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# Persulfonylation of Amines Applied to the Synthesis of Higher Generation Dendrimers

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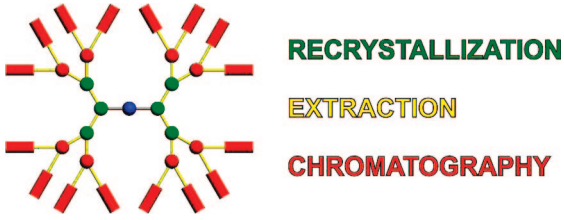


Systematic analysis of the persulfonylation of branched aromatic oligoamines with different arylsulfonyl chlorides allowed optimization of the repetitive steps involved in the synthesis of the sulfonimide-based dendrimers. The optimized procedures afforded the fourth generation *N*- and pentaphenylene-centered dendrimers with 16 and 32 peripheral groups, respectively. Analysis of products of incomplete substitution showed that the amino groups in aromatic oligoamines are persulfonylated consecutively.

Dendritic molecules,[1] such as dendrimers,[1,2] hyperbranched[3] and dendronized[4] polymers, and molecular "bottle brushes"[5] are essential building blocks for both covalent and supramolecular assemblies and have promising technological[6] and biomedical[7] applications. Dendrimers are an example of useful, symmetric, and monodisperse dendritic molecules with considerable molecular weights, but their infamous reputation for labor-intensive and expensive syntheses often precludes their use. The large-scale production of dendrimers is usually performed by the divergent approach[8] in which an accumulation of statistical defects is observed at higher generations.[9] Introduction of the convergent route[10] in the early 1990s enabled the preparation of structurally pure dendrimers with high molecular weights. However, the multiple synthetic steps along with chromatographic workup procedures often take months to prepare reasonable amounts of a structurally perfect high-generation dendrimer. Although there were few reports on dendrimers obtained by one-pot syntheses,[11] they did not receive widespread attention on account of the following limitations. The one-pot synthesis of structurally pure polycarbonate-type dendrimers was restricted to low molar mass (<2 kDa) species,[11a] whereas in two other cases the prepared dendrimers were shown to suffer from either polydispersity[11b] or poor chemical stability.[11c] Therefore, the development of straightforward methods for the preparation of structurally perfect high molecular weight dendrimers still remains a challenge.

Recently we reported the synthesis of "designer dendrimers" which carry sulfonimide units at every branching point.[12] By combining the selectivity of the persulfonylation of primary amines with the repetitive methodology we constructed a number of selectively decorated and differently shaped sulfonimide dendrimers. This synthetic approach has the advantages of a large variety of readily available, inexpensive bulding blocks (arylsulfonyl chlorides), high chemical stability of sulfonimides, and a convenient purification of intermediates by recrystallization. Despite the high flexibility of these synthetic schemes there were several obstacles restricting the synthesis to the low molar mass (not exceeding 3 kDa) dendritic species with up to eight peripheral groups. The major difficulty was the clean conversion of branched intermediates with peripheral *p*-nitrobenzenesulfonyl (*p*-Ns) functional groups into corresponding amines. The second problem preventing the growth of the higher generations was the poor solubility of dendritic sulfonimides with multiple peripheral *p*-Ns units. This completely prevents the purification of the multiply *p*-Ns-substituted dendrimers by means of either

(1) Vögtle, F.; Richardt, G.; Werner, N. *Dendritische Moleküle. Konzepte, Synthesen, Eigenschaften, Anwendungen*; Teubner: Wiesbaden, Germany, 2007.
(2) (a) Archut, A.; Vögtle, F. *Chem. Soc. Rev.* **1998**, *27*, 233–240. (b) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1351–1361. (c) Bosman, A. W.; Jansen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665–1688. (d) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884–905. (e) Newkome, G. R.; Moorefield, C. N.; Vögtle F. *Dendrimers and Dendrons. Concepts, Syntheses, Applications*; Wiley-VCH: Weinheim, Germany, 2001. (f) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3868.
(3) Gao, C.; Yan, D. *Prog. Polym. Sci.* **2004**, *29*, 183–275.
(4) (a) Schlüter, A. D.; Rabe, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 864–883. (b) Frauenrath, H. *Prog. Polym. Sci.* **2005**, *30*, 325–384.
(5) (a) Hadjichristidis, N.; Pitsikalis, M.; Pispas, S.; Iatrou, H. *Chem. Rev.* **2001**, *101*, 3747–3792. (b) Zhang, M.; Müller, A. H. E. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 3461–3481. (c) Hadjichristidis, N; Iatrou, H.; Pitsikalis, M.; Mays, J. *Prog. Polym. Sci.* **2006**, *31*, 1068–1132.
(6) (a) Nierengarten, J. F. *Chem. Eur. J.* **2000**, *6*, 3667–3670. (b) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74–91. (c) Haag, R. *Chem. Eur. J.* **2001**, *7*, 327–335.
(7) (a) Dennig, J. *Top. Curr. Chem.* **2003**, *228*, 227–236. (b) Lee, C. C.; MacKay, J. A.; Fréchet, J. M. J.; Szoka, F. C. *Nat. Biotechnol.* **2005**, *23*, 1517–1526.
(8) (a) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466–2468. (b) Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem., Int. Ed.* **1993**, *32*, 1308–1310. (c) Wörner, C.; Mühlhaupt, R. *Angew. Chem., Int. Ed.* **1993**, *32*, 1306–1308. (d) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K *J. Org. Chem.* **1985**, *50*, 2003–2004. (e) Launay, N.; Caminade, A.-M.; Lahana, R.; Majoral, J.-P. *Angew. Chem., Int. Ed.* **1994**, *33*, 1589–1592. (f) Ruiz, J.; Latuente, H.; Marcen, S.; Ornelas, C.; Lazare, S.; Cloutet, E.; Blais, J.-C.; Astruc, D. *J. Am. Chem. Soc.* **2003**, *125*, 7250–7257. (g) Jayamurugan, G.; Jayaraman, N. *Tetrahedron* **2006**, *62*, 9582–9588. (h) Antoni, P.; Nyström, D.; Hawker, C. J.; Hult, A.; Malkoch, M. *Chem. Commun.* **2007**, *2249*, 2251.
(9) For example, mass spectroscopic analysis of the 5th generation POPAM dendrimer revealed a structural purity of ca. 20%. See: Hummelen, J. C.; van Dongen, J. L. J.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1489–1493.
(10) (a) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647. (b) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed.* **1993**, *32*, 246–248. (c) Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018–1025.
(11) (a) Rannard, S. P.; Davis, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 11739–11730. (b) Okinawa, M.; Takeuchi, K.; Asai, M.; Ueda, M. *Macromolecules* **2002**, *35*, 6232–6238. (c) Ornelas, C.; Aranzaes, J. R.; Cloutet, E.; Astruc, D. *Org. Lett.* **2006**, *8*, 2751–2753.
(12) Lukin, O.; Gramlich, V.; Kandre, R.; Zhun, I.; Felder, T.; Schalley, C. A.; Dolgonos, G. *J. Am. Chem. Soc.* **2006**, *128*, 8964–8974.



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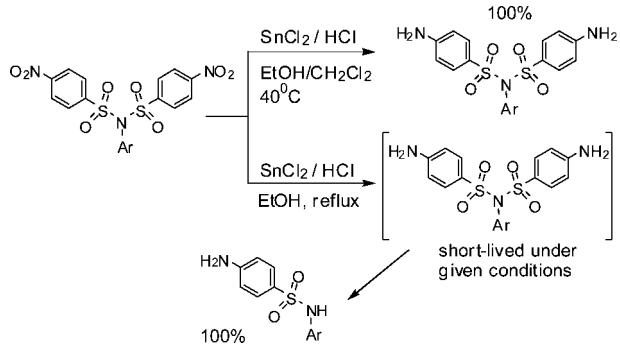
**SCHEME 1. Reduction of *p*-Nitrobenzenesulfonimides with $SnCl_2$**



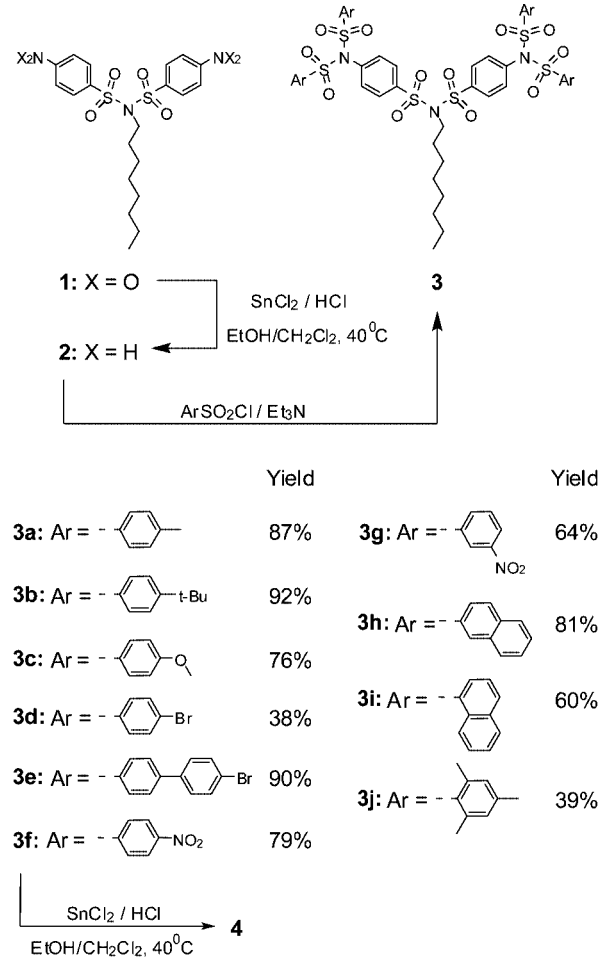

recrystallization or column chromatography. Furthermore, only tosyl (Ts) chloride was used at the final persulfonylation steps and it remained unclear whether other sulfonyl chlorides could be equally suitable for decorating the dendrimer periphery.

In this contribution we describe the successful solution of the encountered synthetic problems.

As mentioned above, the lack of a method allowing a clean quantitative conversion of dendritic oligosulfonimides with multiple peripheral nitroaromatic functional groups into the corresponding amines was the major obstacle that caused reduced yields of the second and third generation dendrimers. Pd- and Raney-Ni-mediated hydrogenation of *p*-Ns-decorated dendritic sulfonimides turned out to be not fully reproducible causing side reactions which could not be rationalized. Additionally, the catalytic hydrogenation caused partial hydrodehalogenation in dendrons bearing bromoaromatic functionalities. The reduction of the *p*-Ns-decorated dendritic sulfonimides with $SnCl_2$ in refluxing ethanol led to the clean reduction but followed by the splitting of *p*-aminobenzenesulfonyl groups giving rise to corresponding aminosulfonamides in quantitative yields (Scheme 1, bottom part). Although the latter process was shown to be advantageous with regard to the selective scissoring out of the peripheral dendrimer branches, it is of no use in the case where a clean reduction securing the rest of the dendrimer structure is needed. Since it was unclear in this reaction whether the reduction precedes the sulfonimide decomposition or vice versa, we carried out a mass-spectrometric investigation of the intermediates of the reduction of different di-*p*-nitrobenzenesulfonimides with a general formula of the starting compound in Scheme 1. It turned out that upon dissolution of all reaction components in hot ethanol the reduction takes place virtually immediately. The electrospray ionization (ESI) mass spectra of the raw products taken right away after the reaction had started showed pronounced peaks of the desired diamines and small peaks of the aminosulfonamides, the decomposition products. After 5 min of reaction time the peaks of the aminosulfonamides were prevailing in the mass spectra. Finally, after 1 h only the aminosulfonamide peaks were observed in the ESI mass spectra. Therefore, as the bottom process in Scheme 1 shows, even though the reduction precedes the decomposition it is difficult to stop the reaction at this stage.

This finding also indicates that the decomposition of the di-*p*-aminobenzenesulfonimides requires somewhat higher activation energy than the foregoing reduction. As illustrated in the top part of Scheme 1, the use of a 1:1 mixture of ethanol and dichloromethane was found to be the key for the clean reduction of nitrobenzenesulfonimides. The reaction proceeds in a homogeneous solution at 40 °C giving rise to corresponding

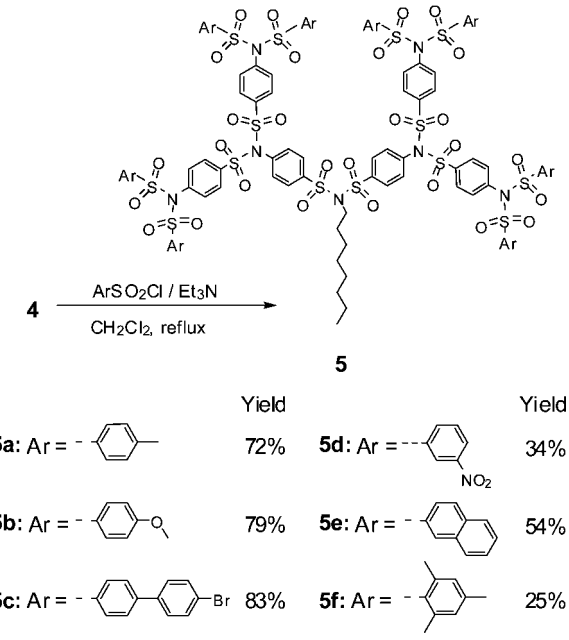
**SCHEME 2. Syntheses of the 2nd Generation Sulfonimide Dendrimers**




diamines in quantitative yields. The straightforward workup consists of pouring the reaction mixture into deionized water and extracting the product with dichloromethane. The amines obtained by this method gave very clean $^1$H NMR and ESI-MS spectra.

The access to multigram amounts of highly pure dendritic sulfonimides with peripheral arylamine groups allowed us to carry out the systematic analysis of their persulfonylation with different arylsulfonyl chlorides to test the applicability of the reaction to the synthesis of higher generation dendrimers. Previously reported arylamine persulfonylation reactions[12] were restricted to the use of *p*-Ns and Ts chlorides giving rise to sulfonimide dendrimers with up to eight peripheral arylsulfonyl groups in good yields. The diamine **2** and the tetraamine **4** were prepared on a 10 g scale by means of the mild $SnCl_2$ reduction of dinitro- and tetranitro-derivatives (**1** and **3f**), respectively. Scheme 2 summarizes the persulfonylation of **2** with different arylsulfonyl chlorides in the presence of triethylamine in refluxing dichloromethane and the isolated yields of the corresponding second generation dendritic sulfonimides purified by recrystallization. Inspection of the yields in Scheme 2 indicates that reactions with para-substituted arylsulfonyl chlorides giving rise to compounds **3a**−**f** are usually high yielding. The exceptions are the moderate yield of reaction with *p*-bromobenzenesulfonyl chloride (compound **3d**) and a completely unsuccessful reaction with *p*-terphenylsulfonyl chloride (not shown) in which the starting compounds were recovered. Given the equal steric

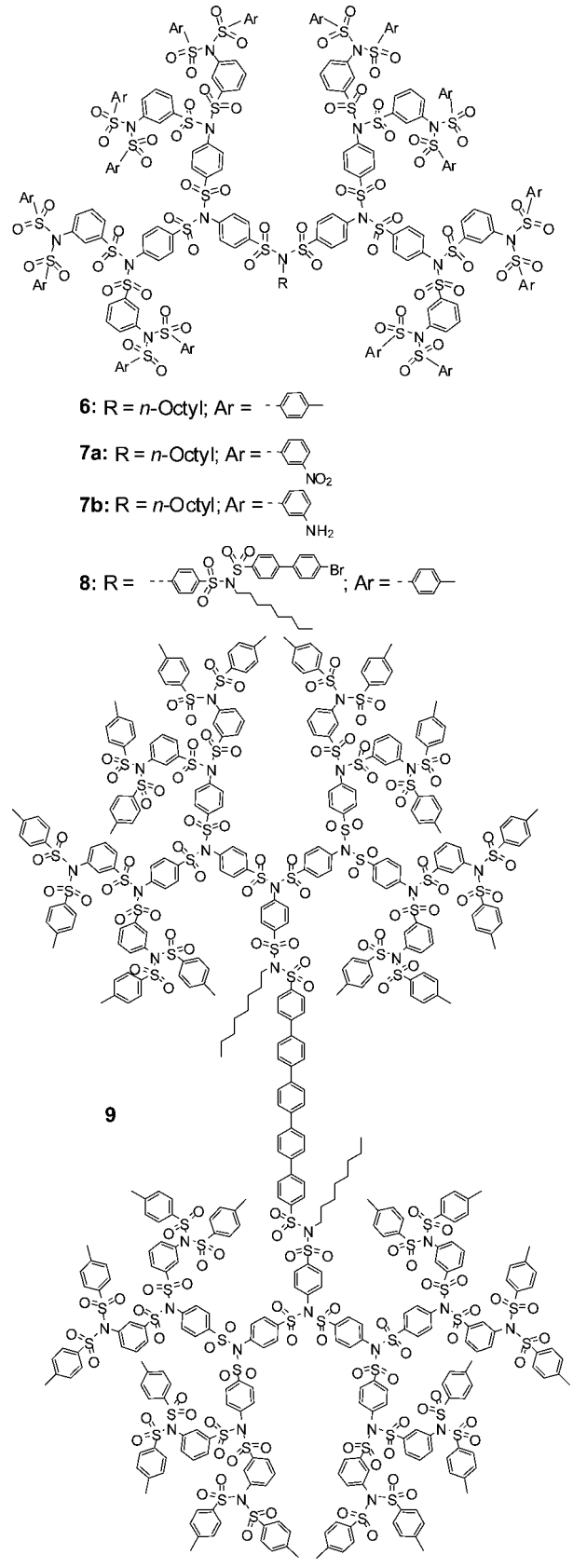
**SCHEME 3. Syntheses of the 3nd generation sulfonimide dendrimers**




load at the reacting sulfur atom in the para-substituted arylsulfonyl chlorides, the last two cases can be attributed to the electronic effects on the arylsulfonyl chloride reactivity. Meta-substituted sulfonyl chlorides (entries **3g** and **3h**) do not show significant drops in yields, whereas the ortho-substituents result in decreased yields (**3i** and **3j**). The decreased yields in reactions with ortho-substitued arylsulfonyl chlorides can also be rationalized by steric and electronic contributions.

The reaction with 1-naphthylsulfonyl chloride gives rise to the dendrimer **3i** in a yield of 60%, while the reaction with structurally similar 5-dimethylamino-1-naphthylsulfonyl (dansyl) chloride resulted in incomplete substitution (discussed below). Therefore, the diminished reactivity of the dansyl chloride can be ascribed to the electronic effects. The reaction of **2** with mesitylenesulfonyl chloride results in **3j** with a moderate yield, whereas the reaction with 2,4,6-triisopropylbenzenesulfonyl chloride (not shown) failed indicating the detrimental factor of the steric overcrowding around the reaction center. All second generation dendrimers except **3f** are very soluble in nonpolar aprotic solvents (solubility in $CHCl_3$ is over 100 mg/mL) and extremely poorly soluble in alcohols. A considerable difference in solubilities is found for isomeric tetranitro-compounds **3f** and **3g**. The chloroform solubility at room temperature of the former is less than 3 mg/mL, while that of the latter is over 150 mg/mL. This finding nicely illustrates how the solubility can be influenced by a small structural change that eliminates the need to attach solubilizing alkyl or oligoethylene glycol chains as is usually done in the case of rigid-rod polymers.

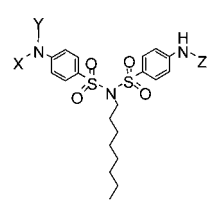
Similar to the trend observed with the second generation dendrimers, the yields of the reactions of **4** with para-substituted arylsulfonyl chlorides resulting in the third generation species being high (Scheme 3), while those with meta- and ortho-substituents are moderate. Octanitro-derivative **5d** as well as other dendrimers in Scheme 3 showed perfect solubility in apolar aprotic solvents making their chromatographic purification straightforward. Notably, the chromatographic purification of sulfonimide dendrimers starts from the third generation species; all preceding workups are done by recrystallization.




Although the octa-*m*-Ns-derivative **5d** was isolated in a rather moderate yield this reaction step provides ca. 3-fold molar mass increase furnishing the product on a gram scale. The dendrimer **5d** was quantitatively reduced to the corresponding octaamine and then subjected to persulfonylation with Ts and *m*-Ns

chlorides giving rise to the first representatives of sulfonimide-based dendrimers of the fourth generation **6** (44%) and **7a** (20%), respectively. The structural purity of the fourth generation species was fully confirmed by means of NMR spectroscopy, MALDI-TOF mass spectrometry, and elemental analyses. An attempt to go further with the divergent growth proved unsuccessful. The involvement of the convergent route at this stage was therefore undertaken. Utilizing previously reported[12] stepwise bis-sulfonylation of *n*-octylamine with *p*-Ns and 4-bromobiphenylsulfonyl chlorides and then following the improved repetitive steps we prepared the fourth generation dendron **8** bearing 16 Ts units on the periphery and the 4-bromobiphenylsulfonyl unit at the focal point. The double Suzuki cross-coupling reaction of the dendron **8** with 1,4-phenylenediboronic acid readily gives the pentaphenylene-centered dendrimer **9** in a yield of 70%. The dendrimer **9** has a molar mass exceeding 10 kDa that makes the compound thus far the largest representative of the branched sulfonimides.

During the systematic investigation of the persulfonylation of amines **2** and **4**, products of incomplete substitution were isolated and characterized in a few cases. Thus, three products of the persulfonylation of **2** with dansyl chloride were isolated chromatographically. The first two fractions were equal amounts of sulfonamide **10** and sulfonimide **11**, while the major fraction (ca. 50%) was the starting diamine **2**. Therefore, the first and the second sulfonylation events took place at the same nitrogen atom despite the accessibility of free amino groups. Column chromatography of the raw products of other persulfonylation reactions of **2** and **4** enabled the isolation of traces of sulfonimide **12** (ca. 3%), the triply substituted derivative **13** (ca. 2%), and the hexasulfonylated intermediate **14** (yield 14%). The isolated byproducts **10**–**14** suggest the following mechanism of the persulfonylation of aromatic amines. The first sulfonylation event generates the aromatic sulfonamide intermediate, which under basic conditions is more reactive than the aromatic amine. Our previous findings[12] revealed that peripheral aromatic amino groups of some sulfonimide dendrimers with a single aliphatic sulfonamide unit were successfully persulfonylated leaving the sulfonamide group intact. Therefore, the reactivity of aromatic and aliphatic sulfonamides and aromatic amines toward sulfonylation under basic conditions decreases in the order $ArSO_2NH$-Ar′ > $ArNH_2$ > $ArSO_2NH$-Alk. The ability to selectively address these functional groups without involving protective groups might become very useful not only in dendrimer research but also in medicinal chemistry.



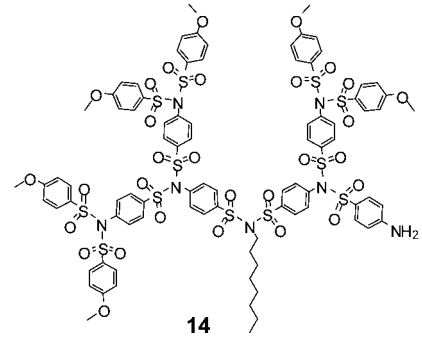
**10 - 13**

**10**: X = Y = H; Z =

**11**: X = Y = ; Z = H

**12**: X = Y = ; Z = H

**13**: X = Y = Z =



**14**

## Experimental Section

**Representative Procedure for the Reduction of Nitroaromatic Intermediates.** A solution of octanitro-derivative **5d** (1 g, 0.4 mmol) in 50 mL of $CH_2Cl_2$ was poured into a stirred solution of $SnCl_2$ (8 g) and 37% HCl (2 mL) in 50 mL of EtOH. The reaction mixture was stirred at 40 °C for 4 h then poured into 300 mL of deionized water and extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic layers were washed with water and saturated $NaHCO_3$, then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting solid residue was dried in vacuum. Yellowish solid; yield 0.86 g (95%); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.78 (t, $^3J_{H,\,H}$ = 6.4 Hz, 3 H, $CH_3$), 1.14 (m, 10 H, $CH_2$), 1.53 (m, 2H, $CH_2$), 3.82 (m, 2 H, $CH_2$), 5.75 (s, 16 H, $NH_2$), 6.83 (m, 8 H, ArH), 6.90 (m, 8 H, ArH), 7.06 (s, 8 H, ArH), 7.24 (m, 8 H, ArH), 7.34 (d, $^3J_{H,\,H}$ = 8.5 Hz, 8 H, ArH), 7.42 (d, $^3J_{H,\,H}$ = 8.5 Hz, 4 H, ArH), 7.85 (d, $^3J_{H,\,H}$ = 8.5 Hz, 8 H, ArH), 8.16 (d, $^3J_{H,\,H}$ = 8.5 Hz, 4 H, ArH) ppm; MS (MALDI-TOF, dithranol + Na-TFA) *m/z* 2322.10 $[M + Na]^+$, $^{12}C_{92}{}^1H_{89}{}^{14}N_{15}{}^{16}O_{28}{}^{32}S_{14}{}^{23}Na$ requires *m/z* 2322.20.

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**Supporting Information Available:** Characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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