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Redox Active, Hybrid Dendrimers Containing Fréchet- and Newkome-Type Blocks

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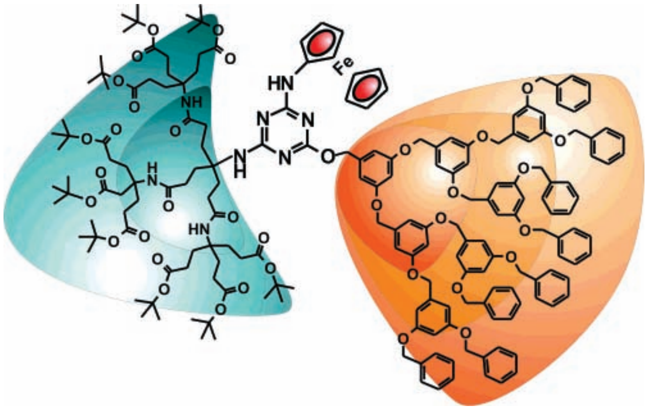
ABSTRACT



A new series of dendrimers was prepared by covalently attaching a Newkome dendron, a Fréchet dendron, and a redox active, aminoferrocene group to a central triazine core. Growth of the Newkome dendron has a more pronounced effect on the half-wave potential for the one-electron oxidation of the ferrocene residue than growth of the Fréchet dendron. All dendrimers show reversible or quasireversible voltammetric behavior at scan rates in the range 0.10–2.0 V s^{-1}.

The design of dendrimer macromolecules has advanced considerably in the past few years. Using the wide diversity of dendritic architectures developed to date, several groups have designed, prepared, and characterized dendrimers with various components in an attempt to endow the resulting macromolecules with suitable drug encapsulation/delivery, gene delivery, amphiphilic, and other properties. Some illustrative examples of this work are the amphiphilic block codendrimers prepared by Gallani and co-workers,[1] the amphiphilic dendrimers reported by Diederich's group,[2] and Imae's amphiphilic surface-block dendrimers,[3] among others.[4] Our work with dendrimers has focused on a general design based on the attachment of redox,[5] fluorescent,[6] or hydrogen bonding[7] units to the focal point of AB$_3$ Newkome-type, ester-terminated dendrons with amide connections between generational layers. We have also prepared and

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(1) Bury, I.; Donnio, B.; Gallani, J.-L.; Guillon, D. *Langmuir* **2007**, *23*, 619.

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(4) (a) Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137. (b) Yamamoto, K.; Higuchi, M.; Shiki, S.; Tsuruta, M.; Chiba, H. *Nature* **2002**, *415*, 509. (c) Maraval, V.; Laurent, R.; Merino, S.; Caminade, A. M.; Majoral, J.-P. *Eur. J. Org. Chem.* **2000**, 3555.

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investigated several series of AB_2 Fréchet-type, aromatic ether dendrimers containing 4,4′-bipyridinium (viologen) units.[5b,8] In this work, we take advantage of the sequential reactivity of the triazine nucleus to combine in the same macromolecule (1) a Fréchet dendron,[9] (2) a Newkome dendron,[10] and (3) a redox active residue, such as ferrocene, leading to novel dendritic frameworks that permit the convenient fine-tuning of the properties of the redox active unit. The specific dendrimer structures discussed here are shown in Figure 1.

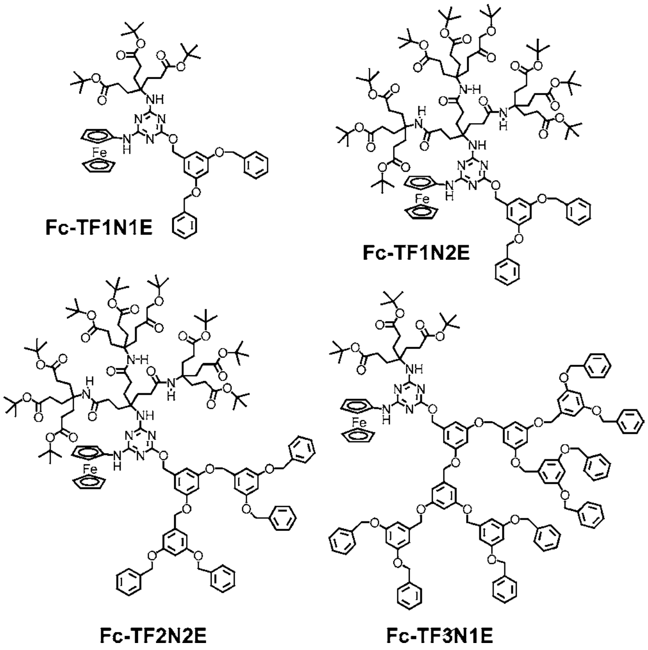
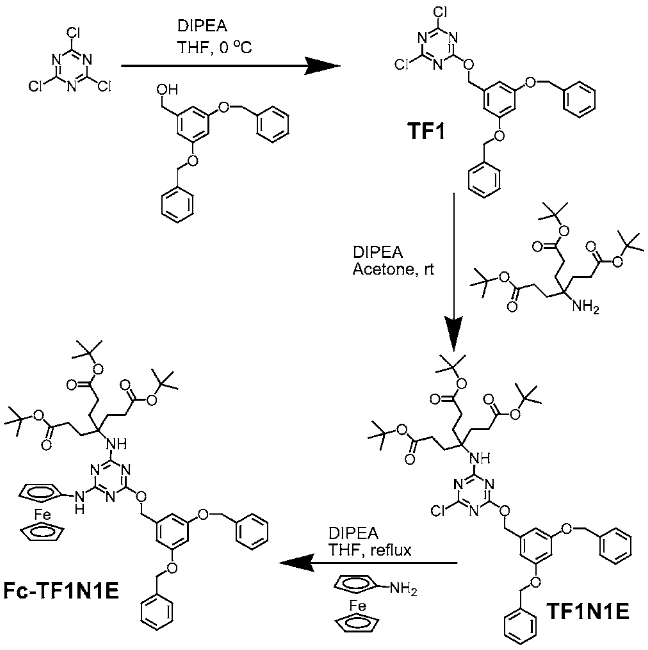


Figure 1. Structures of the hybrid dendrimers reported in this work. The naming system describes the building blocks present in each compound around the triazine nucleus (**T**): **Fc**, ferrocenyl; **F#**, generation number of the Fréchet dendron; **N#E**, ester-terminated generation number of the Newkome dendron.

Scheme 1. Synthetic Steps for the Preparation of Dendrimer **Fc-TF1N1E**[a]



[a] DIPEA = diisopropylethylamine.

The preparation of these dendrimers relies on the differential reactivity of trichlorotriazine (cyanuric chloride) in successive nucleophilic substitution steps. As shown by the groups of Simanek[11] and Wang[12] it is possible to direct the substitution of one, two, or three of the chloro substituents by controlling the temperature of the reaction. First, we reacted cyanuric chloride with 3,5-dibenzyloxybenzyl alcohol (first generation Fréchet dendron or **F1**) at 0 °C in THF to produce the ether **TF1** in 53% yield (Scheme 1). Similar reactions with the second or third generation Fréchet dendrons yield the corresponding ethers **TF2** (61% yield) and **TF3** (43% yield). Reaction of **TF1** with Behera's amine in acetone (2 days at room temperature) led to the isolation of the compound **TF1N1E** (64% yield), which contains first generation Fréchet and Newkome dendrons attached to the triazine core. Again, replacement of Behera's amine by its second or third generation analogues would result in the attachment of the selected amine building block (Newkome dendrons **N2E** or **N3E**) to the triazine core. Finally, treatment of **TF1N1E** with aminoferrocene[13] in dry refluxing THF produces in 2 days a reaction mixture from which the redox active compound **Fc-TF1N1E** was isolated (61% yield) after column chromatography.

All new compounds were characterized with ^{1}H and ^{13}C NMR spectroscopy and either MALDI TOF or FAB mass spectrometry (see the Supporting Information). The NMR spectra of all compounds in which at least one amine is covalently attached to the triazine nucleus shows evidence for the existence of rotamers.[14] This phenomenon has been described already and results from the partial double bond character of the covalent bond between the amine nitrogen and the carbon atom on the triazine core. For instance, at 25 °C the ^{1}H NMR spectrum of **Fc-TF1N1E** shows three different signals for the NH proton in the amine connection between the triazine nucleus and the Newkome dendron, two different signals for the NH proton connected to the ferrocene residue, and three signals for the two adjacent protons on

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(8) (a) Toba, R.; Quintela, J. M.; Peinador, C.; Roman, E.; Kaifer, A. E. *Chem. Commun.* **2001**, 857. (b) Toba, R.; Quintela, J. M.; Peinador, C.; Roman, E.; Kaifer, A. E. *Chem. Commun.* **2002**, 1768.

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the cyclopentadienyl ring of ferrocene, which is directly connected to the triazine nucleus through the −NH− amine group (Figure 2). The splitting of all these resonances clearly reflects the presence of rotamers. Increasing the sample temperature leads to coalescence of each of these signals into broad singlets at ca. 55 °C and gradual sharpening of each of the singlets at higher temperatures (Figure 2).

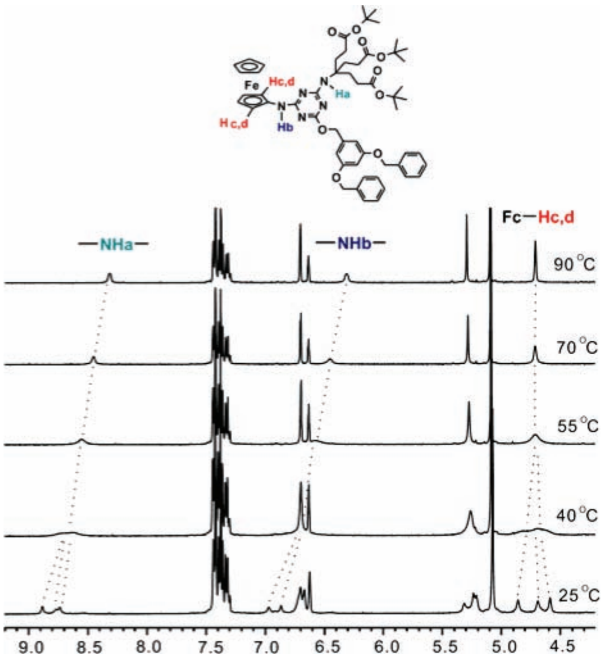

Figure 2. Partial ^{1}H NMR (400 MHz, DMSO-d_6) spectra of **Fc-TF1N1E** at variable temeperatures.

The diffusion coefficients of the hybrid dendrimers were measured by using PGSE NMR techniques[15] in $CDCl_3$, CD_2Cl_2, CD_3CN, and DMSO-d_6 solutions (see Table 1). For each of the dendrimers the diffusion coefficient vs reciprocal solvent viscosity plot is linear, suggesting that each macromolecule maintains an approximately constant hydrodynamic radius in the four solvents surveyed.[16] The corresponding radii (r_H) are given in the last row of Table 1 and generally show the expected trend to increase as larger dendrons are connected to the triazine core. However, the dendrimer with the largest molecular weight (**Fc-TF2N2E**) was found to have a hydrodynamic radius smaller than that of **Fc-TF3N1E**, which suggests that the Newkome dendrons tend to adopt more collapsed structures around the dendrimer core, while the Fréchet dendrons tend to expand out away from the core.

Table 1. Molecular Weights, Diffusion Coefficients ($D_o \times 10^6$ cm^2/s) at 25 °C and Hydrodynamic Radii (r_H, nm) of the Hybrid Dendrimers

	FcTF1N1E	**FcTF1N2E**	**FcTF2N2E**	**FcTF3N1E**
M.W.	1012	2036	2460	2285
$D_o(CDCl_3)^a$	6.36	4.71	4.44	4.22
$D_o(CD_2Cl_2)^a$	8.58	6.24	5.79	5.45
$D_o(CD_3CN)^a$	10.8	7.44	7.38	6.37
$D_o(DMSO)^a$	1.64	1.12	1.22	1.06
r_H (nm)^b	0.49	0.70	0.73	0.83

[a] Measured by PGSE NMR techniques in the indicated solvent. [b] Obtained from D_o vs reciprocal solvent viscosity plots.[16]

The electrochemical behavior of these compounds is also of considerable interest. In the past, we have investigated the electrochemistry of ferrocenyl residues covalently attached to the Newkome dendrons used in this work.[5a] In those dendrimers the ferrocenyl group was directly attached (via an amide linkage) to the focal point of the Newkome dendron. In CH_2Cl_2 solution, the half-wave potentials for the one-electron oxidation of the ferrocene center were found to shift to less positive values as the size of the dendron increased. The displacement of the half-wave potentials is rationalized as the result of the balance between the polarities of the bulk solution and that of the inner phase of the Newkome dendrimers, which is essentially determined by the amide groups. Thus, dendron growth leads to a more polar microenvironment for the ferrocene residue, thermodynamically favoring the formation of positive charge, which is consistent with the observed potential shifts. On the other hand, Fréchet dendron growth has a smaller effect on the redox potentials. For instance, the half-wave potential for the one-electron reduction of viologen-containing dendrimers in acetonitrile solution was found to shift moderately to less negative values with increasing size of the attached Fréchet dendrons,[8] suggesting that the dendrimer inner phase is less polar than the bulk solution. Similarly moderate shifts on the half-wave potential for ferrocene oxidation were observed by Thayumanavan and co-workers with their unsymmetric biaryl phenolic dendrimers.[17]

The combination of both types of dendritic building blocks in the dendrimers surveyed here opens interesting questions regarding their relative effects on the half-wave potential for the one-electron oxidation of the ferrocenyl residue. The recorded voltammetric potential data are given in Table 2.

In dichloromethane solution the growth of the attached Newkome dendron has a marked effect on the half-wave potential, which shifts toward less anodic values. For instance, the replacement of a first generation by a second generation Newkome dendron (from **Fc-TF1N1E** to **Fc-TF1N2E**) causes an anodic shift of 54 mV in the half-wave potential. In comparison to this, the replacement of a first generation by a third generation Fréchet dendron (**Fc-TF1N1E** to **Fc-TF3N1E**) has basically no effect on the $E_{1/2}$ value. In the more polar CH_3CN solutions the effect of dendron replacements on the observed potential values is

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(15) Cohen, Y.; Avran, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520.

(16) The Stokes−Einstein equation [$D_o = kT/(6\pi\eta r_H)$] was used to obtain the hydrodynamic radii (r_H) from the D_o vs η^{-1} plots.

(17) Jayakumar, K. N.; Bharati, P.; Thayumanavan, S. *Org. Lett.* **2004**, *6*, 2547.

much less pronounced, because the polarity of the bulk solution is closer to that of the inner phase of the Newkome dendrons.[5b] Increasing the size of the Fréchet dendrons led again to minimal changes in the observed potential values. This is in agreement with some of the diffusion coefficient data (vide supra) and suggests that the Fréchet dendrons expand as wedges away from the core and have little effect on the microenvironment around the ferrocene center. Overall, the Newkome dendrons appear to be considerably more effective than the Fréchet dendrons at changing the microenvironment surrounding the redox active ferrocene residue. This is probably a consequence of their AB_3 architectural framework and greater flexibility, which allows them to wrap around the ferrocene center in a more effective way.

In the range of scan rates surveyed (0.1−2.0 V s^{-1}) the voltammetric behavior of all these dendrimers falls in the reversible to quasireversible range. At scan rates in the lower end of the range, the behavior is essentially reversible and the measured peak-to-peak splitting (ΔE_p) between the anodic and the cathodic voltammetric peaks is less than 70 mV for all these dendrimers. At faster scan rates, the ΔE_p values increase (see Figure 3), as anticipated for quasireversible electron-transfer processes. Therefore, Nicholson's method[18] can be employed, in conjunction with the diffusion coefficient values previously measured with PGSE NMR techniques, to determine the corresponding standard rate constants ($k°$) for the heterogeneous electron-transfer processes in CH_2Cl_2 solution. The resulting values are given in Table 2. In dichloromethane solution the $k°$ values decrease as the molecular size of the dendrimer increases, as observed before in most dendrimers containing a redox active center at their cores.[19] In acetonitrile solution the voltammetric behavior in all cases was too close to full reversibility and the accurate determination of the rates of electron transfer was not possible by Nicholson's method.

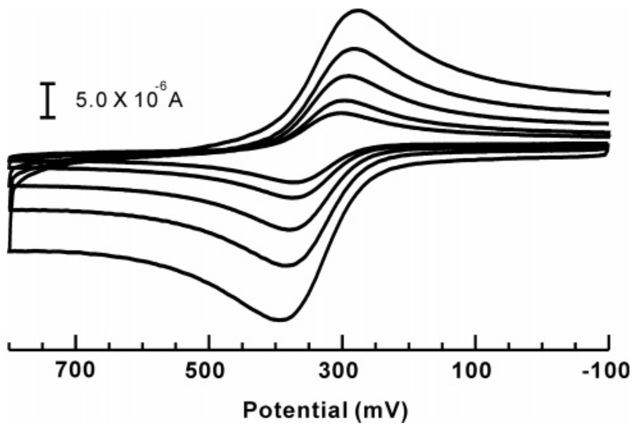

Figure 3. Cyclic voltammetric response on glassy carbon (0.071 cm^2) of a 1.0 mM solution of **Fc-TF2N2E** in 0.2 M $TBA^+PF_6^-/CH_2Cl_2$. Scan rates: 0.1, 0.2, 0.5, 1.0, and 2.0 V s^{-1}.

Table 2. Half-Wave Potentials ($E_{1/2}$, mV vs Ag/AgCl) and Standard Rate Constants ($10^3k°$, cm s^{-1}) at 25 °C for the One-Electron Oxidation of the Ferrocene Group in the Hybrid Dendrimers of Figure 1

	FcTF1N1E	FcTF1N2E	FcTF2N2E	FcTF3N1E
$E_{1/2}(CH_2Cl_2)^a$	372 ± 2	318 ± 2	335 ± 1	376 ± 3
$E_{1/2}(CH_3CN)^a$	317 ± 3	309 ± 3	307 ± 1	318 ± 1
$k°\ (CH_2Cl_2)^a$	86 ± 15	46 ± 8	18 ± 2	26 ± 5

[a] Data obtained in the indicated solvent also containing 0.2 M tetrabutylammonium hexafluorophosphate.

In summary, we have developed a reliable synthetic methodology to combine a Fréchet dendron, a Newkome dendron, and a redox active ferrocene center around a triazine core. The resulting hybrid molecules constitute the first reported dendrimers that contain both Fréchet and Newkome blocks. In this work we also report the relative effects exerted by these two important types of dendritic blocks on the microenvironment of the ferrocene center.

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Supporting Information Available: Complete synthetic details and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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