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Hans-Bernhard Mekelburger[a]; Fritz Vögtle[a]
[a] Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Str. 1, Bonn 1, Germany

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COMMUNICATION

Dendrimers with bulky repeat units using a new repetitive synthetic strategy

HANS-BERNHARD MEKELBURGER and FRITZ VÖGTLE*

Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Str. 1, D-5300 Bonn 1, Germany

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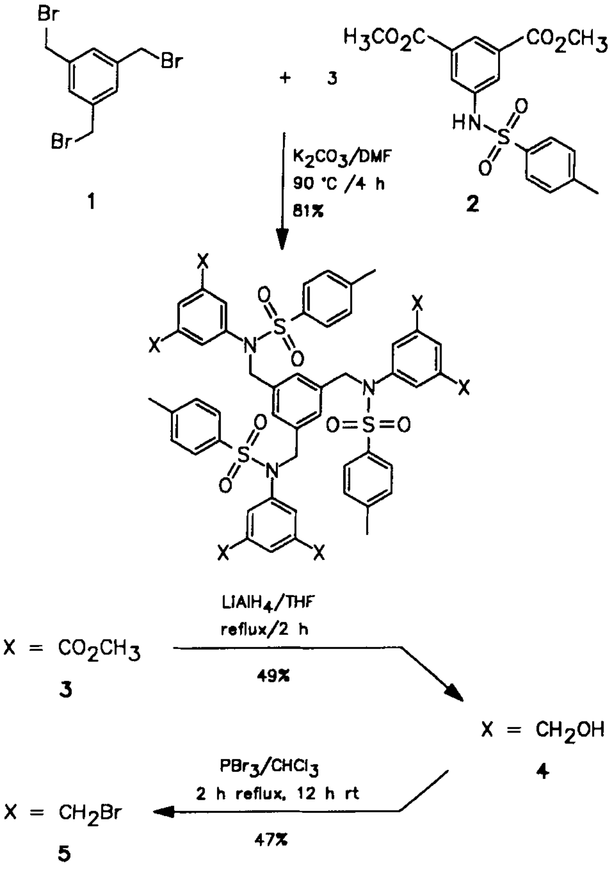
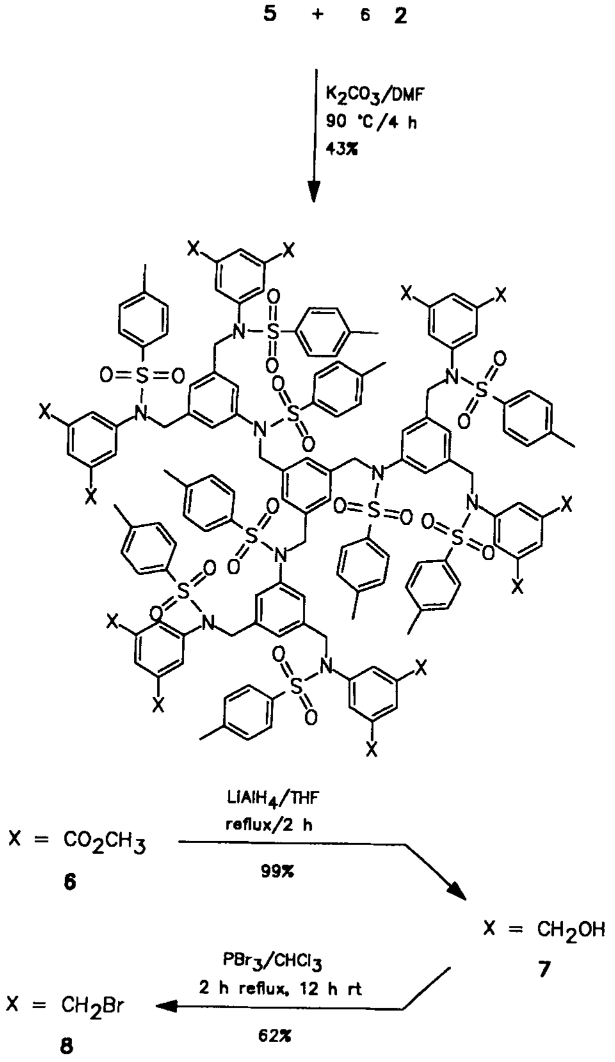
Monodisperse dendrimers with remarkable solubility have been obtained using a new repetitive synthetic strategy. The third generation nanoscale dendrimer 9 having 24 functional groups already reaches a molecular mass of 6910 Da.

In 1978, we reported the repetitive synthesis of noncyclic polyaza compounds, which were the first examples of a 'cascade-like' synthesis of multibranched molecules.[1] In the meantime cascade macromolecules have received considerable attention.[2] In the following pioneering work Denkewalter,[3] Newkome,[4–6] Tomalia,[7,8] Masamune[9] and others used the divergent methodology ('starburst approach') whereas Fréchet,[10–12] Neenan,[13] and Shinkai[14] employed the 'convergent-growth' approach. Recently Newkome[15] introduced a new systematic nomenclature





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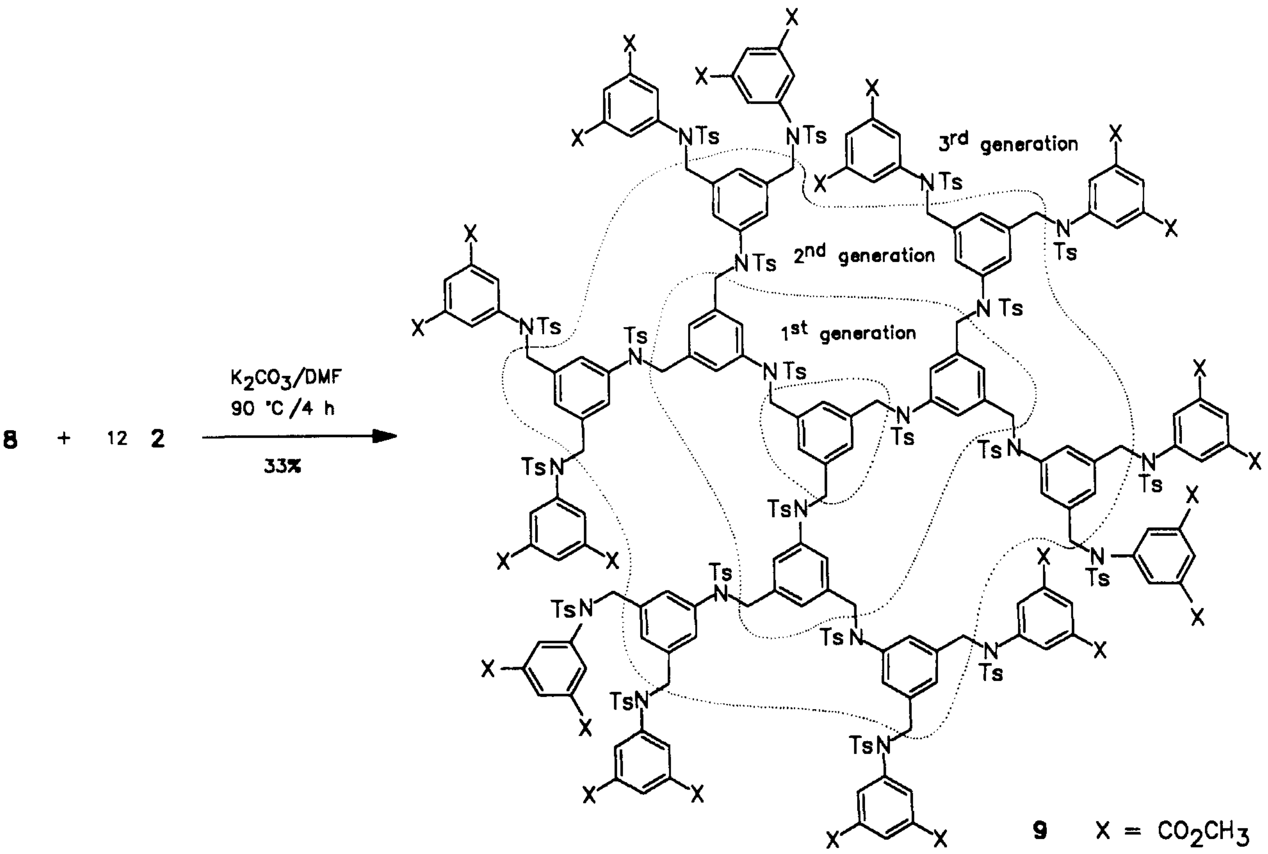
*To whom correspondence should be addressed.

for cascade molecules due to obvious disadvantages of current nomenclature rules for branched polymers.

We now report the divergent synthesis of a new family of monodisperse dendritic molecules (**3** to **9**) using large and bulky repeat units. They are tied together in a more or less rigid way, yet the dendrimers of all generations are still well soluble in common organic solvents. The monomeric building blocks can be prepared in a single step from commercially available starting materials. These dendrimers were designed to incorporate a balanced mixture of aryl and alkyl groups. This is advantageous for the characterization of the various products by ^{1}H- and ^{13}C-NMR spectroscopy as well as for the solubility in organic solvents.

Synthesis of the core, 1,3,5-tris(bromomethyl)benzene (**1**), by NBS bromination[16] was as easily accomplished as was the tosylation of dimethyl 5-aminoisophthalate to give building block **2**.[17] Treatment of **1** and three equivalents of **2** in DMF with potassium carbonate, as base, led to hexaester **3** in 81% yield.[18] After reduction of **3** with $LiAlH_4$ in THF, alcohol **4** was obtained in a moderate (49%) yield after recrystallization.[19] This is probably due to the low solubility of **4** in THF; however, attempts to carry out the reduction in ether failed. After transformation (55%) of alcohol **4** with PBr_3 to bromide **5**,[20] one cycle of the repetitive synthetic strategy was completed. Subsequent treatment of the hexabromide **5** with six equivalents of **2** gave (43%) the dodecaester **6** after chromatographic purification. Reduction of **6** to alcohol **7** was carried out almost quantitatively, followed by bromination in 62% yield to **8**. The yield of the second reduction increased considerably because dodecaalcohol **7** is more soluble than hexaalcohol **4**. The dendrimer of the third generation with 24 ester groups (**9**) was prepared in the same fashion (33% yield after column chromatographic purification) but now 12 equivalents of building block **2** were used.

All products, which were obtained as colourless solids, were identified by elemental analysis,[21] and ^{1}H- and ^{13}C-NMR spectroscopy.[22] The change of functional groups could be easily recognized in the spectra. All products except **9**, were confirmed by FAB mass spectrometry. Besides the $[M + H]^+$ peak, the $[M - Ts]^+$ peak was observed. Due to instrument and technique limitations, the molecular ion of the third generation ester **9** could not be detected. A molecular weight determination of the dendritic esters **3**, **6** and **9** by osmometry showed a somewhat lower weight.[23] This deviation increased with growing size of the dendrimers. However, using a narrow-dispersity



9 X = CO_2CH_3

polystyrene standard (M = 3770 Da; $M_w/M_n < 1.04$) instead of benzil (M = 210 Da) for calibration, the deviation was smaller. One of the reasons for these lower values may be the solvent residues which are 'captured' in the pores of the dendrimers. Even after drying **9** under reduced pressure for several days, solvent molecules such as DMF and ethyl acetate could be detected by mass spectrometry. Another reason might be the fact that dendrimers progressively become denser and more compact as the molecular weight increases.[2,7,8,11] A molecular weight of 6910.6 Da (as for **9**) is huge for a dendrimer of the third generation. Also the size of these new dendrimers increase in large steps as the number of generations increases. Thus the order of magnitude considered for nanoscale architecture[24] can be reached with a small number of generations.

We believe that this general synthetic strategy can be applied to higher generations, to other core units, and to 'functional dendrimers' containing structural units, thus rendering them as dyes, strong metal complexing agents, light switches, and liquid crystals. Further studies are currently under investigation in our laboratory.

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18 **3**: In an argon-flushed apparatus, a solution of **1** (7.14 g, 0.02 mol) and **2** (21.8 g, 0.06 mol) in dry DMF (300 ml) was added within 30 min to a suspension of K_2CO_3 (20.73 g, 0.15 mol) in dry DMF (120 ml). The reaction mixture was heated to 90°C for 4 h. The cooled mixture was filtered to remove the salts and most of the solvent was evaporated under reduced pressure. The product was precipitated from the concentrated solution and collected by filtration. Recrystallization from toluene/methylcyclohexane, 4:1, yielded 19.5 g (81%) of white crystals, m.p. 193–194°C.

19 **4**: To a suspension of $LiAlH_4$ (7.60 g, 0.2 mol) in dry THF (1 l), solid **3** (24.10 g, 0.02 mol) was added in several portions. The mixture was refluxed for 2 h and, after cooling, cautiously hydrolysed by dropwise addition of water. The solvent was evaporated under reduced pressure and diluted hydrochloric acid was added to the residue. After the mixture had been cooled, the liquid was again decanted and the crude product recrystallized from ethanol yielding 10.15 g (49%) of a white solid, m.p. 210–211°C.

20 **5**: In an argon-flushed apparatus, a solution of PBr_3 (5.8 ml, 0.06 mol) in dry $CHCl_3$ (30 ml) was added within 30 min to a suspension of **4** (10.36 g, 0.01 mol) in dry $CHCl_3$ (250 ml). The mixture was refluxed 2 h and stirred at 25°C for another 12 h. After hydrolysis with water, the aqueous and organic phases were separated, and the aqueous phase was washed with $CHCl_3$. The organic phases were combined, washed with water, and dried over Na_2SO_4. The solvent was removed and the crude product column chromatographed on silica gel eluting with $CHCl_3$ to afford 7.76 g (55%) of **5**, m.p. 76–77°C.

21 Elemental analyses for N: **3** 3.42 (calc. 3.49), **4** 3.90 (calc. 4.06), **6** 4.13 (calc. 4.06), **7** 4.59 (calc. 4.55), **9** 4.40 (calc. 4.25).

22 For example, **3**: ^{1}H-NMR (250 MHz, $CDCl_3$) $\delta = 2.43$ (s, 9H), 3.88 (s, 18H), 4.52 (s, 6H), 6.95 (s, 3H), 7.27 (d, 6H, J = 8.1 Hz), 7.42 (d, 6H, J = 8.1 Hz), 7.75 (d, 6H), 8.46 (t, 3H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) $\delta = 21.45$ (CH_3), 52.41 (CH_3), 53.51 (CH_2), 127.52 (CH), 127.55 (CH), 129.61 (CH), 129.73 (CH), 131.35 (C), 133.03 (CH), 134.40 (C), 136.26 (C), 139.63 (C), 144.17 (C), 165.08 (C).

6: ^{1}H-NMR (250 MHz, $CDCl_3$) $\delta = 2.34$ (s, 18H), 2.38 (s, 9H), 3.78 (s, 36H), 4.36 (s, 6H), 4.50 (s, 12H), 6.78 (s, 6H), 6.80 (s, 3H), 6.95 (s, 3H), 7.13–7.20 (m, 24H), 7.38 (d, 12H, J = 8.1 Hz), 7.70 (d, 12H), 8.45 (t, 6H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) $\delta = 21.42$ (CH_3), 52.35 (CH_3), 53.67 (CH_2), 54.06 (CH_2), 126.20 (CH), 127.15 (CH), 127.24 (CH), 127.57 (CH), 128.00 (CH), 129.54 (CH), 129.63 (CH), 129.70 (CH), 131.39 (C), 133.28 (CH), 134.45 (C), 134.86 (C), 136.76 (C), 137.01 (C), 139.91 (C), 140.12 (C), 143.75 (C), 144.02 (C), 165.06 (C).

9: ^{1}H-NMR (250 MHz, $CDCl_3$) $\delta = 2.35$ (s, 63H), 3.78 (s, 72H), 4.3–4.6 (m, 42H), 6.6–7.1 (m, 30H), 7.1–7.25 (d, 60H), 7.35–7.45 (d, 24H), 7.72 (d, 24H), 8.45 (t, 12H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) $\delta = 21.52$ (CH_3), 52.42 (CH_3), 53.81 (CH_2), 53.90 (CH_2), 54.05 (CH_2), 127.41 (CH), 127.68 (CH), 129.80 (CH), 131.47 (C), 133.39 (CH), 134.58 (C), 137.24 (C), 140.06 (C), 144.09 (C), 165.15 (C).

23 M = 1021 Da (calc. 1204.32 Da) for **3**, M = 2367 Da (calc. 3108.45 Da) for **6**, M = 3903 Da (calc. 6916.76 Da) for **9**, calibrated with benzil; M = 4780 Da for **9**, calibrated with a polystyrene standard (M = 3770 Da).

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