Synthesis and Properties of Redox-Active Dendrimers Containing Phenothiazines

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In memory of Annemarie Christensen

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A new family of redox-active dendrimers based on a poly(propylene imine) core with phenothiazines as the redox active unit have been prepared, and some of their properties have been investigated.

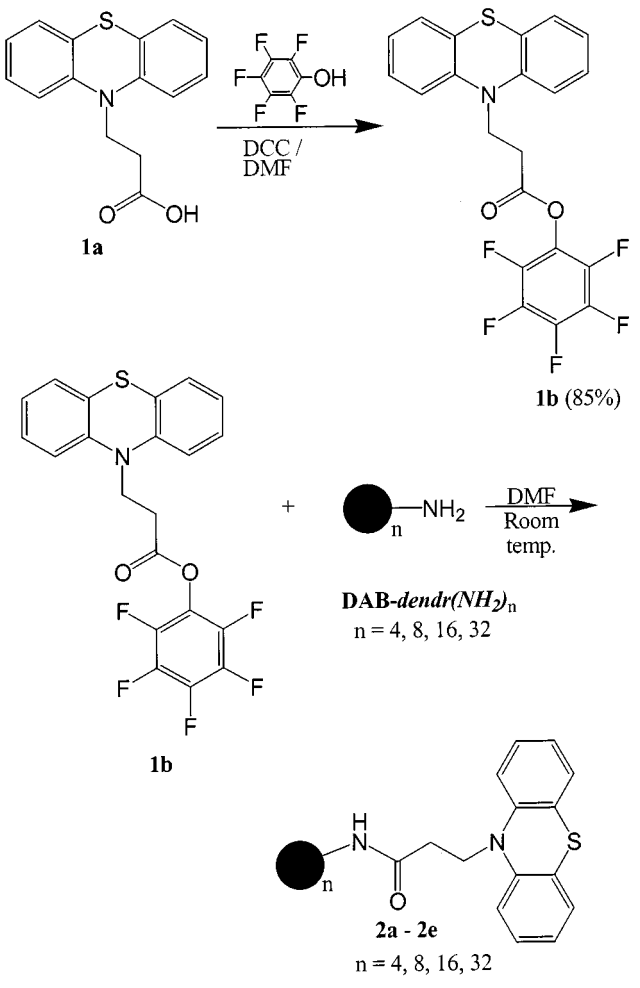
Introduction

In the field of materials science the concept of developing all-organic based materials with properties ranging from semiconductivity to superconductivity has proven to be extremely fruitful, the basic idea being to use overlapping π-electrons in open-shell electron systems instead of the s, p and d electrons available in an inorganic metal in the solid state to form the necessary conduction band.[1]

Considering the utility and diverse behavior of metal clusters the logical step would be to prepare and study all-organic based clusters consisting of organic subunits with an open shell electron system, organized in a suitable manner. The vast majority of organic molecules are closed-shell systems, and the simplest way of getting organic open electron shell systems is to use redox active molecules that can subsequently either be oxidized or reduced under controllable conditions. The most efficient way of organizing a large number of redox active subunits, without having to rely on possible self-organization or self-assembly, is to utilize the concept of dendritic growth.

Dendrimers are the common name of the family of highly branched discrete macromolecules. The idea of building polymers by repetitive branching is old and goes back to the work by Flory.[2] However it was not before the work by Vögtle[3] on "cascade synthesis", Tomalia's[4] PAMAM dendrimers, Newkome's[5] arborols, Balzani's multinuclear Ru/Os complexes[6] and Frechet's[7] wedges that the concept of dendritic growth was used to make discrete macromolecules. The field of dendrimers is evolving rapidly as evidenced by a number of recent reviews.[8–11]

Although redox-active dendrimers have attracted increasing interest in recent years,[12–14] only a few non metal-containing systems are known.[13–17] We were interested in studying the properties and applications of organic metal



Scheme 1. Synthesis of the compounds **1b**–**2e**

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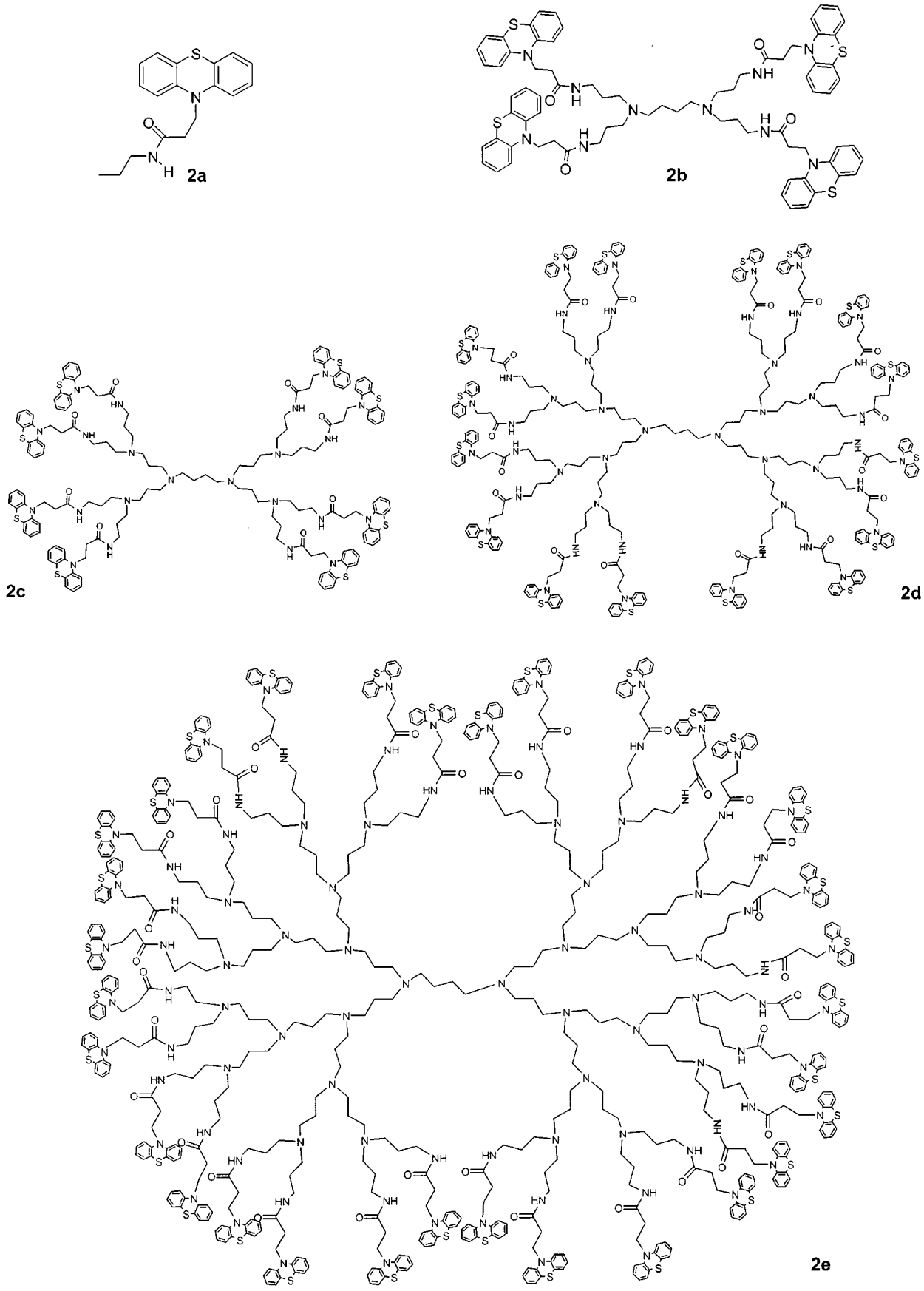

Figure 1. The phenothiazine substituted dendrimers synthesized

clusters, and as an initial step we decided to look at a simple system consisting of a family of dendrimers modified with redox-active end groups. The poly(propylene imine) dendrimers[17] [abbreviated DAB-*dendr*$(NH_2)_x$ in the following] were chosen as the dendritic unit. Phenothiazine was the choice for the redox active unit because it has a well-defined electrochemistry and a known history in the study of redox active polymers[19−21] and light harvesting systems.[22,23]

The derivative used in this work was 3-(10-phenothiazinyl)propionic acid (**1a**),[24] which was attached to the dendrimers through an amide bond. This derivative was used because it has proven useful as a mediator in an electrochemically based glucose sensor,[25] and as a mediator for various oxido-reductases of industrial interest;[26] hence our dendrimers could find applications in sensing or electrocatalysis. Furthermore the redox properties can be modified by appropriate substitution in the skeleton without affecting the chemistry necessary for attaching the phenothiazine to the dendrimer. In this work we want to present our results on the synthesis, characterization and properties of these compounds.

Results and Discussion

Poly(propylene imine) dendrimers are close to, but not completely, monodisperse macromolecules, and start to contain a small number of defect sites from generation 3 (DAB-*dendr*$(NH_2)_{16}$].[27] These defects are secondary amines formed either by a retro-Michael addition of acrylonitrile or by reductive ring closure of two arms to form an *N*-monoalkylated 1,5-diazacyclooctane during the synthesis (for a detailed analysis see ref.[27]).

Model studies of simple linear polyamines completely acylated with **1a** showed that the phenothiazine units in such systems are strongly interacting,[28] and we decided to synthesize the completely acylated dendrimers in order to see if the phenothiazine group could be used to probe the defect sites. Initial experiments on acylation of DAB-*dendr*$(NH_2)_{16}$ with the known *N*-hydroxysuccinimide ester[22] of **1a** showed that complete acylation did not take place.[29] The pentafluorphenyl ester derivative (**1b**) proved to be more reactive, and was used for the acylations as shown in Scheme 1. The dendrimers prepared are shown in Figure 1.

IR spectroscopy is very suitable for studying hydrogen bonding, and the IR spectra of the dendrimers **2b**−**2f** in CH_2Cl_2 solution are shown in Figure 2. The spectra show two absorptions in the region 3500−3200 cm^{-1}. The first absorption, at 3440 cm^{-1}, is assigned to unbound amide protons and the second absorption around 3360 cm^{-1} is due to hydrogen-bonded amide protons. The slightly decreasing absorption at 3440 cm^{-1} combined with the increasing and red-shifted absorption at 3360 − 3250 cm^{-1} is indicative of stronger hydrogen bonding taking place upon going to a higher generation of the dendrimers and thus an increased number of amide groups at the surface of the dendrimer.

The ^1H NMR spectra of the dendrimers **2b**−**2f** has some interesting features. Figure 3 shows a combined plot of the chemical shifts for the different types of protons as function of generation (= number of end groups). The chemical shift of the core protons in the 1,4-butandiamine center ($NCH_2-CH_2CH_2-CH_2N$), in particular, is influenced by the presence of the phenothiazine groups at the surface of the dendrimers. The effect is largest for generation 1 and 2, and levels off at higher generations, thus excluding acylated

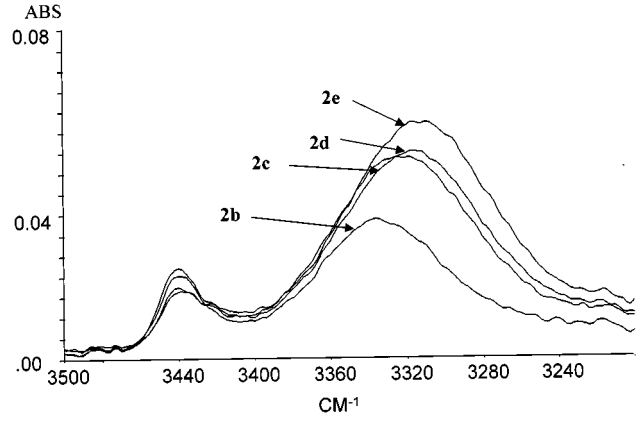

Figure 2. IR spectra of **2b**−**2e** recorded in CH_2Cl_2 solution; concentration: 25 mM (based on end groups)

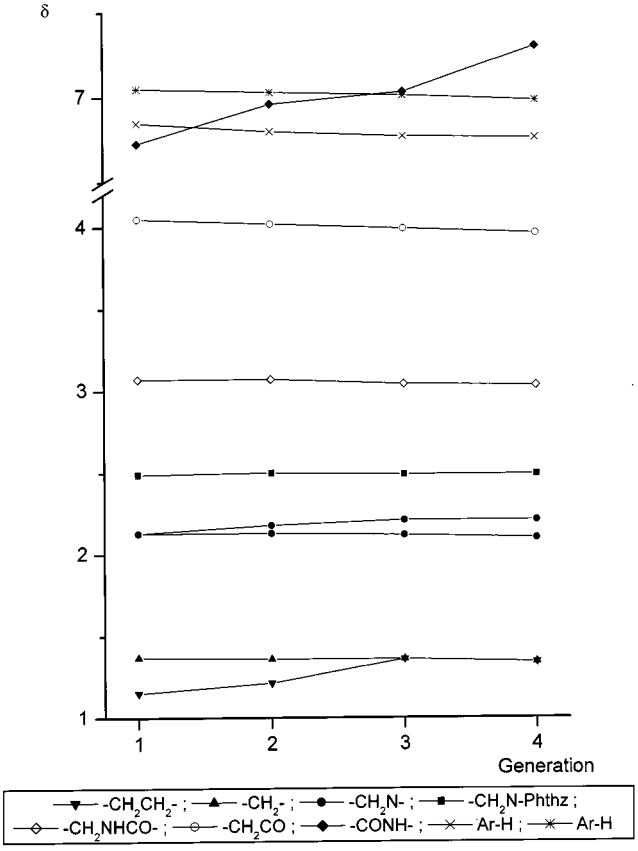

Figure 3. Plot of the ^1H NMR chemical shifts as a function of dendrimer generation; recorded in $CDCl_3$ at 333 K; concentration: 25 mM (based on end groups)

defect sites as the cause, since defects are only present from generation 3 and above. Comparing ^{1}H NMR spectroscopic data from other acylated poly(propylene imine) dendrimers indicates that the observed shift is a downfield shift because the normal chemical shift for these protons is $\delta = 1.4$.[30] There are two possible explanations for this phenomenon: (i) The phenothiazine end groups are folding back into the dendrimer in the lowest generations causing shielding of the core protons by the π-system, similar to the behavior seen for the bridge protons in 9,10-methanoannulene.[26] At the same time there is a competing hydrogen bond formation at the surface of the dendrimer, and this interaction gains importance on going to higher generations, placing the phenothiazines outside the dendritic shell. This is reflected in the up field shift of the amide protons and the lack of downfield shifts of the other protons above generation 3. (ii) The lower generations of the dendrimers are forming aggregates, where the phenothiazine end groups are in close vicinity of the core in neighboring molecules, thus causing the π-system shielding observed.

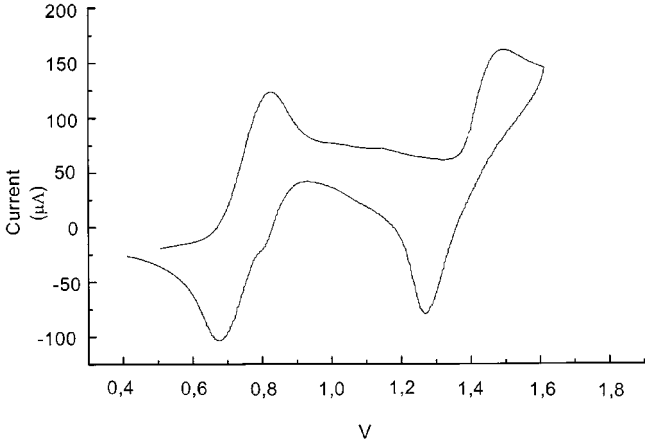

Figure 4. Cyclic voltammogram of compound **2a**; for details see Table 1

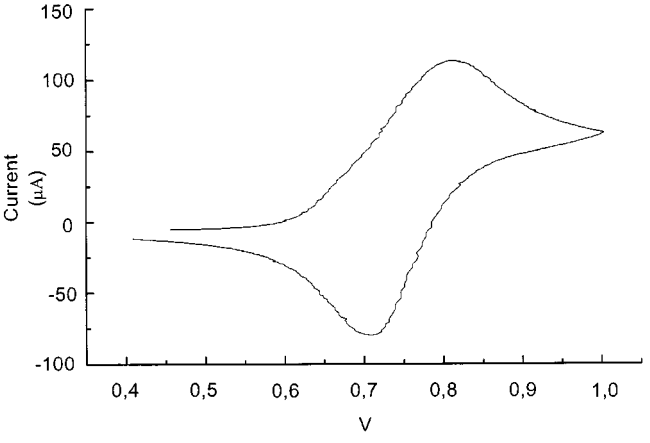

Figure 5. Cyclic voltammogram of compound **2b**; for details see Table 1

Preliminary cyclic voltammetry experiments were performed in CH_2Cl_2 solution. The CV curve for the model amide **2a** is shown in Figure 4. The compound undergoes two oxidations corresponding to the formation of the +1 and +2 states. Coulometry was performed, and we were able to show that the oxidation at 0.293 V vs. Fc/Fc^+ is a one-electron process giving the $1^{+\cdot}$ ion. On going to the dendrimers (**2b**−**2f**), the picture changes slightly. A typical CV curve is shown in Figure 5. Only one oxidation wave is observed, and attempts to oxidize further leads to degradation apparently due to severe Coulomb repulsion between the individual phenothiazine-radical cations. The oxidation potentials are collected in Table 1, and they are very similar for all generations. Combining the NMR results with the electrochemical data suggests that the redox properties are not greatly affected by the closer proximity in the higher generations. Coulometry was attempted in order to see whether all phenothiazine groups were oxidized. However, massive absorption of the dendrimers at the electrode surface occurs irrespective of the solvent used, and we were thus not able to unambiguously demonstrate that all units are oxidized.

Table 1. E^0 values for compounds **2a**−**2e**; Pt versus Fc/Fc^+ measured in CH_2Cl_2 containing 0.1 M Bu_4NPF_6; scan rate: 0.2 V/sec; concentration: 0.15−2.2 mM

Compound	E_1^0 (V)	E_2^0 (V)
2a	0.293	1.05
2b	0.280	–
2c	0.291	–
2c	0.279	–
2d	0.280	–
2e	0.280	–

Conclusion

A new family of redox-active phenothiazine containing dendrimers has been synthesized and characterized. IR and ^{1}H NMR spectroscopy suggests that there is either a distinct difference in tertiary structure between lower and higher generations, with the phenothiazine end groups backfolding into the interior of the dendrimers in the lower generations, or the presence of very stable aggregates, where the end groups are in close proximity to the neighboring molecule cores. The phenothiazine group shows the expected two oxidation states in a model compound, but, upon attachment to the dendrimers, only one oxidation state is observed due to severe Coulomb repulsion between the oxidized units.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were obtained using a Varian Gemini 300 NMR or a Varian Unity 400 NMR. Mass spectra were obtained using a Jeol JMS-HX 110 A Tandem Mass Spectrometer or a Voyager-DE (Perceptive Biosystems) Mass Spectrometer. IR spectra were recorded on a Perkin−Elmer 1605 Series FT. All melting points are uncorrected. The elemental analysis was performed

by Mrs. Karin Linthoe, Department of Organic Chemistry, University of Copenhagen. All chemicals were used as received.

Pentafluorophenyl 3-(10-Phenothiazinyl)propionate (1b): 3-(10-Phenothiazinyl)propionic acid (**1a**; 9.30 g, 34 mmol) and pentafluorophenol (7.60 g, 41 mmol) were dissolved in DMF (150 mL). DCC (7.00 g, 34 mmol) was added and the mixture was stirred at room temperature overnight. The formed DCU was removed by filtration, and the crude product precipitated by addition of water. Crystallization of the wet material from 2-propanol gave 12.70 g (85%) of white crystals. M.p. 121−123 °C. − $C_{21}H_{12}F_5NO_2S$ (437.38): calcd. C 57.67, H 2.77, N 3.20; found C 57.43, H 2.95, N 3.12. − MS (EI): *m*/*z*: 437 [M^+], 362, 344, 212, 180, 152, 109. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (m, 4 H), 4.35 (m, 2 H), 6.90 (m, 4 H), 7.20 (m, 4 H).

***N*-(1-Propyl) 3-(10-Phenothiazinyl)propionamide (2a):** 1-Propylamine (1 mL, 12 mmol) was added to a solution of **1b** (1.40 g, 3.2 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred overnight, washed with 1 M NaOH (3 × 20 mL), and 1 M HCl (3 × 20 mL) and dried over Na_2SO_4. The CH_2Cl_2 was removed in vacuo, and the crude material crystallized from 2-propanol to give 0.38 g (38%) of the amide. M.p. 131 − 133 °C. − $C_{18}H_{20}N_2OS$ (312.43): calcd. C 69.20, H 6.45, N 8.97, S 10.26; found C 69.03, H 6.45, N 8.87. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, 3 H), 1.31 (m, 2 H), 2.55 (m, 2 H), 3.04 (m, 2 H), 4.10 (m, 2 H), 6.03 (broad s, 1 H), 6.94 (m, 4 H), 7.16 (m, 4 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 22.5, 34.2, 41.1, 43.3, 115.6, 122.9, 125.6, 127.4, 127.6, 144.6, 170.7. − MS: *m*/*z* = 312 [M^+], 282, 270, 253, 225, 212, 198, 180, 154, 127, 114, 106.

General Procedure for the Acylation of the Dendrimers: To a solution of DAB-*dendr*$(NH_2)_4$ (250 mg, 0.79 mmol) in DMF (10 mL) was added **1b** (1.52 g, 3.5 mmol). The reaction mixture was stirred at room temperature overnight. The flask was covered with aluminium foil to protect the reaction mixture against light. Next day, the mixture was poured into water (100 mL) and made slightly basic by addition of 2 M NaOH (this induces the precipitation of the crude product). The mixture was filtered and washed with water. The crude material was dissolved in DMF (50 mL) and precipitated by slow addition of 2 M NaOH (50 mL). This treatment was repeated, even though the product separates as a gum after the initial precipitation. Finally the product was dissolved in CH_2Cl_2, washed with water and dried over Na_2SO_4. The solvent was removed in vacuo, although we found that, in order to get rid of all the solvent, it was important to conduct the concentration in such a way that the dendrimer forms a foam towards the end of evaporation. This foam was further dried in vacuum (40 °C/0.01 Torr) for 2 days. Appearance: Yellow foams or yellow glassy materials.

DAB-*dendr*$(NHCOCH_2CH_2Ptz)_4$ (2b): Yield: 1.05 g (98%). − $C_{76}H_{84}N_{10}O_4S_4$ (1329.8): calcd. C 68.64, H 6.37, N 10.53; found C 67.92, H 6.39, N 10.79. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (m, 4 H), 1.37 (m, 8H), 2.13 (m, 12 H), 2.49 (q, *J* = 7 Hz, 8 H), 3.07 (t, *J* = 6 Hz, 8 H), 4.05 (t, *J* = 7 Hz), 6.73 (t, *J* = 5 Hz, 4 H), 6.85 (m, 16 H), 7.05 (m, 16 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.1, 43.3, 115.5, 122.8, 125.1, 127.4, 127.5, 144.6, 170.9. − FAB-MS: *m*/*z* = 1329.8 [M^+].

DAB-*dendr*$(NHCOCH_2CH_2Ptz)_8$ (2c): Yield: 1.70 g (96%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (m, 4 H), 1.36 (m, 24 H), 2.13 (m, 36 H), 2.18 (m, 20 H), 2.50 (t, *J* = 7 Hz, 16 H), 3.07 (q, *J* = 6 Hz, 16 H), 4.02 (t, *J* = 7 Hz, 16 H), 6.80 (m, 32 H), 6.96 (t, *J* = 7 Hz, 8 H), 7.03 (m, 32 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.7, 26.5, 33.8, 37.6, 43.2, 51.0, 51.6, 51.8, 115.3, 122.5, 124.7, 127.2, 127.2, 144.4, 170.8. − $C_{160}H_{184}N_{22}O_8S_8$ (2799.8): calcd. C 68.64, H 6.62, N 11.01; found C 67.92, H 6.39, N 10.79. − FAB-MS: *m*/*z* = 2799.7 [M^+]

DAB-*dendr*$(NHCOCH_2CH_2Ptz)_{16}$ (2d): Yield: 1.29 g (75%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (m, 60 H), 2.12 (m, 50 H), 2.21 (m, 34 H), 2.49 (m, 32 H), 3.04 (m, 32 H), 6.77 (m, 64 H), 7.01 (m, 64 H), 7.03 (broad s, 32 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 33.9, 37.6, 43.4, 51.1, 53.3, 115.4, 122.6, 124.8, 124.9, 127.4, 144.6, 170.9. − $C_{328}H_{392}N_{46}O_{16}S_{16}$ (5748.0): calcd. C 68.64, H 6.88, N 11.23, found C 68.10, H 6.71, N 11.07. − MALDI-TOF: *m*/*z* = 5740 [M^+]. − FAB-MS: *m*/*z* = 5739.8 [M^+].

DAB-*dendr*$(NHCOCH_2CH_2Ptz)_{32}$ (2e): Yield: 0.68 g (68%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (m, 124 H), 2.10 (m, 180 H), 2.50 (m, 64 H), 3.01 (m, 64 H), 6.77 (m, 128 H), 6.99 (m, 128 H), 7.30 (broad s, 32 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 31.3, 33.9, 36.3, 37.6, 43.3, 51.1, 115.3, 122.6, 127.3, 144.6, 162.0,171.0. − $C_{664}H_{784}N_{94}O_{32}S_{32}$ (11620): calcd. C 68.63, H 6.80, N 11.33; found C 67.73, H 6.70, N 11.14. − MALDI-TOF: *m*/*z* = 11620 [M^+].

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