2+} metal dendrimer and the mixed Dawson heteropolyanion were more recently shown to be active for electrocatalytic reduction of iodate⁹¹.

Redox sensors

The specific topology of dendrimers inherently involves denser peripheral packing as the generation number increases, which narrows the inter-branch channels and favours tight contacts between hosts and guests for the recognition process. In this way, dendrimers containing recognition sites at their periphery mimic viruses and behave as exo-receptors.

Before such studies with dendrimers, Beer's group had demonstrated the use of endo-receptors attached to metallocenes — such as cryptands, calixarenes and others — for the recognition of anions based on the combination of electrostatic, supramolecular (such as H-bonding) and topological (encapsulation) effects⁹². In a seminal report on dendrimer sensing, it has been reported that amidoferrocenyl-terminated dendrimers could function as redox sensors, that is, exo-receptors for the recognition of oxo-anions. A strong positive dendritic effect was observed, in which the recognition capability increased with dendrimer generation. This effect arises because the potential shift of the ferrocenyl wave, observed by CV

on addition of the salt of the anion into the electrochemical cell, increased with increasing dendrimer generation. This in turn has a topological effect on the dendrimer branches, which on increasing in number define a narrow inter-branch spacing that leads to better recognition, and in turn sensing ability⁹³.

Other dendrimers were also found to give rise to a positive dendritic effect: cobalticinium-terminated dendrimers also showed good redox sensing properties for oxo-anions^{5,37}. Later, it was also shown that gold-nanoparticle-cored dendrimers terminated by silylferrocenyl groups were excellent redox sensors for oxo-anions including ATP⁹⁴, as are the click (triazolyl-ferrocenyl-terminated) metallodendrimers mentioned above^{83,84}. In 2010, triazolylbiferrocenyl-terminated dendrimers (Fig. 9) were also found to behave as redox sensors for both transition-metal cations such as Pd(II) with their inner ferrocenyl groups and for oxo-anions such as ATP with the outer ferrocenyl groups. These dendrimers constructed with 1→3 connectivity were available until G₄ (that is, bearing a theoretical number of redox termini of 729), although adsorption onto Pt electrodes for derivatization was already excellent for generation 2⁹⁵. The specific roles of the outer and inner ferrocenyl centres during the redox sensing of oxo anions (ATP) can be followed by CV (Fig. 9b shows the CV waves for the dendrimer G₂, which bears 81 biferrocenyl termini).

The derivatization of electrodes with redox systems has long been known⁹⁶ and has been utilized by the groups of Casado, Losada and Abruña to immobilize dendrimers on the surface of electrodes^{97–99}. Ferrocenyl-terminated dendrimers, among others, were studied using an electrochemical quartz crystal microbalance, and shown to adsorb onto a platinum electrode surface. At a potential of 0.0 V versus SCE, where the ferrocenyl sites are in the reduced form and the dendrimers are therefore neutral, dendrimers present in solution adsorb onto the electrode — the thermodynamics were well-characterized by the Langmuir adsorption isotherm.

This adsorption allowed derivatization of electrodes with ferrocenyl dendrimers, which proved useful for sensing⁹⁸. Fixation of dendrimers onto metal surfaces is indeed all the easier as these metallodendrimers are larger, and also presents the advantage of recycling, because the modified electrode is robust enough to retain its dendrimers even on washing⁹⁴. The use of adsorbed ferrocenyl dendrimer as biosensors, pioneered by the groups of Losada and Casado for glucose titration using glucose oxidase¹⁰⁰, has increased^{101–103}, including for DNA and protein detection^{94,104–106}. The principle relies on the measurement of the intensity of redox-catalytic electrochemical waves of the chemically and electrochemically reversible Fe(III)/Fe(II) redox system that mediates the (otherwise slow) electron transfer between the electrode and the enzyme. The intensity of this wave is proportional to the quantity of analyte in solution. Surface-adsorbed ferrocenyl dendrimers have also proved useful for other sensing applications, including for CO sensing¹⁰⁷, and gold electrodes modified with redox-active polythiophene dendrimers were also reported to sense carcinogenic polycyclic aromatic hydrocarbons through their electrocatalytic oxidation¹⁰⁸.

Dendritic molecular printboards

A promising field at the interface between electrode surfaces, redox-active dendrimers and nanoparticles is that of molecular electronics on surfaces. When gold nanoparticles were deposited over ferrocenyl dendrimer layers, and a self-assembled monolayer consisting of six ferrocenyl hexanethiol groups was built onto the gold surfaces, electrochemical communication with the ferrocene groups still occurred, possibly through pinholes in the dendrimers array¹⁰⁹. Reinhoudt's group has remarkably demonstrated the use of ferrocenyl and biferrocenyl dendrimer–cyclodextrin assemblies at the interface of an aqueous solution as molecular printboards^{110–115}. The dendrimers form a stable monolayer at the cyclodextrin self-assembled monolayer owing to multivalent host–guest interactions. The

immobilization of the dendrimers at the cyclodextrin self-assembled monolayer can be under electrochemical control because ferrocene forms stable inclusion complexes with cyclodextrin, whereas ferricinium does not.

Organic dendrimers

Fully organic dendrimers can also contain redox sites at their cores, on the branches or at the periphery, such as viologen, pyrene or tetrathiafulvalene (TTF) derivatives. With dendrimers containing inner viologen groups, complete charge pooling was prevented due to the electrostatic effect^{116,117}. The methylviologen-cored G₁, G₂ and G₃ dendrimers that bear Fréchet-type dendrons could be hosted by a molecular tweezer, which comprised a naphthalene moiety and four benzene components bridged by four methylene units. The assembly/disassembly process could be monitored by fluorescence and electrochemical measurements¹¹⁸. Distinction between the anodic CV waves of inner and peripheral redox centres was also observed for poly(aryl)amine dendrimers for which the electrostatic effect creates a gradient of oxidation processes¹¹⁹.

Other organic redox species have also served to endow dendrons with electrochromic properties: the group of Gingras, Ceroni and Balzani reported dendrimers with a polysulfurated pyrene core whose reversible monoelectronic oxidation produced a deep-blue radical cation¹²⁰. In several other examples of redox centres buried deep inside dendrimers, however, the redox activity of the core was too slow to be observable¹²¹. Finally, the Bryce group and others have developed the synthesis and electrochemistry of TTF dendrimers in which the TTF units are located at the core or periphery, as well as their materials properties as π -electron donors with charge and electron-transfer interactions including sensing applications. Each TTF unit undergoes two single-electron oxidations, thus these organic dendrimers exhibit multi-electron transfer properties¹²².

Conclusion and prospects

Electron transfer — the most elementary chemical reaction, widely occurring in biological systems^{1,25,26} and materials^{2,3,123,124} — is revealed to be efficient and versatile in nanoscience. This is especially true in nanosystems involving redox dendrimers, because the nature and topology of these macromolecules allows scientists to precisely locate redox sites and study the electron-transfer parameters. The increasing sophistication of the engineering of the interface between solids and redox dendrimers has recently appeared as a very promising research area, and will lead to improved applications in surface patterning, sensing and materials science including nanobatteries and electrocatalysis. Not only electron-transfer, but also charge transfer^{122,125} should accommodate such applications.

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Acknowledgements

I am grateful to the colleagues and students cited in references for their ideas and hard work that have greatly contributed to our research on electron-transfer processes in dendrimers and their applications, and to financial assistance from the Universit   Bordeaux 1, the Centre National de la Recherche Scientifique and the Agence Nationale pour la Recherche.

Additional information

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