Towards a Selective Functionalization of Amino-Terminated Dendrimers

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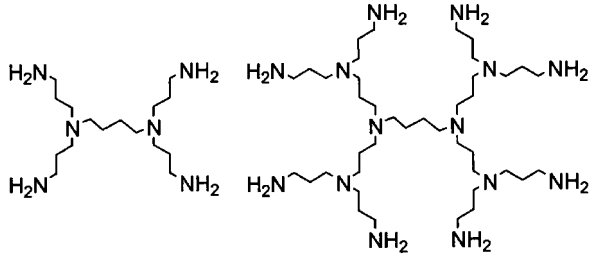
Selective functionalization of the periphery of commercial polypropyleneamine (POPAM) and polyamidoamine (PAMAM) dendrimers has been investigated in preparative scale. The first generation (G1) POPAM dendrimer was for the first time selectively *N*,*N*-bis(sulfonylated) with tosyl chloride and the corresponding mono-, di-, tri-, and tetra-*N*-tosylsulfonamides were isolated and fully characterized. Unexpectedly, similar persulfonylation of G2 POPAM results in splitting of a central C–N bond and only fully and partially sulfonylated halves of the initial dendrimer could be isolated. Higher generations of POPAM are also split during the persulfonylation yielding complex mixtures of persulfonylated dendritic fragments which could hardly be identified. A plausible mechanism of the POPAM decomposition on the basis of the reaction product analysis is proposed. *N*-Sulfonylation of a peripheral octasulfonamide of G2 POPAM with tosyl chloride also leads to the destruction of the dendrimer, while its *N*-alkylation with benzyl bromide proved to be not selective yielding a completely alkylated derivative. Unlike POPAM dendrimers, PAMAM dendrimers were shown to be more stable during their sulfonylation and no decomposition of the dendritic backbone was detected. In contrast to the POPAM dendrimers, PAMAM dendrimers were shown to be rather inert with respect to the formation of *N*-tosylsulfonamides since they could only be *N*-monosulfonylated at all peripheral amino groups. The combination of MALDI-TOF and ESI-FT-ICR tandem mass spectrometry has been shown to be an effective method for structure assignment and purity check of selectively or fully persulfonylated dendritic oligoamines.

Introduction

Control over the peripheral functionalization of biological and synthetic macromolecules constitutes a considerable challenge. In order to introduce or to amplify stability, solubility, adsorption, catalytic activity, photophysical properties and chemical reactivity of the macromolecules, their surface modification is usually performed by means of covalent or supramolecular chemistry. Preparation of unnatural DNA[1] and DNA complexes with positively charged polymers,[2] solubilization of carbon nanotubes[3] as well as selective functionalization[4−6] and hydrolytic activation[7] of dendrimers exemplify the macromolecular surface alteration. Selective peripheral functionalization of dendritic molecules having a well-defined constitution and a perfect shape is of high importance, because dendrimer research is currently associated with numerous technological and biomedical applications such as coatings and films,[8] in vivo contrast agents in X-ray and magnetic resonance imaging,[9] gene transfection agents,[7,10] materials for antibodies and inhibitors of nonspecific protein adsorption.[11] Additionally, selectively derivatized dendrimers and dendrons are important subunits for the preparation of more elaborate macromolecular assemblies − "dendritic networks".[6,12] With a few exceptions, the functionalization of dendritic species is usually restricted to the complete functionalization at each of the peripheral groups. Commercially available polypropylene amine dendrimers (POPAM)[13] such as **1** and **2**, and polyamidoamine dendrimers (PAMAM)[14] such as **3** belong to the most frequently studied branched species and numerous reports on POPAM and PAMAM dendrimers decorated with various functional groups can be found in



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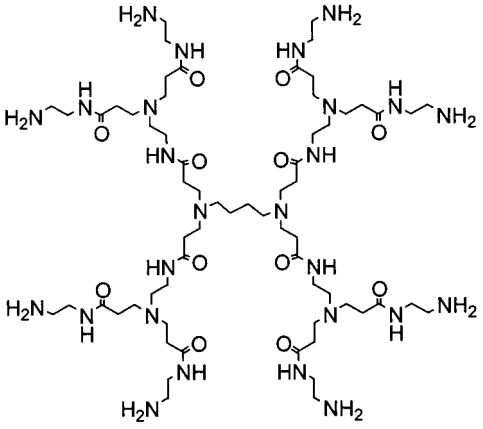

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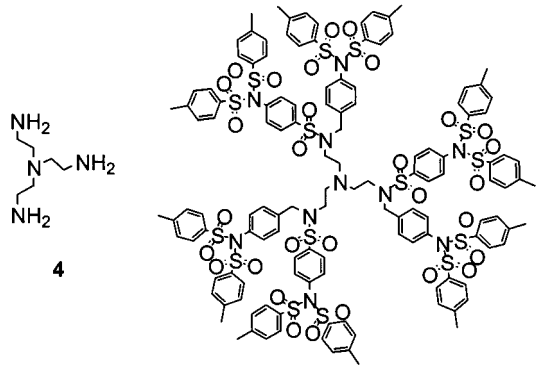

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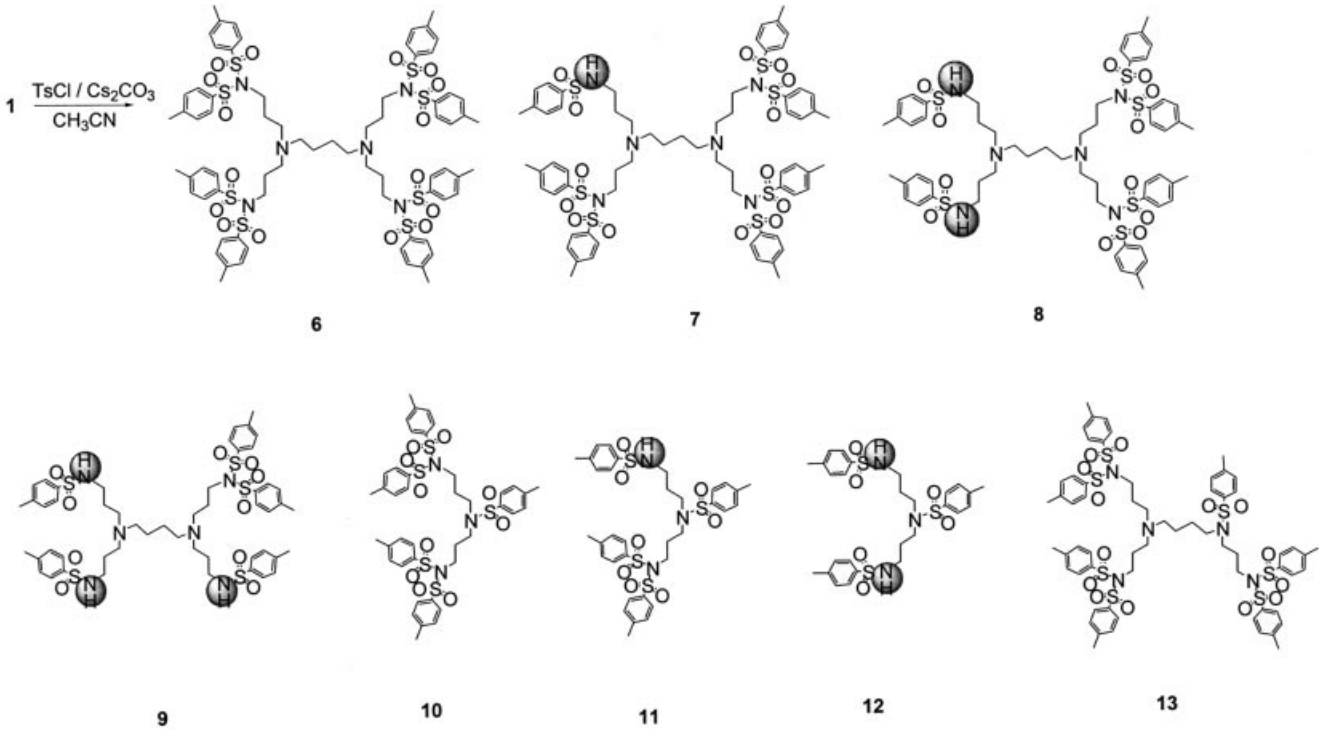
the literature. For example, Meijer et al. have attached urea functions to the periphery of POPAM dendrimers and studied their guest-binding affinities in solutions and in the gas phase,[15] while our group has been successful in functionalizing POPAM dendrimers of various generations with photoactive units.[16]

We have recently described an efficient method for the controllable selective functionalization of low-molecular weight dendritic oligoamines via *N*,*N*-bis(sulfonylation).[5] The latter method is an important synthetic innovation, because it represents a simple one-pot procedure while formerly described procedures for preparations of aliphatic *N*-alkylsulfonamides consisted of two synthetic steps.[17] Our new procedure was tested with tris(2-aminoethyl)amine (**4**) and shown to be sequence specific and regioselective.[5] We also demonstrated that aromatic oligoamines can be efficiently one-pot persulfonylated yielding thus a novel type of *N*-alkylsulfonamide-decorated dendrimers such as **5**. Herein, we expand the concept of selective perfunctionalization towards higher molecular weight dendritic species such as POPAM and PAMAM dendrimers.

Results and Discussion

a) Functionalization of POPAMs: Reactions of POPAM dendrimers of first and second generations with tosyl chloride carried out in acetonitrile in the presence of caesium carbonate are outlined in Scheme 1 and Scheme 2, respectively. Sulfonylation of the first generation POPAM dendrimer **1** gives rise to a mixture of *N*-tosylsulfonamides

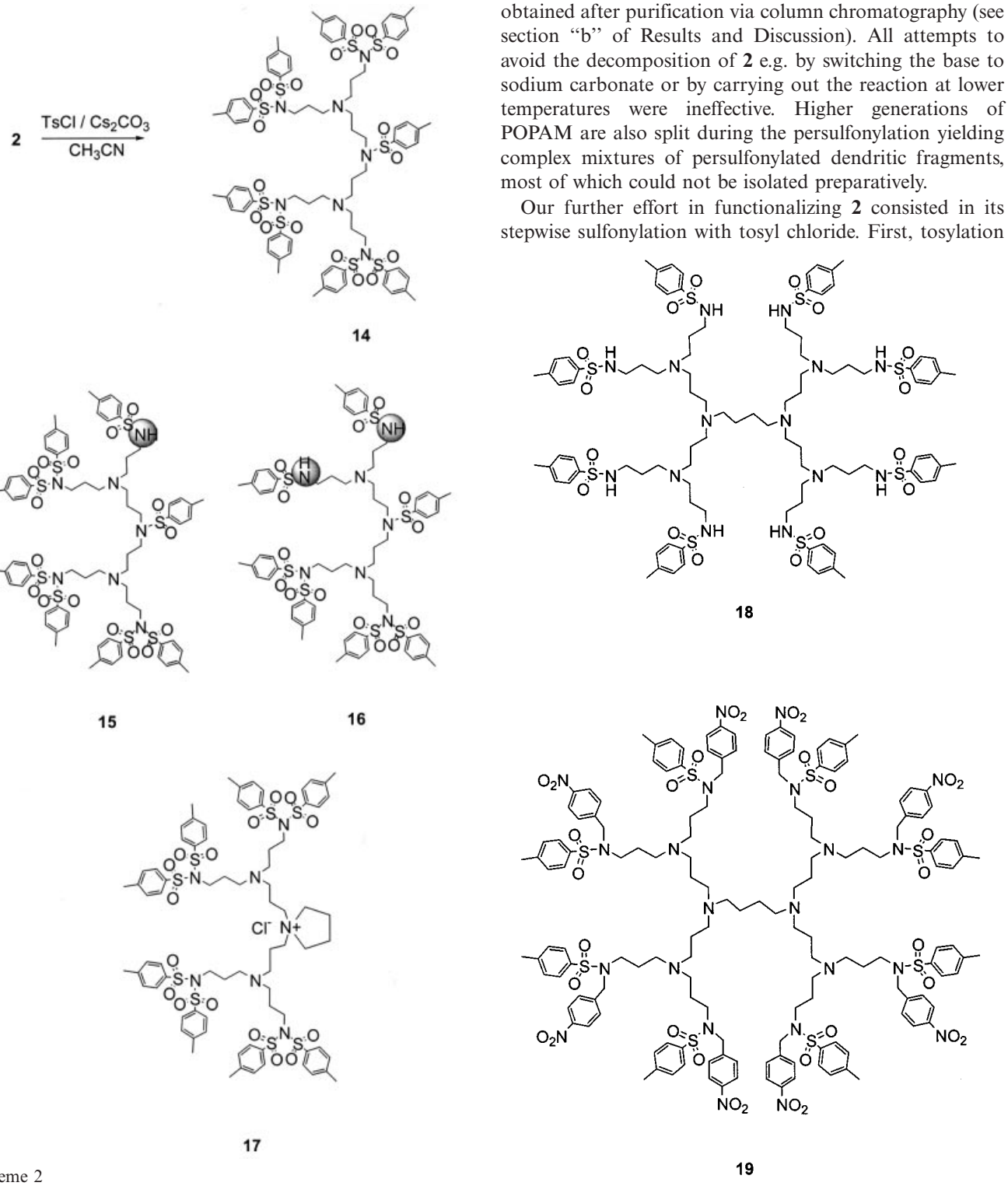


Scheme 1

6−**13**. The latter *N*-tosylsulfonamides were completely separated and purified with the aid of conventional column chromatography on silica gel (see Exp. Sect.). Besides *N*-tosylsulfonamides **6**−**9** which were desirable products of selective persubstitution of dendrimer **1**, compounds **10**−**12** were unexpectedly obtained in an overall yield of 30%. Isolation of **13** was afforded with the aid of HPLC, since it cannot be separated from persulfonylated dendrimer **6**. Compound **13** isolated in a less than 1% yield originates from an impurity in the commercial POPAM that was formerly detected by Meijer et al.[13] by means of size exclusion chromatography.

Astonishingly, analogous sulfonylation of the second generation POPAM dendrimer **2** with tosyl chloride as shown in Scheme 2 does not yield detectable amounts of expected products of complete or partial persubstitution. Only completely or partly persulfonylated "halves" **14**−**17** could be obtained after purification via column chromatography (see section "b" of Results and Discussion). All attempts to avoid the decomposition of **2** e.g. by switching the base to sodium carbonate or by carrying out the reaction at lower temperatures were ineffective. Higher generations of POPAM are also split during the persulfonylation yielding complex mixtures of persulfonylated dendritic fragments, most of which could not be isolated preparatively.

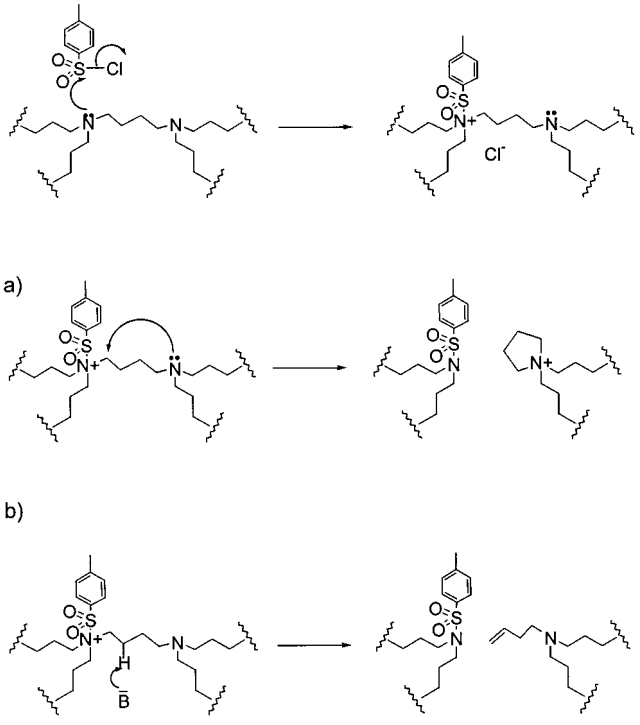
Our further effort in functionalizing **2** consisted in its stepwise sulfonylation with tosyl chloride. First, tosylation



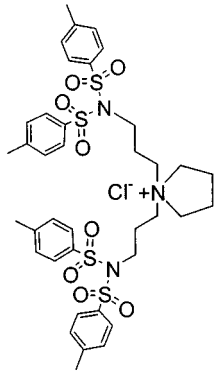
Scheme 2

of **2** in the presence of triethylamine afforded octasulfonamide **18**. Further sulfonylation of **18** in the presence of caesium carbonate, however, resulted again in the complete splitting of the dendrimer into two halves and only the products shown in Scheme 2 could be detected. On the other hand, alkylation of **18** with *p*-nitrobenzyl bromide proved to be nonselective yielding octa-*N*-alkylated octasulfonamide **19** as the single product.

b) Mechanism of POPAM Dendrimer Decomposition: The type of POPAM dendrimer decomposition described above can be associated with two mechanisms as depicted in Scheme 3. As shown there, the initial attack of the most nucleophilic central tertiary amine on the sulfur atom of tosyl chloride produces an acylium-type intermediate that can either undergo an internal attack on the carbon atom nearest to the positive charge by the second central nitrogen (Scheme 3, a) or experience a Hoffmann-type elimination producing an olefin (Scheme 3, b). However, identification of the decomposition pathway constitutes considerable difficulties since products of both pathways "a" and "b" in Scheme 3 should give rise to molecular ions of identical elemental composition which fragment through the same patterns thus providing the same product ions. In addition, the remarkably complex signal pattern in the ^{1}H NMR spectrum of the decomposition product does not allow for an unambiguous conclusion on its structure. Nevertheless, convincing arguments in favour of an ionic structure as shown in Scheme 3 (a) are a much lower TLC R_f value of **17** compared to the structurally very similar **14** and an anion exchange experiment performed mixing concentrated CH_2Cl_2 solutions of **17** and silver trifluoromethanesulfonate that results in a white precipitate of silver chloride. Additional evidence against an olefin structure (Scheme 3, b) comes from its lack of dimerization in the presence of the Grubbs catalyst. It is noteworthy, similar dendrimer splitting of the first generation POPAM dendrimer **1** also occurs resulting in *N*-tosylsulfonamides **10**, **11** and sulfonamide **12**. Although the ionic product **20** could not be isolated chromatographically, probably due to its lower liphophilicity compared to **17**, it can be observed in the mass spectra of the raw product obtained after persulfonylation of **1**. It should be stressed that the chemical destruction of the dendritic backbone observed by us and shown in Scheme 3 (a) is reminiscent the gas-phase fragmentation of unsubstituted POPAM dendrimers discovered by Meijer et al. by means of electrospray (ESI) mass spectrometry.[18]



Scheme 3



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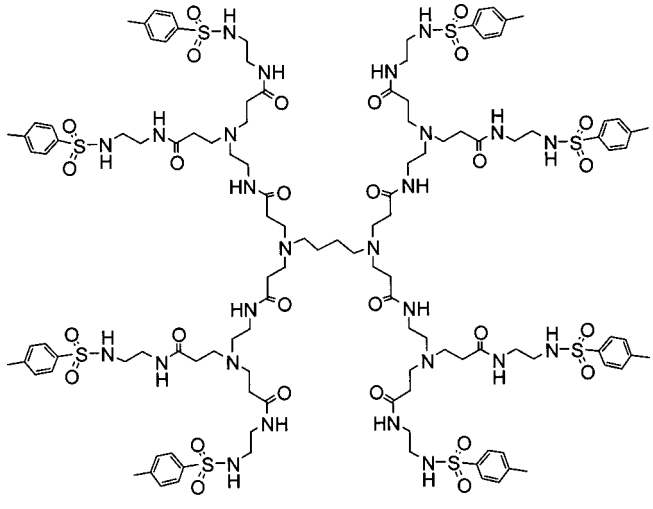
c) Functionalization of PAMAMs: Similarly to POPAM dendrimers, PAMAM dendrimers such as **3** bear numerous peripheral aliphatic amino groups. However, sulfonylation of **3** with tosyl chloride in presence of caesium carbonate carried out in acetonitrile and in dioxane both at room temperature and at reflux resulted in octasulfonamide **21**. On the other hand, no dendritic backbone decomposition of **3** was observed highlighting its − compared to POPAM



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dendrimers − higher chemical stability even at harsh reaction conditions.

d) Characterization of *N*-Tosylsulfonamides: The structure of isolated *N*-tosylsulfonamides **6**−**12** and **14**−**17** was fully confirmed by means of ^{1}H NMR spectroscopy, FAB, MALDI-TOF and ESI mass spectrometry techniques as well as elemental analysis. In several cases, HPLC was invoked for an additional purification of the products. Although the aliphatic area in proton spectra of the above *N*-tosylsulfonamides consisting of the numerous overlapping signals of methylene groups can hardly be interpreted, the aromatic protons of the tosyl units show usually easy and insightful signal patterns in which *N*-tosylsulfonamide and sulfonamide moieties can be seen and integrated separately. As it is mentioned in the preceding section, mass spectrometric analysis of the synthesized *N*-tosylsulfonamides provides a conclusive means for characterizing their structure, degree of persubstitution as well as their purity. As shown in Figure 1, the successive loss of tosyl groups from four *N*-tosylsulfonamide moieties of **17** is reflected in its MALDI-TOF spectrum by the presence of a molecular peak and four fragments. An analogous fragmentation pattern was observed for persulfonylated aromatic hexaamines, such as **5**, that reveals its molecular peak along with six peaks of its fragments reflecting the successive splitting of tosyl groups. The fact that upon the laser-induced excitation each *N*-tosylsulfonamide moiety releases only one arylsulfonyl unit shows that MALDI-TOF spectrometry is the method of choice for determining the number of persulfonylated amino groups. ESI-FT-ICR (electrospray Fourier-transform ion-cyclotron-resonance) mass spectrometric analysis of POPAM *N*-tosylsulfonamides, in turn, reveals the loss of complete branches while no expulsion of tosyl groups is observed at all. The latter process was formerly investigated for parent POPAM dendrimers by Meijer et al.[18] is caused by protonation of the tertiary amine moieties and subsequent intramolecular nucleophilic attack of another amine unit resulting in the splitting of a quaternary ammonium cation such as that shown in Scheme 3 (a). These two aspects make both types of ionization complementary to each other so that mass spectrometry becomes the method of choice for an unambiguous characterization of these dendritic structures.

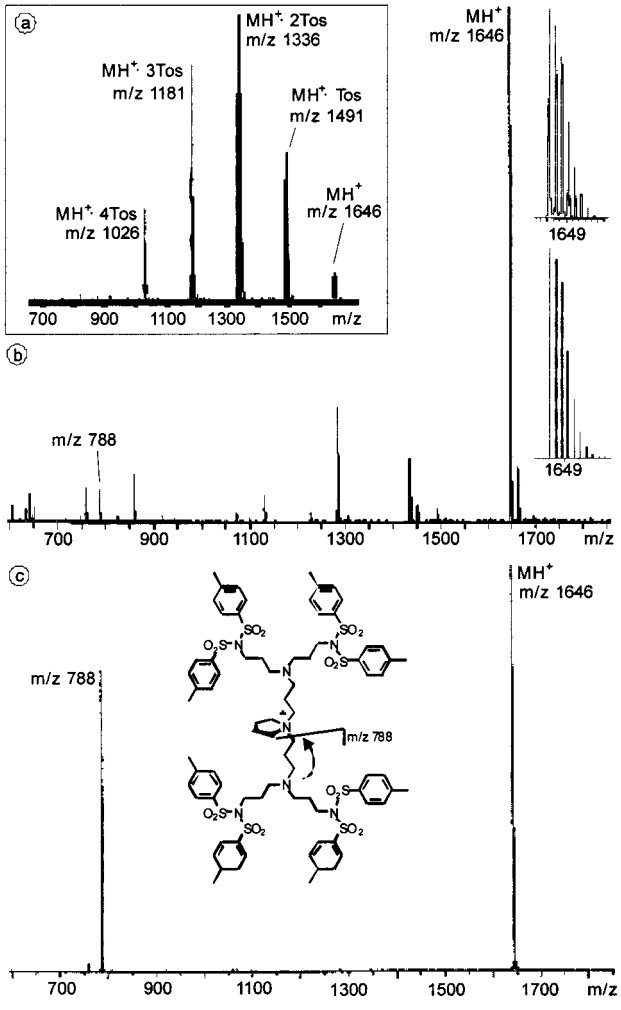

Figure 1. a) MALDI-TOF mass spectrum of **17** showing the successive losses of tosyl groups from the parent ion. These fragmentations must be directly related with an excitation of the tosyl substituents by the laser beam, because they are not at all observed in the ESI mass spectrum. b) ESI-FT-ICR mass spectrum of a ca. 30 μM methanol solution of **17** (1% acetic acid added for facilitated ionization). The insets on the right show the experimental isotope pattern (top) and that calculated on the basis of natural abundances (bottom). c) Collision-induced decay (CID) spectrum of mass selected **17**. Upon collisional activation, the ion is cleaved as shown in the structure at the bottom giving rise to bond cleavage at a central position. No tosyl losses are observed indicating that they occur in the MALDI spectrum due to direct activation of the adjacent aromatic π system by the MALDI laser.

Conclusion

The current study on the selectivity of the peripheral functionalization of oligoamine dendrimers shows that whilst G1 POPAM **1** can be persulfonylated in a complete and selective manner, a similar reaction of higher generations of POPAMs unexpectedly leads to the decomposition of their dendritic backbones. The advantage of the POPAM persulfonylation is that all the products are easily isolated and purified using conventional column chromatography.

The isolated selectively functionalized products can be useful synthons for further reactions. For example, monosulfonamides such as **7**, **11** and **15** can be used as dendrons, whereas *N*-tosylsulfonamides bearing two or three amide functions such as **8**, **9**, **12** and **16** can serve as building blocks for the construction of linear and branched dendritic networks which represent the important novel concept of shaping "*dendrons from dendrimers*" unlike the usual construction of "*dendrimers from dendrons*".

Despite the fact that the decomposition of POPAM dendrimers of second and higher generations upon persulfonylation limits the possibilities of the selective peripheral functionalization of dendritic oligoamines of the POPAM type, it has certain advantages, because the partially persubstituted fragments can be used as dendrons similar to the sulfonylated derivatives of **1** mentioned above. Moreover, the

less perfectly sulfonylated fragments bearing quaternary ammonium centers such as **17** can be useful for biomedical applications e.g. as potential gene delivery agents.[10] As gene transfection studies reveal,[7] a partly destroyed dendrimer exhibits higher transfection efficiencies compared to the initial perfect structure in some cases. Alkylation of sulfonamide-decorated G2 POPAM **18** showed the lack of selective substitution.

In unexpected contrast to the behaviour of tris(2-aminoethyl)amine (**4**), aromatic and POPAM-type oligoamine dendrimers, sulfonylation of PAMAM dendrimers shows on the one hand their relative inertness resulting in their fully sulfonamide-decorated derivatives. On the other hand, sulfonylation of PAMAM dendrimers gives no molecular decomposition observed in case of POPAM dendrimers. As a consequence, this study demonstrates that despite the similarity of their terminal aliphatic amino groups, POPAM and PAMAM dendrimers exhibit strikingly different stability and reactivity offering therefore different options for functionalization.

The future sulfonylation of amine-terminated dendrimers that can be performed with other sulfonyl chlorides e.g. aliphatic ones bearing long chains, chiral substituents or even dendritic sulfonyl chlorides will lead to further selective functionalizations and new material properties, and will also yield diverse dendritic structures including those with missing branches in a very pure form. In this connection, a new nomenclature that relates dendrimers with missing branches to the perfect dendrimers and dendrons should be developed.[19] Finally, we believe that dendrimer research will be a most rewarding area for material and life sciences, once the problem of selective functionalization and perfect purification of existing dendrimers and those to come is solved.

Experimental Section

General Remarks: Melting points were determined with a Reichert Thermovar microscope and are uncorrected. NMR spectra were recorded using 300 and 400 MHz Bruker instruments; the solvent signals were used for internal calibration. Mass spectra were recorded using a MALDI-TofSpec-E from MICROMASS, GB (MALDI) and a Concept 1H from Kratos Analytical Ltd., Manchester, GB (FAB). Preparation of octaalkylated octasulfonamide **19** was carried out in accord to the previously published by us procedure.[20] . Newkome's nomenclature system[12a] was applied to name dendrimers **18** and **21**.

FT-ICR Mass Spectrometry: ESI mass spectra and MS/MS spectra were recorded with a Bruker APEX IV Fourier-transform ion-cyclotron-resonance (FT-ICR) mass spectrometer with an Apollo electrospray ion source equipped with an off-axis 70° spray needle. Typically, methanol (with 1% HOAc) served as the spray solvent and 30 μM solutions of the analytes were used. Analyte solutions were introduced into the ion source with a syringe pump (Cole-Palmers Instruments, Series 74900) at flow rates of ca. 3−4 μL/min. Ion transfer into the first of three differential pump stages in the ion source occurred through a glass capillary with 0.5 mm inner diameter and nickel coatings at both ends. Ionization parameters were adjusted as follows: capillary voltage: −4.3 to −4.6 kV; endplate voltage: −3.6 to −3.9 kV; capexit voltage: +100 to +150 V; skimmer voltages: +11 to +16 V; temperature of drying gas: 250 °C. The flows of the drying and nebulizer gases were kept in a medium range (ca. 10 psi). The ions were accumulated in the instruments hexapole for ca. 3 s, introduced into the FT-ICR cell, which was operated at pressures below 10^{-10} mbar, and detected by a standard excitation and detection sequence. For each measurement 8 to 64 scans were averaged to improve the signal-to-noise ratio. For MS/MS experiments, the whole isotope patterns of the ion of interest were isolated by applying correlated sweeps, followed by shots to remove the higher isotopes (due to the high *m*/*z* of 3612.9 Da the whole isotope pattern of **6** was isolated and subjected to the CID experiment). After isolation, argon was introduced into the ICR cell as the collision gas through a pulsed valve at a pressure of ca. 10^{-8} mbar. The ions were accelerated by a standard excitation protocol and detected after a 2 s pumping delay. A sequence of several different spectra was recorded at different excitation pulse attenuations in order to get at least a rough and qualitative idea of the effects of different collision energies on the fragmentation patterns.

HPLC Separation: The separations were performed at 25 °C on a line consisting of an analytical pump series 1050 (Hewlett−Packard), a Rheodyne injector 7125, an LCD 2084 UV-Detector (Techlab) and a preparative Kromasil column (material: silica gel, particle size 5 micron). In all cases a mixture of 2-propanol/diethyl ether (100:1) was used as the eluent.

General Procedure for the Persulfonylation of G1 POPAM Dendrimer 1: *N*,*N*,*N*′,*N*′-Tetrakis(3-aminopropyl)-1,4-diaminobutane (**1**) (0.63 mmol) and 4-methylbenzenesulfonyl chloride (10.12 mmol) were dissolved in dry acetonitrile (150 mL). Dry Cs_2CO_3 (10.12 mmol) was added to the acetonitrile solution and the resulting suspension was allowed to stir either at room temperature under argon for seven days or at reflux for 3 h. Then an excess of Cs_2CO_3 was filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in 100 mL of dry dichloromethane and the precipitated CsCl was filtered and the solvent was washed with water (2 × 150 mL), dried with Na_2SO_4 and then evaporated in vacuo. The crude product was purified on silica gel.

1,4-Diaminobutane Derivative 6: R_f = 0.84 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 6%; m.p. 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, $^3J_{H,H}$ = 6.7 Hz, 4 H, CH_2), 1.84 (m, 4 H, CH_2), 2.40 (s, 24 H, CH_3), 2.41 (s, 8 H, CH_2), 3.60 (s, 8 H, CH_2), 3.73 (t, $^3J_{H,H}$ = 6.8 Hz, 8 H, CH_2), 7.28 (d, $^3J_{H,H}$ = 8.4 Hz, 16 H, ArH), 7.84 (d, $^3J_{H,H}$ = 8.2 Hz, 16 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.72, 30.48, 45.98, 50.71, 64.66, 70.70, 128.32, 129.86, 136.99, 145.06 ppm. FAB MS: $C_{72}H_{88}N_6O_{16}S_8$ calcd. $[M]^+$ 1550.0; found 1549.6 $[M^+]$.

1,4-Diaminobutane Derivative 7: R_f = 0.54 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 4%; m.p. 88−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, $^3J_{H,H}$ = 7.3 Hz, 4 H, CH_2), 1.88 (br. s, CH_2), 2.37 (s, 3 H, CH_3), 2.39 (s, 18 H, CH_3), 2.40 (s, 6 H, CH_2), 2.42 (m, CH_2), 3.59 (s, 6 H, CH_2), 3.70−3.74 (m, 6 H, CH_2), 5.29 (s, 1 H, NH), 7.23−7.32 (m, 14 H, ArH), 7.68−7.73 (m, 2 H, ArH), 7.84 (d, $^3J_{H,H}$ = 8.3 Hz, 12 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.27, 21.58, 21.71, 29.46, 30.48, 40.31, 45.93, 47.71, 50.73, 53.11, 64.63, 70.67, 127.20, 128.30, 129.84, 136.99, 137.16, 143.16, 145.03 ppm. FAB MS: $C_{65}H_{82}N_6O_{14}S_7$ calcd. $[M]^+$ 1395.8; found 1395.5 $[M^+]$.

1,4-Diaminobutane Derivative 8: R_f = 0.38 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 4%; m.p. 90 °C. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 1.35 (t, $^3J_{H,H}$ = 7.2 Hz, 4 H, CH_2), 1.70 (m, CH_2), 1.86−1.95 (m, CH_2), 2.37−2.40 (m, 18 H, CH_3), 2.42 (s, 2 H, CH_2), 2.56−2.85 (m, CH_2), 3.59 (s, CH_2), 3.71 (m, CH_2), 6.11 (s, 2 H, NH), 7.24−7.30 (m, 12 H, ArH), 7.70−7.74 (m, 6 H, ArH), 7.83 (d, $^3J_{H,H}$ = 8.3 Hz, 6 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.56, 21.72, 45.89, 47.51, 50.85, 53.11, 70.66, 127.21, 128.33, 129.77, 129.88, 136.83, 137.02, 143.20, 145.12 ppm. FAB MS: $C_{58}H_{76}N_6O_{12}S_6$ calcd. $[M]^+$ 1241.6; found 1241.5 $[M^+]$.

1,4-Diaminobutane Derivative 9: R_f = 0.30 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 71%; brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (br. s, CH_2), 2.31 (s, 9 H, CH_3), 2.35−2.37 (m, CH_2), 2.39 (s, 6 H, CH_3), 3.40−3.47 (m, CH_2), 3.52 (br. s, CH_2), 3.78 (m, CH_2), 5.27 (s, 3 H, NH), 7.13 (d, $^3J_{H,H}$ = 7.9 Hz, 5 H, ArH), 7.25 (d, $^3J_{H,H}$ = 8.2 Hz, 5 H, ArH), 7.70−7.74 (m, 10 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.34, 21.70, 46.00, 52.83, 53.51, 57.07, 63.26, 125.95, 128.46, 128.80, 129.95, 135.73, 139.82, 142.91, 145.54 ppm. FAB MS: $C_{51}H_{70}N_6O_{10}S_5$ calcd. $[M]^+$ 1087.5; found 1087.4 $[M^+]$.

4-Methylbenzenesulfonamide Derivative 10: R_f = 0.91 (dichloromethane/ethyl acetate, 10:1); yield 14%; m.p. 66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83−190 (m, 4 H, CH_2), 2.35 (s, 12 H, CH_3), 2.37 (br. s, 3 H, CH_3), 3.03 (t, $^3J_{H,H}$ = 7.0 Hz, 4 H, CH_2), 3.57 (t, $^3J_{H,H}$ = 7.7 H, 4 Hz, CH_2), 7.20 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, ArH), 7.23 (d, $^3J_{H,H}$ = 8.2 Hz, 8 H, ArH), 7.55 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.77 (d, $^3J_{H,H}$ = 8.4 Hz, 8 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.64, 21.77, 28.78, 45.72, 46.88, 127.31, 128.40, 129.88, 129.95, 136.27, 136.82, 143.58, 145.12 ppm. FAB MS: $C_{41}H_{47}N_3O_{10}S_5$ calcd. $[M]^+$ 902.2; found 902.2 $[M^+]$. $C_{41}H_{47}N_3O_{10}S_5$ (902.1): calcd. C 54.59, H 5.25, N 4.66, S 17.77; found C 54.63, H 5.19, N 4.37, S 17.65.

4-Methylbenzenesulfonamide Derivative 11: R_f = 0.75 (dichloromethane/ethyl acetate, 10:1); yield 5%; m.p. 61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73−1.80 (m, 2 H, CH_2), 1.89−1.96 (m, 2 H, CH_2), 2.40 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 2.45 (s, 6 H, CH_3), 3.03 (br. s, 2 H, CH_2), 3.09 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H, CH_2), 3.67 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH_2), 5.13 (s, 1 H, NH), 7.27−7.33 (m, 8 H, ArH), 7.63 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, ArH), 7.74 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.82 (d, $^3J_{H,H}$ = 8.4 Hz, 4 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.60, 21.64, 21.78, 29.36, 29.54, 40.02, 46.43, 47.01, 47.56, 127.14, 127.28, 128.33, 129.86, 129.89, 130.03, 135.64, 136.76, 137.27, 143.40, 143.85, 145.23 ppm. FAB MS: $C_{34}H_{41}N_3O_8S_4$ calcd. $[M]^+$ 747.9; found 748.1 $[M^+]$. $C_{34}H_{41}N_3O_8S_4$ (748.0): calcd. C 54.60, H 5.52, N 5.62, S 17.15; found C 54.55, H 5.46, N 5.47, S 16.75.

4-Methylbenzenesulfonamide Derivative 12: R_f = 0.25 (dichloromethane/ethyl acetate, 10:1); yield 13%; m.p. 52−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67−1.74 (m, 4 H, CH_2), 2.41 (s, 6 H, CH_3), 2.42 (s, 3 H, CH_3), 2.95 (br. s, 4 H, CH_2), 3.10 (t, $^3J_{H,H}$ = 6.8 Hz, 4 H, CH_2), 5.27 (s, 2 H, NH), 7.29 (d, $^3J_{H,H}$ = 7.9 Hz, 6 H, ArH), 7.63 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, ArH), 7.72 (d, $^3J_{H,H}$ = 8.3 Hz, 4 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.61, 29.38, 40.23, 46.91, 127.15, 127.23, 129.87, 130.03, 135.63, 137.05, 143.52, 143.88 ppm. FAB MS: $C_{27}H_{35}N_3O_6S_3$ calcd. $[M]^+$ 593.8; found 594.1 $[M^+]$. $C_{27}H_{35}N_3O_6S_3$ (593.8): calcd. C 54.62, H 5.94, N 7.08, S 16.20; found C 54.52, H 5.83, N 6.84, S 15.01.

General Procedure for the Persulfonylation of G2 POPAM Dendrimer 2: 4,17-Bis(3-aminopropyl)-8,13-bis{3-[bis(3-aminopropyl)-amino]propyl}-1,20-diamino-4,8,13,17-tetraazaeicosan (**2**) (0.26 mmol) and 4-methylbenzenesulfonyl chloride (12.6 mmol) were dissolved in dry acetonitrile (100 mL). Dry Cs_2CO_3 (12.6 mmol) was added to the acetonitrile solution and the resulting suspension was allowed to stir at room temperature under argon for seven days. Then an excess of Cs_2CO_3 was filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in 100 mL of dry dichloromethane and the precipitated CsCl was filtered and the solvent was washed with water (2 × 150 mL), dried with Na_2SO_4 and then evaporated in vacuo. The crude product was purified on silica gel.

4-Methylbenzenesulfonamide Derivative 14: R_f = 0.91 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 15%; m.p. 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, $^3J_{H,H}$ = 7.2 Hz, 18 H, CH_2), 2.30−2.32 (m, 27 H, CH_3), 3.51 (br. s, 10 H, CH_2), 3.65 (br. s, 8 H, CH_2), 7.20 (d, $^3J_{H,H}$ = 6.9 Hz, 16 H, ArH), 7.54 (m, 4 H, ArH), 7.76 (d, $^3J_{H,H}$ = 8.2 Hz, 16 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.24, 21.72, 21.77, 30.48, 45.99, 64.66, 70.70, 127.28, 128.35, 129.38, 129.88, 136.90, 137.23, 144.98, 145.05 ppm. FAB MS: $C_{81}H_{99}N_7O_{18}S_9$ calcd. $[M]^+$ 1747.3; found 1747.6 $[M^+]$.

4-Methylbenzenesulfonamide Derivative 15: R_f = 0.65 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 24%; m.p. 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, $^3J_{H,H}$ = 7.3 Hz, 10 H, CH_2), 1.73 (t, $^3J_{H,H}$ = 6.2 Hz, 4 H, CH_2), 2.32−2.37 (m, CH_2), 2.40−2.42 (m, 24 H, CH_3), 3.60 (br. s, 6 H, CH_2), 3.72−3.76 (m, 6 H, CH_2), 5.30 (s, 1 H, NH), 7.26−7.31 (m, 14 H, ArH), 7.64 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, ArH), 7.70 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.74 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.84−7.86 (m, 12 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.23, 21.55, 21.70, 21.73, 29.31, 30.47, 40.26, 45.98, 47.02, 47.33, 50.70, 64.68, 70.68, 127.18, 127.24, 128.30, 128.33, 129.84, 129.87, 137.00, 137.20, 143.16, 143.33, 144.99, 145.07 ppm. FAB MS: $C_{74}H_{93}N_7O_{16}S_8$ calcd. $[M]^+$ 1593.1, found 1592.5 $[M^+]$.

4-Methylbenzenesulfonamide Derivative 16: R_f = 0.36 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 48%; m.p. 84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, $^3J_{H,H}$ = 7.3 Hz, 10 H, CH_2), 2.28 (s, 6 H, CH_3), 2.37−2.45 (m, 27 H, CH_3, CH_2), 3.60 (br. s, 8 H, CH_2), 3.73 (m, 6 H, CH_2), 5.30 (s, 2 H, NH), 6.96 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, ArH), 7.29−7.35 (m, 8 H, ArH), 7.50 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, ArH), 7.60−7.74 (m, 8 H, ArH), 7.84−7.86 (m, 8 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.26, 21.42, 21.61, 21.76, 29.82, 30.49, 46.04, 47.58, 50.64, 64.78, 70.71, 126.93, 127.25, 128.31, 128.64, 129.83, 129.91, 136.97, 137.00, 140.78, 140.99, 143.32, 145.12 ppm. FAB MS: $C_{67}H_{87}N_7O_{14}S_7$ calcd. $[M]^+$ 1438.9, found 1438.5 $[M^+]$.

Pyrrolidinium Chloride 17: R_f = 0.24 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 12%; m.p. 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, $^3J_{H,H}$ = 7.4 Hz, 24 H, CH_2), 2.39−2.42 (m, 30 H, CH_3, CH_2), 3.60 (br. s, 14 H, CH_2), 7.27 (d, $^3J_{H,H}$ = 8.1 Hz, 16 H, ArH), 7.73−7.81 (m, 16 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.25, 21.74, 22.14, 30.48, 45.99, 47.70, 64.68, 70.71, 128.29, 129.91, 136.76, 145.19 ppm. FAB MS: $C_{78}H_{100}N_7O_{16}S_8^+$ calcd. $[M]^+$1648.2, found 1646.4 $[M^+]$.

8-Cascade: 1,4-Diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1-azapropylidene)^2:4-methylbenzenesulfonamide (18): 4,17-Bis(3-aminopropyl)-8,13-bis{3-[bis(3-aminopropyl)-amino]-propyl}-1,20-diamino-4,8,13,17-tetraazaeicosan (**2**) (0.13 mmol) and Et_3N (3.15 mmol) were dissolved in dichloromethane (100 mL). A dichloromethane solution of a sulfonyl chloride (3.15 mmol) was added with intensive stirring under argon. The reaction mixture was then allowed to stir at room temperature for seven days. The solvent was removed under reduced pressure and the solid residue was chromatographed on silica gel. R_f = 0.28 (dichloromethane/methanol/triethylamine, 10:0.5:0.15); yield 65%; yellow viscous oil. ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 1.28 (t, $^3J_{H,H}$ = 7.3 Hz, 30 H, CH_2), 1.66 (m, 12 H, CH_2), 2.29 (s, 8 H, CH_2), 2.32−2.34 (m, 24 H, CH_3), 2.59 (br. s, 16 H, CH_2), 2.84 (t, $^3J_{H,H}$ = 6.2 Hz, 14 H, CH_2), 5.25 (s, 8 H, NH), 7.20 (d, $^3J_{H,H}$ = 7.9 Hz, 16 H, ArH), 7.67 (d, $^3J_{H,H}$ = 8.2 Hz, 16 H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.43, 25.01, 25.43, 41.51, 46.14, 47.00, 50.87, 51.59, 53.49, 127.07, 129.62, 136.95, 143.01 ppm. MALDI-TOF MS: $C_{96}H_{144}N_{14}O_{16}S_8$ calcd. $[M]^+$ 2006.8, found 2006.0 $[M^+]$.

8-Caskade: 1,4-Diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1,4-diaza-5-oxaheptylidene)^2: 4-methylbenzenesulfonamide (21): (92 mg, 0.250 mmol) of caesium carbonate and (50 mg, 0.250 mmol) of tosyl chloride were added to a stirred solution of (20 mg, 0.014 mmol) PAMAM dendrimer **3** in 5 mL acetonitrile. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the solid residue was purified by column chromatography on aluminium oxide giving a white solid. Yield 70%; m.p. 95 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.68 (d, $^3J_{H,H}$ = 8 Hz, 16 H, ArH), 7.33 (d, $^3J_{H,H}$ = 8 Hz, 16 H, ArH), 3.35−2.25 (m, 148 H, CH_2) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ = 173.8, 173.5, 143.3, 137.4, 129.4, 126.6, 55.6, 55.6, 55.5, 49.7, 49.4, 42.1, 39.0, 37.1, 33.2, 33.1, 20.1 ppm. MALDI-TOF MS: $C_{120}H_{180}N_{26}O_{28}S_8$ calcd. $[M]^+$ 2691.4, found 2690.9 $[M^+]$.

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[19] A visionary nomenclature system of dendrimers with missing branches might become necessary with the experimental progress in selective functionalization and purification of less perfect future dendrimers of high generations. We suggest building up this new nomenclature system on the basis of the currently used Newkome's classification of dendrimers (ref.[12a]) by taking the systematic name of the corresponding perfect dendrimer as the starting point and then adding one or more prefixes to it (subtractive type of nomenclature unlike the usually applied additive modular nomenclature). The prefixes should contain the generation number as well as the number of branches lost from this generation. For example: {G3−2}16-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1-azabutylidene)^3:*N*-[4-thiodioxo-4′-(dimethylamino)azobenzene] would mean the two lost branches of the third generation {see braces} assuming the conservation of the perfect structure for the second and the first generations. The system of prefixes can also be used for partially substituted perfect dendrimers, if we consider the peripheral substituents to be the branches of the last generation. Additionally, the prefixes can be readily adopted for dendritic molecules in which the lost branches are replaced with other substituents.
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