Synthesis and Characterization of Water-Soluble Tin-Based Metallodendrimers

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Introduction of ionic or nonionic hydrophilic terminal groups into the hydrophobic dendritic backbone $Si(CH_2CH_2Sn)_4$ led to a variety of first-generation water-soluble tin-based dendrimers. Functionalization of the hydridotin dendrimer $Si(CH_2CH_2SnH_3)_4$ (**1**) via 12-fold hydrostannation reaction of acrylic acid derivatives served as the key step. **1** reacts with methyl acrylate to give $Si[CH_2CH_2Sn(CH_2CH_2COOCH_3)_3]_4$ (**2**), which by means of alkaline hydrolysis was converted into the water-soluble carboxylate-terminated dendrimers $Si[CH_2CH_2Sn(CH_2CH_2COOM)_3]_4$ [M = Na (**3**), K (**4**)]. Reduction of **2** afforded the dendritic polyalcohol $Si[CH_2CH_2Sn(CH_2CH_2CH_2OH)_3]_4$ (**5**). A clearly enhanced water solubility due to nonionic surface functionalization of **2** was obtained by its reaction with 2-aminoethanol, formally yielding $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_{2.5}(CH_2CH_2COOCH_3)_{0.5}]_4$ (**6**). The hydrostannation of O-protected *N*-(2-hydroxyethyl)acrylamides by **1**, however, gave the monodisperse derivatives $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OR)_3]_4$ [R = $CO_2{}^tBu$ (**7**), $SiMe_2{}^tBu$ (**8**)]; deprotection of **8** with tetra-*n*-butylammonium fluoride yielded the water-soluble $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_3]_4$ (**9**). Also via hydrostannation reaction by **1**, the ester-substituted analogue $Si[CH_2CH_2Sn(CH_2CH_2COOCH_2CH_2OH)_3]_4$ (**10**), showing a clearly lower hydrolytic stability, and the homologous amide-substituted dendrimer $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OCH_2CH_2OH)_3]_4$ (**11**) were synthesized. The new organotin dendrimers were characterized by elemental analysis, multinuclear NMR spectroscopy (^1H, ^{13}C, ^{119}Sn), and mass spectrometry (MALDI-TOF, ESI). With respect to the potential use of water-soluble tin-based metallodendrimers as X-ray contrast agents, **6** was studied in vivo in mice, roughly estimating its LD_{50} to 3 mmol Sn/kg body weight.

Introduction

The increasing attention the metallodendrimers receive within the broad field of dendrimer chemistry reflects the growing interest in potential applications of this relatively young class of synthetically demanding as well as aesthetically pleasing compounds due to their specific properties.[1] Metal atoms have been incorporated into the different sites of the dendritic structure: the core unit, the branches, the branching centers, or the periphery of the dendrimer.[2] Using transition metals mainly, metallodendrimers with beneficial properties for catalysis,[3] host−guest chemistry,[4] and electro- and photochemical[5] or medicinal application[6] have been synthesized. There are some interesting lanthanide-containing metallodendrimers known.[7] Only a few main group metals have been used in dendrimer chemistry so far: Crown ether-based dendrimers that bind alkali metal ions have been reported.[8] A unique organobismuth dendrimer has been synthesized with 10 bismuth atoms connected via phenylene branches.[9]

Recently, we systematically opened up the field of organotin dendrimers in analogy to the organo-

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silicon[10] and the organogermanium[11] dendrimers known. Before, already a few triorganotin derivatives could be found in the literature, which are classified as dendrimers but that have not been synthesized from this aspect: $E(SnMe_3)_4$ (E = Sn, Si,[12] C)[13] and $E(CH_2SnMe_3)_4$ (E = Sn,[14] Si)[15] have been reported in connection with NMR sprectroscopic investigations; $Si(CH_2SnBu_3)_4$ represents a derivatization product of a novel polylithiated compound.[16] Furthermore, a tin phthalocyanine complex containing four tetraaza macrocycles may be classified as a metallodendrimer with the tin atom located in the core.[17] We established the divergent synthesis of tin-based dendrimers, reporting on the first generation metallodendrimers $Si(CH_2CH_2SnR_3)_4$ with R = Ph, Br, and H as valuable intermediates for the further approach to surface-functionalized or higher order organotin dendrimers with the metal atoms as branching sites.[18]

In this paper, we disclose our comprehensive work on solubilizing the hydrophobic dendritic backbone $Si(CH_2CH_2Sn)_4$ via ionic or nonionic hydrophilic functionalization of the dendrimer surface. Aiming for stable, water-soluble molecules with a high metal content for the use as iodine-free X-ray contrast agents,[19] the first water-soluble tin-based metallodendrimers were synthesized and characterized.

Experimental Section

General Comments. All reactions involving air-sensitive reagents were carried out in a protective atmosphere of nitrogen using dried, freshly distilled solvents. The N-substituted acrylamide derivatives $CH_2{=}CHCONHCH_2CH_2OH$ and $CH_2{=}CHCONHCH_2CH_2OCH_2CH_2OH$ were prepared according to a literature procedure.[20] The O-protected derivatives $CH_2{=}CHCONHCH_2CH_2OCO_2C(CH_3)_3$ and $CH_2{=}CHCONHCH_2CH_2OSi(CH_3)_2C(CH_3)_3$ were prepared by standard protection methods.[21,22] The hydridotin dendrimer $Si(CH_2CH_2SnH_3)_4$ (**1**) was prepared as reported previously.[18] CHN analyses were performed on a Perkin-Elmer CHNS/O Analyzer 2400; Sn contents (as well as some of the CHN analyses) were determined by Analytische Laboratorien Reuter & Partner GmbH (Lindlar, Germany). NMR spectra were recorded on Bruker spectrometers ARX 200 (^{1}H, 200.1 MHz; ^{13}C{^{1}H}, 50.32 MHz) and ARX 400 (^{1}H, 400.1 MHz; ^{13}C{^{1}H}, 100.6 MHz; ^{119}Sn{^{1}H inverse gated}, 149.2 MHz); chemical shifts are referenced to $(CH_3)_4Si$ (^{1}H and ^{13}C) and $(CH_3)_4Sn$ (^{119}Sn), respectively.

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry was performed in the reflectron mode of an Applied Biosystems Voyager-Elite or a PerSeptive Biosystems Voyager-DE-STR mass spectrometer equipped with a nitrogen laser emitting at 337 nm. Acceleration voltage was set to 20 and 25 kV, respectively, with positive or negative ionization. The mass spectrometers were externally calibrated with a mix of three synthesized peptides. Sample solutions were prepared with an approximate concentration of 1 mM in tetrahydrofuran or methanol. The matrixes 2,5-dihydroxybenzoic acid (DHB) and α-cyano-4-hydroxycinnamic acid (ACCA) were employed in 3:1 acetonitrile/water. For all samples, 1 μL of analyte was mixed with 1 μL of matrix solution, and 1 μL of the mixture was pipetted onto the target and allowed to dry at room temperature. Electrospray ionization (ESI) mass spectra were acquired using a Micromass Platform LCZ single quadrupole instrument. Typical ionization parameters were capillary 3.25 kV, cone 40 V. The source temperature was set to 100 °C and the desolvation temperature to 150 °C. All samples were dissolved in 1:1 acetonitrile/water with an approximate concentration of 100 mM; 0.01% trifluoroacetic acid was added. A syringe pump was used to infuse the sample solution at a flow rate of 100 μL/min; nitrogen was used separately as nebulizer gas with a flow rate of 400 L/h.

$Si[CH_2CH_2Sn(CH_2CH_2COOCH_3)_3]_4$ (2). A stirred solution of **1** (3.42 g, 5.45 mmol) and AIBN (406 mg, 2.47 mmol) in toluene (50 mL) was treated with freshly distilled methyl acrylate (7.04 g, 81.8 mmol) at 0 °C. After stirring the reaction mixture for 1 h at room temperature and 1 h at 45 °C, all volatiles were carefully removed in vacuo at 45 °C. The crude product (8.8 g) was purified by column chromatography (silica gel, diethyl ether/hexane/dichloromethane, 2:1:1) to afford **2** as a colorless oil (2.75 g, 30%). ^{1}H NMR (200.1 MHz, C_6D_6): δ 1.00 (m, 8H, $SiCH_2CH_2Sn$), 1.04 (m, 8H, $SiCH_2CH_2Sn$), 1.06 (t, $|^3J(^1H^1H)| = 7.7$ Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1H^{117/119}Sn)| = 48.9/51.2$ Hz), 2.55 (t, $|^3J(^1H^1H)| = 7.7$ Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1H^{117/119}Sn)| = 58.7/61.5$ Hz), 3.40 (s, 36H, OCH_3). ^{13}C{^{1}H} NMR (50.32 MHz, C_6D_6): δ 2.69 ($SiCH_2CH_2Sn$; $|^1J(^{13}C^{117/119}Sn)| = 336.2/351.9$ Hz), 4.61 ($SnCH_2CH_2CO$; $|^1J(^{13}C^{117/119}Sn)| = 310.3/324.7$ Hz), 7.07 ($SiCH_2CH_2Sn$; $|^2J(^{13}CSn)| = 33.0$ Hz), 30.99 ($SnCH_2CH_2CO$; $|^2J(^{13}CSn)| = 20.6$ Hz), 51.23 (OCH_3), 175.64 (CO; $|^3J(^{13}CSn)| = 37.2$ Hz). ^{119}Sn{^{1}H} NMR (149.2 MHz, C_6D_6): δ −3.5. MALDI-TOF MS (ACCA, THF): *m/z* 1683 $[M + Na]^+$ (calcd 1683), 1699 $[M + K]^+$ (calcd 1699). Anal. Calcd for $C_{56}H_{100}O_{24}SiSn_4$ (1660.24): C, 40.51; H, 6.07; Sn, 28.60. Found: C, 40.61; H, 6.11; Sn, 28.51.

$Si[CH_2CH_2Sn(CH_2CH_2COONa)_3]_4$ (3). A stirred solution of **2** (480 mg, 0.289 mmol) in tetrahydrofuran (100 mL) was treated with sodium hydroxide (693 mg, 17.3 mmol) dissolved in water (12.5 mL). Methanol (40 mL) was added to almost clear up the reaction suspension, and ultrasound was applied during 60 min. After stirring for 18 h, two layers had formed, and the upper layer was discarded. The solvents were removed in vacuo, and the solid residue was dissolved in water, filtered, and dried again to give **3** as a white solid (0.50 g, 99%). ^{1}H NMR (200.1 MHz, D_2O): δ 0.40−0.70 (m, 16H, $SiCH_2CH_2Sn$), 0.81 (t, $|^3J(^1H^1H)| = 8.6$ Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)| = 49.0$ Hz), 2.12 (t, $|^3J(^1H^1H)| = 8.6$ Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1HSn)| = 41.0$ Hz). ^{13}C{^{1}H} NMR (50.32 MHz, D_2O): δ 0.00 ($SiCH_2CH_2Sn$; $|^1J(^{13}C^{117/119}Sn)| = 316.2/331.3$ Hz), 4.28 ($SnCH_2CH_2CO$; $|^1J(^{13}C^{117/119}Sn)| = 296.0/309.8$ Hz), 5.70 ($SiCH_2CH_2Sn$; $|^2J(^{13}CSn)| = 31.6$ Hz), 34.33 ($SnCH_2CH_2CO$; $|^2J(^{13}CSn)| = 18.1$

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Hz), 185.29 (CO; $|^3J(^{13}C^{117/119}Sn)|$ = 56.3/58.9 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −0.2. MALDI-TOF MS (DHB, CH_3OH): *m/z* 1756 $[M]^-$ (calcd 1756). Anal. Calcd for $C_{44}H_{64}Na_{12}O_{24}SiSn_4$ (1755.70): C, 30.10; H, 3.67; Sn, 27.04. Found: C, 29.85; H, 3.80; Sn, 26.84.

Si[$CH_2CH_2Sn(CH_2CH_2COOK)_3$]$_4$ (4). In analogy with the synthesis of **3**, **2** (500 mg, 0.301 mmol) and potassium hydroxide (1.01 g, 18.0 mmol) were reacted and worked up to give **4** as a white solid (0.53 g, 90%). ^1H NMR (200.1 MHz, D_2O): δ 0.50−0.80 (m, 16H, $SiCH_2CH_2Sn$), 0.87 (t, $|^3J(^1H^1H)|$ = 8.7 Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)|$ = 48.5 Hz), 2.18 (t, $|^3J(^1H^1H)|$ = 8.7 Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1HSn)|$ = 40.0 Hz). $^{13}C\{^1H\}$ NMR (50.32 MHz, D_2O): δ 0.15 ($SiCH_2CH_2Sn$; $|^1J(^{13}C^{117/119}Sn)|$ = 317.2/332.1 Hz), 4.31 ($SnCH_2CH_2CO$; $|^1J(^{13}C^{117/119}Sn)|$ = 294.8/308.5 Hz), 5.81 ($SiCH_2CH_2Sn$; $|^2J(^{13}CSn)|$ = 32.1 Hz), 34.41 ($SnCH_2CH_2CO$; $|^2J(^{13}CSn)|$ = 17.8 Hz), 185.32 (CO; $|^3J(^{13}C^{117/119}Sn)|$ = 56.6/59.1 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −0.2. Anal. Calcd for $C_{44}H_{64}K_{12}O_{24}SiSn_4$ (1949.00): C, 27.12; H, 3.31; Sn, 24.36. Found: C, 26.63; H, 2.81; Sn, 24.53.

Si[$CH_2CH_2Sn(CH_2CH_2CH_2OH)_3$]$_4$ (5). A solution of **2** (1.48 g, 0.891 mmol) in diethyl ether (10 mL) was slowly added to a stirred suspension of lithium aluminum hydride (812 mg, 21.4 mmol) in diethyl ether (50 mL) at room temperature. After refluxing for 24 h, the reaction mixture was hydrolyzed with water (1.6 mL, 90 mmol) in dioxane (5 mL) at 0 °C and concentrated in vacuo. The precipitate formed was extracted with methanol (50 and 30 mL). Removal of the solvent in vacuo gave the solid crude product (1.1 g, 93% crude yield). A portion of it (380 mg) was purified by preparative thin-layer chromatography (silica gel, methanol/hexane, 8:1) to yield **5** as a colorless viscous oil (58 mg, corresponding to 14%). ^1H NMR (200.1 MHz, CD_3OD): δ 0.75−1.05 (m, 40H, $SiCH_2CH_2SnCH_2$), 1.75 (tt, 24H, $SnCH_2CH_2CH_2OH$), 3.49 (t, $|^3J(^1H^1H)|$ = 6.7 Hz, 24H, $SnCH_2CH_2CH_2OH$). $^{13}C\{^1H\}$ NMR (50.32 MHz, CD_3OD): δ 1.86 ($SiCH_2CH_2Sn$), 5.14 ($SnCH_2CH_2CH_2OH$; $|^1J(^{13}C^{117/119}Sn)|$ = 287.8/301.3 Hz), 9.92 ($SiCH_2CH_2Sn$), 30.94 ($SnCH_2CH_2CH_2OH$; $|^2J(^{13}CSn)|$ = 18.4 Hz), 66.46 ($SnCH_2CH_2CH_2OH$; $|^3J(^{13}CSn)|$ = 60.7 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, CD_3OD): δ −3.5. MALDI-TOF MS (ACCA, CH_3OH): *m/z* 1325 $[M + H]^+$ (calcd 1325). Anal. Calcd for $C_{44}H_{100}O_{12}SiSn_4$ (1324.12): C, 39.91; H, 7.61; Sn, 35.85. Found: C, 39.70; H, 7.45; Sn, 35.71.

Si[$CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_{2.5}(CH_2CH_2COOCH_3)_{0.5}$]$_4$ (6). A solution of **2** (2.50 g, 1.51 mmol) and 2-aminoethanol (2.21 g, 36.1 mmol) in methanol (120 mL) was vigorously refluxed for 4 days. The methanol was removed, and the oily residue was taken up in diethyl ether (70 mL) and water (90 mL). After separation of the phases, the organic phase was washed with water and the combined aqueous phases were evaporated to dryness. The crude product (2.3 g) was purified by column chromatography (silica gel, methanol/hexane, 10:1) to yield **6** as a colorless oil (1.65 g, 56%). ^1H NMR (200.1 MHz, D_2O): δ 0.40−0.80 (m, 16H, $SiCH_2CH_2Sn$), 0.91 (t, $|^3J(^1H^1H)|$ = 8.1 Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)|$ = 48.9 Hz), 2.32 (t, $|^3J(^1H^1H)|$ = 8.1 Hz, 20H, $SnCH_2CH_2CON$), 2.47 (t, $|^3J(^1H^1H)|$ = 7.7 Hz, 4H, $SnCH_2CH_2COO$), 3.15 (t, $|^3J(^1H^1H)|$ = 5.6 Hz, 20H, NCH_2CH_2O), 3.49 (t, $|^3J(^1H^1H)|$ = 5.6 Hz, 20H, NCH_2CH_2O), 3.53 (s, 6H, OCH_3). $^{13}C\{^1H\}$ NMR (50.32 MHz, D_2O): δ 0.78 ($SiCH_2CH_2Sn$), 3.80 ($SnCH_2CH_2CO$), 5.85 ($SiCH_2CH_2Sn$), 30.50 ($SnCH_2CH_2COO$), 32.33 ($SnCH_2CH_2CON$; $|^2J(^{13}CSn)|$ = 17.6 Hz), 41.18 (NCH_2CH_2O), 51.88 (OCH_3), 59.71 (NCH_2CH_2O), 177.83, 177.91 (CO). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −1.4, −1.5, −1.6. MALDI-TOF MS (ACCA, CH_3OH): *m/z* 2031 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_{12} + Na]^+$ (calcd 2032), 2003 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_{11}(CH_2CH_2COOCH_3) + Na]^+$ (calcd 2003), 1975 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_{10}(CH_2CH_2COOCH_3)_2 + Na]^+$ (calcd 1974), 1946 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_9(CH_2CH_2COOCH_3)_3 + Na]^+$ (calcd 1945), 1918 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_8(CH_2CH_2COOCH_3)_4 + Na]^+$ (calcd 1916), 1887 $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_7(CH_2CH_2COOCH_3)_5 + Na]^+$ (calcd 1887). Anal. Calcd for $C_{66}H_{130}O_{24}N_{10}SiSn_4$ (1950.66): C, 40.64; H, 6.72; N, 7.18; Sn, 24.34. Found: C, 39.64; H, 6.89; N, 6.92; Sn, 23.35.

Si{$CH_2CH_2Sn[CH_2CH_2CONHCH_2CH_2OCO_2C(CH_3)_3]_3$}$_4$ (7). A stirred solution of **1** (284 mg, 0.453 mmol) and V-70 (100 mg, 0.324 mmol) in toluene (30 mL) was treated with *N*-(2-*tert*-butylcarbonatoethyl)acrylamide (1.95 g, 9.06 mmol) at 0 °C. After stirring the reaction mixture for 90 min at 10 °C and for a further 90 min at 30 °C under exclusion of light, hexane (40 mL) was added at 0 °C. The oily phase that formed was separated, redissolved in toluene (20 mL), and again precipitated by adding hexane (20 mL). After separation, the oil was washed with hexane and dried in vacuo to yield **7** as an off-white solid (0.99 g, 68%). ^1H NMR (200.1 MHz, $CDCl_3$): δ 0.40−0.70 (m, 16H, $SiCH_2CH_2Sn$), 0.90 (t, $|^3J(^1H^1H)|$ = 7.5 Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)|$ = 50.1 Hz), 1.36 (s, 108H, $OCCH_3$), 2.33 (t, $|^3J(^1H^1H)|$ = 7.5 Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1HSn)|$ = 53.1 Hz), 3.38 (m, 24H, NCH_2CH_2O), 4.01 (t, $|^3J(^1H^1H)|$ = 5.0 Hz, 24H, NCH_2CH_2O), 6.77 (m, NH). $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ 1.41 ($SiCH_2CH_2Sn$), 4.50 ($SnCH_2CH_2CO$; $|^1J(^{13}CSn)|$ = 313.5 Hz), 6.22 ($SiCH_2CH_2Sn$), 27.46 ($OCCH_3$), 32.70 ($SnCH_2CH_2CO$; $|^2J(^{13}CSn)|$ = 15.3 Hz), 38.35 (NCH_2CH_2O), 65.45 (NCH_2CH_2O), 81.97 ($OCCH_3$), 153.06 (COO), 175.08 (CON). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$): δ −3.0. MALDI-TOF MS (ACCA, CH_3OH): *m/z* 3236 $[M + Na]^+$ (calcd 3232). Anal. Calcd for $C_{128}H_{232}N_{12}O_{48}SiSn_4$ (3210.15): C, 47.89; H, 7.28; N, 5.24; Sn, 14.79. Found: C, 47.91; H, 7.15; N, 5.26; Sn, 14.58.

Si{$CH_2CH_2Sn[CH_2CH_2CONHCH_2CH_2OSi(CH_3)_2C(CH_3)_3]_3$}$_4$ (8). In analogy with the synthesis of **7**, **1** (685 mg, 1.09 mmol) and V-70 (160 mg, 0.519 mmol) in toluene (10 mL) were reacted with *N*-(2-*tert*-butyldimethylsiloxyethyl)acrylamide (3.76 g, 16.4 mmol) for 1 h at 10 °C, for 2 h at 35 °C, and, after adding further V-70 (40 mg, 0.130 mmol), for another 2 h at 40 °C. The reaction mixture was chromatographed on silica gel using 1:1 ethyl acetate/hexane to elute the excess acrylamide and 9:1 ethyl acetate/hexane to elute the product. **8** was obtained as a colorless solid (2.8 g, 76%). ^1H NMR (200.1 MHz, $CDCl_3$): δ 0.04 (s, 72H, $SiCH_3$), 0.55−0.75 (m, 16H, $SiCH_2CH_2Sn$), 0.87 (s, 108H, $SiCCH_3$), 1.01 (t, $|^3J(^1H^1H)|$ = 8.1 Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)|$ = 48.4 Hz), 2.40 (t, $|^3J(^1H^1H)|$ = 8.1 Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1HSn)|$ = 51.6 Hz), 3.29 (dt, $|^3J(^1H^1H)|$ = 5.5 Hz, 24H, NCH_2CH_2O), 3.63 (t, $|^3J(^1H^1H)|$ = 5.5 Hz, 24H, NCH_2CH_2O), 6.64 (m, NH). $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ −5.34 ($SiCH_3$), 1.66 ($SiCH_2CH_2Sn$), 4.75 ($SnCH_2CH_2CO$; $|^1J(^{13}C^{117/119}Sn)|$ = 306.1/320.4 Hz), 6.46 ($SiCH_2CH_2Sn$), 18.25 ($SiCCH_3$), 25.88 ($SiCCH_3$), 33.09 ($SnCH_2CH_2CO$), 41.70 (NCH_2CH_2O), 61.84 (NCH_2CH_2O), 175.03 (CO; $|^3J(^{13}CSn)|$ = 45.5 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$): δ −4.0. MALDI-TOF MS (ACCA, CH_3OH): *m/z* 3413 $[M + K]^+$ (calcd 3417). ESI MS: *m/z* 3380 $[M]^+$ (calcd 3378). Anal. Calcd for $C_{140}H_{304}N_{12}O_{24}Si_{13}Sn_4$ (3379.89): C, 49.75; H, 9.07; N, 4.97; Sn, 14.05. Found: C, 49.75; H, 9.05; N, 4.73; Sn, 13.84.

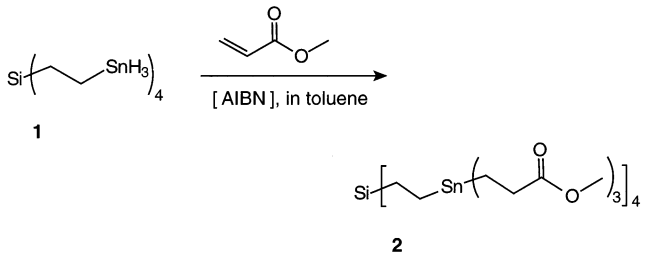
Si[$CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_3$]$_4$ (9). A stirred solution of **8** (860 mg, 0.254 mmol) in tetrahydrofuran (4 mL) was treated with water (0.2 mL) and a 1 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (3.05 mL, 3.05 mmol) at room temperature. After stirring the reaction mixture for 2.5 h, a colorless oil had formed, which was separated from the clear solution, washed with tetrahydrofuran (3 × 5 mL), and dried in vacuo. The crude product (800 mg) was purified by preparative HPLC (Bondapak C 18, 15 μm, 2 × 40 × 100 mm; water/acetonitrile, 9:1); traces of residual tetra-*n*-butylammonium species could be removed by ion exchange (Amberlite IRC-50, Amberlite IRA-67), yielding **9** as a colorless viscous oil (177 mg, 35%). ^1H NMR (200.1 MHz, D_2O): δ 0.40−0.80 (m, 16H, $SiCH_2CH_2Sn$), 0.88 (t, $|^3J(^1H^1H)|$ = 8.2 Hz, 24H, $SnCH_2CH_2CO$; $|^2J(^1HSn)|$ = 49.3 Hz), 2.30 (t, $|^3J(^1H^1H)|$ = 8.2 Hz, 24H, $SnCH_2CH_2CO$; $|^3J(^1HSn)|$ = 50.9 Hz), 3.13 (t,

$|^3J(^1H^1H)|$ = 5.6 Hz, 24H, NCH_2CH$_2$O), 3.46 (t, $|^3J(^1H^1H)|$ = 5.6 Hz, 24H, NCH$_2$CH_2O). $^{13}C\{^1H\}$ NMR (50.32 MHz, D_2O): δ 0.97 (SiCH$_2$*C*H$_2$Sn), 3.93 (Sn*C*H$_2$CH$_2$CO; $|^1J(^{13}C^{117/119}Sn)|$ = 297.0/310.8 Hz), 5.97 (Si*C*H$_2$CH$_2$Sn), 32.50 (SnCH$_2$*C*H$_2$CO; $|^2J(^{13}CSn)|$ = 17.6 Hz), 41.33 (N*C*H$_2$CH$_2$O), 59.85 (NCH$_2$*C*H$_2$O), 178.06 (CO; $|^3J(^{13}CSn)|$ = 46.5 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −1.4. MALDI-TOF MS (ACCA, CH$_3$OH): *m*/*z* 2033 $[M + Na]^+$ (calcd 2032), 2049 $[M + K]^+$ (calcd 2048). ESI MS: *m*/*z* 2008 $[M]^+$ (calcd 2009). Anal. Calcd for $C_{68}H_{136}N_{12}O_{24}SiSn_4$ (2008.74): C, 40.66; H, 6.82; N, 8.37; Sn, 23.63. Found: C, 40.43; H, 6.85; N, 8.37; Sn, 23.38.

Si[CH$_2$CH$_2$Sn(CH$_2$CH$_2$COOCH$_2$CH$_2$OH)$_3$]$_4$ (10). To a solution of **1** (585 mg, 0.933 mmol) and freshly distilled 2-hydroxyethyl acrylate (1.62 g, 14.0 mmol) in tetrahydrofuran (14 mL) was added V-70 (130 mg, 0.421 mmol) at 0 °C. The stirred reaction solution was allowed to warm to room temperature during 3 h and stirred for a further 0.5 h at this temperature, for 2 h at 35 °C, and for 18 h again at room temperature. After removal of the solvent in vacuo, the residue was dissolved in water, and the insoluble solid was filtered off. The aqueous solution was extracted with ethyl acetate (2 × 40 mL) and afterward freed from the water in vacuo. The crude product (1.55 g) was purified by column chromatography (silica gel, dichloromethane/methanol, 10:1 → 5:1) to give **10** as a colorless viscous liquid (0.37 g, 20%). ^1H NMR (200.1 MHz, D_2O): δ 0.50−0.80 (m, 16H, SiCH$_2$CH$_2$Sn), 0.93 (t, $|^3J(^1H^1H)|$ = 7.8 Hz, 24H, SnCH_2CH$_2$CO; $|^2J(^1HSn)|$ = 48.6 Hz), 2.53 (t, $|^3J(^1H^1H)|$ = 7.8 Hz, 24H, SnCH$_2$CH_2CO; $|^3J(^1HSn)|$ = 56.1 Hz), 3.66 (t, $|^3J(^1H^1H)|$ = 4.7 Hz, 24H, OCH$_2$CH_2OH), 4.05 (t, $|^3J(^1H^1H)|$ = 4.7 Hz, 24H, OCH_2CH$_2$OH). $^{13}C\{^1H\}$ NMR (50.32 MHz, D_2O): δ 1.39 (SiCH$_2$*C*H$_2$Sn), 3.30 (Sn*C*H$_2$CH$_2$CO; $|^1J(^{13}C^{117/119}Sn)|$ = 305.8/319.5 Hz), 6.17 (Si*C*H$_2$CH$_2$Sn), 30.60 (SnCH$_2$*C*H$_2$CO; $|^2J(^{13}CSn)|$ = 18.2 Hz), 59.45 (OCH$_2$*C*H$_2$OH), 65.87 (O*C*H$_2$CH$_2$OH), 177.03 (CO; $|^3J(^{13}CSn)|$ = 43.4 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −0.6. MALDI-TOF MS (DHB, THF): *m*/*z* 2043 $[M + Na]^+$ (calcd 2043). Anal. Calcd for $C_{68}H_{124}O_{36}SiSn_4$ (2020.56): C, 40.42; H, 6.19; Sn, 23.50. Found: C, 40.27; H, 6.18; Sn, 23.29.

Si[CH$_2$CH$_2$Sn(CH$_2$CH$_2$CONHCH$_2$CH$_2$OCH$_2$CH$_2$OH)$_3$]$_4$ (11). A stirred solution of **1** (492 mg, 0.784 mmol) and V-70 (93 mg, 0.302 mmol) in tetrahydrofuran (5 mL) was treated with a solution of *N*-[2-(2-hydroxyethoxy)ethyl]acrylamide (1.87 g, 11.7 mmol) in tetrahydrofuran (10 mL) at 0 °C under exclusion of light. The reaction mixture was stirred for 1 h at this temperature, for 1 h at 5 °C, and for a further 24 h at 10 °C. The oily phase that formed was separated, washed with tetrahydrofuran (3 × 20 mL), and dried in vacuo. The residue was dissolved in water, the insoluble solid was filtered off, and the water was removed in vacuo to leave the highly viscous crude product (1.8 g, 90% crude yield). A portion of it (350 mg) was purified by preparative thin-layer chromatography (silica gel, dichloromethane/methanol, 5:3) to yield **11** as a colorless viscous oil (75 mg, corresponding to 19%). ^1H NMR (200.1 MHz, D_2O): δ 0.50−0.80 (m, 16H, SiCH$_2$CH$_2$Sn), 0.89 (t, $|^3J(^1H^1H)|$ = 8.0 Hz, 24H, SnCH_2CH$_2$CO; $|^2J(^1HSn)|$ = 49.4 Hz), 2.30 (t, $|^3J(^1H^1H)|$ = 8.0 Hz, 24H, SnCH$_2$CH_2CO; $|^3J(^1HSn)|$ = 50.3 Hz), 3.21 (t, $|^3J(^1H^1H)|$ = 5.4 Hz, 24H, NCH_2CH$_2$O), 3.45 (m, 48H, NCH$_2$CH_2OCH_2CH$_2$OH), 3.55 (t, $|^3J(^1H^1H)|$ = 5.0 Hz, 24H, OCH$_2$CH_2OH). $^{13}C\{^1H\}$ NMR (50.32 MHz, D_2O): δ 1.01 (SiCH$_2$*C*H$_2$Sn), 3.98 (Sn*C*H$_2$CH$_2$CO; $|^1J(^{13}C^{117/119}Sn)|$ = 291.1/304.6 Hz), 5.96 (Si*C*H$_2$CH$_2$Sn), 32.46 (SnCH$_2$*C*H$_2$CO; $|^2J(^{13}CSn)|$ = 17.0 Hz), 38.90 (N*C*H$_2$CH$_2$O), 60.25 (OCH$_2$*C*H$_2$OH), 68.72 (NCH$_2$*C*H$_2$O), 71.45 (O*C*H$_2$CH$_2$OH), 177.86 (CO; $|^3J(^{13}CSn)|$ = 46.1 Hz). $^{119}Sn\{^1H\}$ NMR (149.2 MHz, D_2O): δ −1.1. MALDI-TOF MS (ACCA, CH$_3$OH): *m*/*z* 2559 $[M + Na]^+$ (calcd 2560). Anal. Calcd for $C_{92}H_{184}N_{12}O_{36}SiSn_4$ (2537.38): C, 43.55; H, 7.31; N, 6.62; Sn, 18.71. Found: C, 43.36; H, 7.27; N, 6.82; Sn, 18.53.

Scheme 1



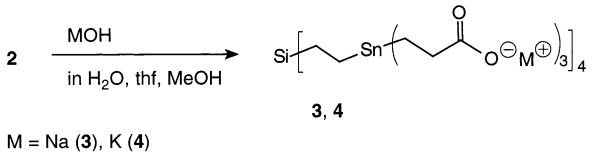
Results and Discussion

Water-Insoluble Starting Material. The reactive key intermediate of the divergent route toward polarly funtionalized tin-based dendrimers, the 12-fold hydride-substituted organotin dendrimer tetrakis(2-stannylethyl)silane (**1**), was prepared by a high-yield three-step synthesis involving the hydrostannation reaction of the core molecule tetravinylsilane, the selective bromination of the resulting tetrakis[2-(triphenylstannyl)ethyl]-silane, and the lithium aluminum hydride reduction of the tetrakis[2-(tribromostannyl)ethyl]silane as described earlier.[18] The high reactivity of the Sn−H bonds in the dendritic organotin hydride **1** toward activated double bonds[23] could be utilized for its functionalization via a 12-fold hydrostannation reaction. **1** exothermically reacts with an excess of methyl acrylate in the presence of 3 mol % of the free radical forming catalyst AIBN at room temperature and for completion of the reaction at 45 °C to give tetrakis{2-(tris[2-(methoxycarbonyl)ethyl]-stannyl)ethyl}silane (**2**) in almost quantitative crude yield; chromatographic purification, however, reduced the yield to 30% (Scheme 1). The 12-fold addition reaction exclusively follows the anti-Markownikow rule.

The ^1H NMR spectrum of **2** shows two triplet signals of the 2-carbonylethyl group attached to the tin atom at 1.06 and 2.55 ppm with their typical two-bond and three-bond hydrogen tin coupling constants $|^2J(^1H^{117/119}Sn)|$ = 48.9/51.2 Hz and $|^3J(^1H^{117/119}Sn)|$ = 58.7/61.5 Hz, respectively. The magnitude of the carbon tin coupling constants $|^nJ(^{13}C^{117/119}Sn)|$ observed for the resonances in the $^{13}C\{^1H\}$ NMR spectrum of **2** reflects the constitution of the molecule according to $|^1J| > |^3J| > |^2J|$: The two carbon atoms attached directly to the tin atom show the by far largest coupling constants $|^1J(^{13}C^{117/119}Sn)|$ = 336.2/351.9 Hz (SiCH$_2$*C*H$_2$Sn) or 310.3/324.7 Hz (Sn*C*H$_2$CH$_2$CO), the two carbon atoms next to those show the smallest coupling constants $|^2J(^{13}CSn)|$ = 33.0 Hz (Si*C*H$_2$CH$_2$Sn) or 20.6 Hz (SnCH$_2$-*C*H$_2$CO), respectively, and for the carbonyl carbon atom $|^3J(^{13}CSn)|$ = 37.2 Hz was observed. The MALDI-TOF mass spectrum of **2** reveals signals at *m*/*z* 1683 and 1699 corresponding to the molecular ion augmented by sodium and potassium, respectively. The well-resolved isotopic multiplets of high intensity bear a close resemblance to the calculated isotopic distribution. The absence of significant peaks at *m*/*z* values lower than that of the molecular ion rules out any lower molecular weight impurities of the dendritic product.[24] **2** is a water-insoluble colorless oil.

(23) (a) van der Kerk, G. J. M.; Noltes, J. C. *J. Appl. Chem.* **1959**, *9*, 106. (b) Neumann, W. P.; Niermann, H.; Sommer, R. *Liebigs Ann. Chem.* **1962**, *659*, 27.

Scheme 2



3, 4

M = Na (**3**), K (**4**)

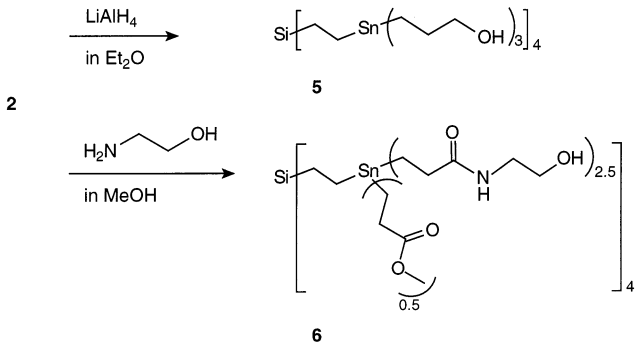
Water Solubility via Ionic Functionality. By means of alkaline hydrolysis the methyl ester end groups in the dendrimer **2** could be converted into the corresponding ionic carboxylate groups. A solution of **2** in tetrahydrofuran reacts with an aqueous solution of a 5-fold excess of sodium hydroxide in the presence of mediating methanol[25] and with application of ultrasound[26] to quantitatively yield tetrakis{2-(tris[sodium(2-carboxyethyl)]stannyl)ethyl}silane (**3**) (Scheme 2). While in organotin esters bearing the ester group in the α-position with respect to the tin atom the carbon−tin bond is not stable toward alkaline hydrolysis,[27] the carboxylate-terminated dendrimer **3** formed as a water-stable white solid. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of **3** resemble those of **2**, yet the missing resonances due to the methoxy protons or carbon atom, respectively, and the typical shift of the ^{13}C resonance of the carbonyl group in **2** from 175.64 to 185.29 ppm for the corresponding carboxylate group in **3** are obvious. The MALDI-TOF mass spectrometric analysis of **3** succeeded in the negative ion mode, generating the molecular ion $[M]^-$ at *m*/*z* 1756.

The 12 peripheral carboxylate functionalities bring about the water solubility of **3** determined to be 490 mg/mL = 0.28 M at room temperature. Yet, due to the high basicity of its aqueous solution, **3** is not suitable for an in vivo application. Under physiological conditions at a pH < 7.5 the water solubility observed for **3** is not sufficient; a partial protonation of the carboxylate end groups reduces the solubility (see below).

The potassium salt tetrakis{2-(tris[potassium(2-carboxyethyl)]stannyl)ethyl}silane (**4**) was synthesized analogously by reacting **2** with an excess of potassium hydroxide (Scheme 2). Acidification of an aqueous solution of **4** with hydrochloric acid afforded the corresponding polyacid. This protonated carboxy-terminated dendrimer showed to be insoluble in water, as expected.[25] Its likewise very low solubility in common organic solvents and its instability, as described for monofunctional triorganostannyl propionic acid derivatives,[27] prevented it from being fully characterized. Yet, the NMR spectra of the freshly prepared product in deuterated tetrahydrofuran revealed the typical resonances for the hydroxylic proton of the carbonic acid group at 10.3 ppm and for the carboxy carbon atom at 178 ppm.

Water Solubility via Nonionic Hydrophilic Functionality. Aiming for hydrophilic surface functionalization of the organotin dendrimers without the use of ionic ligands, the ester-substituted dendrimer **2** was converted into the corresponding polyalcohol. Reduction of **2** with lithium aluminum hydride[28] afforded tetrakis{2-[tri(3-hydroxypropyl)stannyl]ethyl}silane (**5**) (Scheme 3). Purification of the crude product with preparative thin-layer chromatography, though, resulted in only a low yield. The NMR resonances of the additional methylene group generated in **5** are the typical ones observed for a hydroxy-bearing CH_2 group: δ ^{1}H = 3.49 ppm and δ ^{13}C = 66.46 ppm. The MALDI-TOF mass spectrum of **5** shows the expected molecular ion peak $[M + H]^+$ as a well-resolved isotopic multiplet at *m*/*z* 1325. In addition, there are fragment ion peaks with an observed mass difference of 59 amu between the centers of the contiguous multiplets that correspond to the successive loss of all 12 $CH_2CH_2CH_2OH$ groups from the parent molecular ion. Dendrimer **5** is easily soluble in methanol; yet, its water solubility observed is not yet adequate.

Scheme 3



To attain an enhanced solubility in water, an additional carbonic acid amide besides a hydroxy functionality was to be introduced into the outer sphere of the organotin dendrimer. The ester-terminated dendrimer **2** was reacted with a double molar amount of 2-aminoethanol[29] in refluxing methanol for 4 days to achieve the synthesis of the corresponding *N*-(2-hydroxyethyl)amide-terminated dendrimer. By portioning the crude product between diethyl ether and water, the water-soluble product was separated from unreacted dendritic starting material; afterward surplus 2-aminoethanol was removed via column chromatography. Yet, elemental analysis and proton NMR investigation of the isolated product revealed that on average only 10 out of the 12 ester end groups in **2** had reacted to the *N*-(2-hydroxyethyl)amide groups, formally affording Si-$[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_{2.5}(CH_2CH_2COOCH_3)_{0.5}]_4$ (**6**) (Scheme 3). Variation of the reaction parameters in time, temperature, solvent, or stoichiometry did not bring about any improvement. The ^{1}H NMR spectrum of **6** clearly shows the resonances of the residual ester groups at 2.47 ppm (CH_2COO) and 3.53 ppm ($COOCH_3$); the ^{13}C{^{1}H} NMR spectrum of **6** shows them as small peaks at 30.50 ppm (CH_2COO) and 51.88 ppm ($COOCH_3$) and as an additional peak in the carbonyl region. The main resonances, of course, are due to the 2-[*N*-(2-hydroxyethyl)carbamido]ethyl groups and

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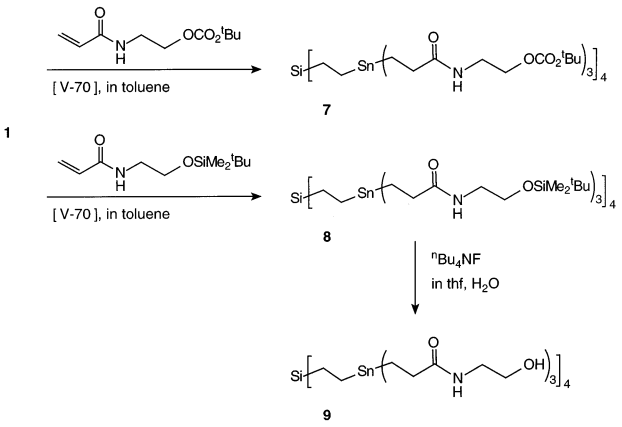
the $Si(CH_2CH_2Sn)_4$ backbone of **6**. The ethylene protons of the former group show two dominant pairs of triplet signals at 0.91 and 2.32 ppm ($SnCH_2CH_2CON$) and at 3.15 and 3.49 ppm (NCH_2CH_2O); the corresponding ethylene carbon atoms resonate at 3.80 and 32.33 ppm ($SnCH_2CH_2CON$) and at 41.18 and 59.71 ppm (NCH_2CH_2O). The lack of monodispersity of **6** is clearly illustrated by the three different $^{119}Sn\{^1H\}$ NMR resonances observed. Also, the MALDI-TOF mass spectrum represents differently substituted dendritic species; the mass differences of 29 amu between the isotopic multiplets corresponding to the sodium ion adducts $[Si(CH_2CH_2Sn)_4(CH_2CH_2CONHCH_2CH_2OH)_x(CH_2CH_2COOCH_3)_{12-x} + Na]^+$ with $x = 7-12$ reflects the gradual conversion of the ester to the amide groups.

Despite the residual ester end groups—the ester-terminated starting material **2** is water-insoluble—the nonionic dendrimer **6** shows a water solubility of 600 mg/mL = 0.31 M at room temperature due to its peripheral *N*-(2-hydroxyethyl)amide functionalities. After 6 weeks at room temperature, a beginning decomposition of the aqueous solution of **6** was detected NMR spectroscopically. This slight hydrolytic instability observed[29] is in accordance with our failed attempt to react **6** with additional 2-aminoethanol in refluxing water during 15 h, which also led to some decomposition.

The acute toxicity of **6**, showing an analyzed tin content of 23.35%, was roughly estimated by intravenous administration of its neutral aqueous solution (859 mmol Sn/L) into mice. Both mice used survived a dose of 2 mmol Sn/kg body weight during an observation time of 7 days, whereas a dose of 4 mmol Sn/kg killed two mice out of two. From that, the acute toxicity of **6** derives to $LD_{50} \approx 3$ mmol Sn/kg. This tolerance in its order of magnitude compares to the LD_{50} of ca. 5 mmol Gd/kg determined for the metal-containing reference substance, the clinically used, yet ionic MRI contrast medium Gd-DTPA (Magnevist).[30] Heat sterilization—essential for all parenteral drugs—failed for the dendrimer **6** though, the precipitate indicating some degradation.

Pursuing the intended synthesis of the monodisperse molecule $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OH)_3]_4$, we attempted the radically initiated hydrostannation reaction of *N*-(2-hydroxyethyl)acrylamide[20] with the dendritic organotin hydride **1**. Yet, the problem of solubility of the water-instable dendritic starting material on one hand and the water-soluble product on the other hand stopped a complete conversion of **1** via the planned 12-fold addition reaction. Despite variing the parameters, all reactions run brought about only partially hydrostannated intermediates, which precipitated out of the organic solvent used, eluding its further conversion. Gel permeation chromatography of the products obtained indicated differently substituted dendrimers as well as oligomerized acrylamides. Eventually, O-protection of the *N*-(2-hydroxyethyl)acrylamide with the *tert*-butyloxycarbonyl (BOC) or *tert*-butyldimethylsilyl (TBDMS) group made a success of synthesizing the corresponding 12-fold hydrostannated, water-insoluble dendrimers $Si[CH_2CH_2Sn(CH_2CH_2CONHCH_2CH_2OR)_3]_4$. The BOC group originally was chosen for amine protection of the mono-N-substituted acrylamide; yet, *N*-(2-hydroxyethyl)acrylamide submitted to a standard protection method with di-*tert*-butyl dicarbonate in the presence of amines[21] yielded *N*-(2-*tert*-butylcarbonatoethyl)acrylamide. This O-protected acrylic derivative as well as *N*-(2-*tert*-butyldimethylsiloxyethyl)acrylamide,[22] each employed in excess, react with the dendritic organotin hydride **1** in a homolytic process in toluene to give the monodisperse dendrimers tetrakis{2-[tris(2-[*N*-(2-*tert*-butylcarbonatoethyl)carbamido]ethyl)stannyl]ethyl}silane (**7**) and tetrakis{2-[tris(2-[*N*-(2-*tert*-butyldimethylsiloxyethyl)carbamido]ethyl)stannyl]ethyl}silane (**8**), respectively (Scheme 4). During the reaction the product stayed in solution and was worked up by precipitating on addition of hexane (**7**) or by chromatographic purification (**8**), respectively, for separation of the excess acrylamide. The advantageous use of V-70 [2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)], the lowest temperature azo free-radical initiator commercially available,[31] instead of AIBN (2,2′-azobisisobutyronitrile) avoided any oligomerization byproducts due to its approximately 35 °C lower half-life decomposition temperature, which made the hydrostannation reaction start at a temperature as low as 10 °C. The ^1H NMR spectra of the O-protected dendrimers **7** and **8**, recorded in d-chloroform, clearly show the resonances of the amido protons at around 6.7 ppm as well as the methyl proton resonances of the protection groups besides the typical signals already observed for the dendrimer backbone and the N-substituted carbamidoethyl functionality of **6** in D_2O. The MALDI-TOF mass spectra of **7** and **8** show signals at *m*/*z* 3236 and 3413 corresponding to the sodium and potassium ion adducts of the dendrimers, respectively; the low resolution of the spectra, which prevents any isotopic pattern of the signals from being seen, might be due to the low miscibility of the samples and the matrix used. In addition, **8** was subjected to an ESI mass spectrometric analysis, revealing a well-resolved multiplet for the molecular ion $[M]^+$.

Scheme 4



Removal of the BOC group by treatment of **7** in tetrahydrofuran with dilute hydrochloric acid[32] did not succeed to completion. Yet, the complete cleavage of the

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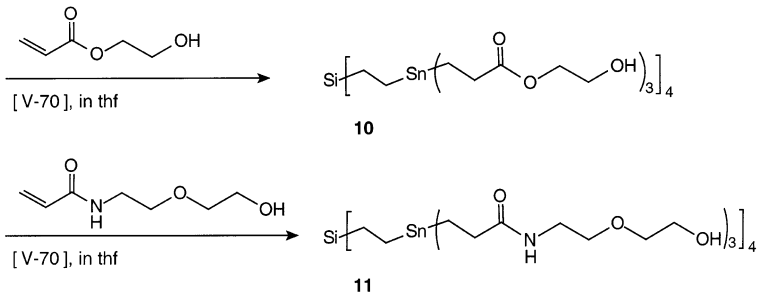
Scheme 5



TBDMS protective groups in **8** was successful by exposing **8** to an equivalent amount of tetra-*n*-butylammonium fluoride in tetrahydrofuran[22] and some water at room temperature (Scheme 4). The hydrophilic reaction product separated as a second phase; careful washing with tetrahydrofuran removed any hydrophobic byproducts. Purification by preparative HPLC afforded the desired product tetrakis{2-[tris(2-[*N*-(2-hydroxyethyl)-carbamido]ethyl)stannyl]ethyl}silane (**9**) contaminated with traces of residual tetra-*n*-butylammonium species, which could be removed by ion exchange. Also, using a smaller molar ratio of $^{n}Bu_4NF$:dendrimer **8** of only 5:1 instead of 12:1 afforded a complete deprotection brought about by this catalytic amount of fluoride ions. Yet, employment of polymer-supported fluoride (Amberlyst A-26 F^- form)[33] did not succeed at all. The monodispersity of the water-soluble dendrimer **9** is documented by the single resonance observable in its $^{119}Sn\{^1H\}$ NMR spectrum at −1.4 ppm. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **9** exclusively show the resonances due to the 2-[*N*-(2-hydroxyethyl)carbamido]ethyl functionality and the dendrimer backbone as they were observed for the nonmonodisperse dendrimer **6** as main peaks. The MALDI-TOF mass spectrum also ascertains the completeness of the synthetic route toward **9** with isotopic multiplets centered at *m*/*z* 2033 and 2049 corresponding to the alkali ion adducts of **9**. The only additional signals observable arise from the two fragment ions due to the loss of a $CH_2CH_2CONHCH_2CH_2OH$ unit from the parent ions $[M + Na/K]^+$. The ESI mass spectrum of **9** shows the well-resolved molecular ion multiplet centered at *m*/*z* 2008.

Alternatively used deprotection methods for the silyl ether moiety in **8** such as mildly acidic conditions (acetic acid, water, tetrahydrofuran),[22] pyridinium *p*-toluenesulfonate in ethanol,[34] or palladium(II) catalysis [dichlorobis(acetonitrile)palladium(II) in acetone][35] were not successful. The palladium catalyst induced a tin−carbon bond scission, yielding the β-H elimination product *N*-(2-*tert*-butyldimethylsiloxyethyl)acrylamide.

The ester-substituted analogue of dendrimer **9** could be synthesized by the 12-fold hydrostannation reaction of 2-hydroxyethyl acrylate employed in excess with the dendritic organotin hydride **1** in tetrahydrofuran initiated by 3 mol % of the catalyst V-70 (Scheme 5). Unlike during the attempted analogous reaction of **1** and unprotected *N*-(2-hydroxyethyl)acrylamide, the hydrostannation product stayed in solution. After separation of any water-insoluble byproduct, chromatographic purification yielded the water-soluble dendrimer tetrakis{2-(tris[2-(2-hydroxyethoxycarbonyl)ethyl]stannyl)-ethyl}silane (**10**). Yet, besides the chromatographically detected reduced polarity as compared to the amido-substituted analogue **9**, **10** moreover shows a clearly lower hydrolytic stability. The ^1H NMR spectroscopic monitoring of a freshly prepared aqueous solution of **10** reveals slight decomposition already within 1 day; macroscopic indication of the decomposition of **10** in water was a second phase forming after a few days. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **10** resemble those of **9**. The only obvious difference is shown by the resonances due to the ester versus amide methylene group. Its triplet proton resonance is shiftet downfield from 3.13 ppm ($CONHCH_2$) to 4.05 ppm ($COOCH_2$), as is its carbon resonance from 41.33 ppm ($CONHCH_2$) to 65.87 ppm ($COOCH_2$). The MALDI-TOF mass spectrum of **10** reveals the dendrimer sodium ion adduct as an isotopically resolved multiplet at *m*/*z* 2043.

The synthesis of the amide-substituted dendrimer with an additional ether group in its terminal N-substituent as compared to dendrimer **9** was realized by the V-70-initiated hydrostannation reaction of *N*-[2-(2-hydroxyethoxy)ethyl]acrylamide with the dendritic organotin hydride **1** at 10 °C in tetrahydrofuran (Scheme 5). From the crude product, which formed as a second phase, the desired tetrakis{2-(tris[2-(*N*-[2-(2-hydroxy-ethoxy)ethyl]carbamido)ethyl]stannyl)ethyl}silane (**11**) could be isolated by preparative thin-layer chromatography, yet only in low yield. Probably partially hydrostannated side products and oligomerized acrylamides had formed as well. A slightly enhanced polarity of **11** as compared to **9** was indicated chromatographically. The NMR spectra of the water-soluble dendrimer **11**, which shows an enhanced hydrolytic stability as compared to **6** as well to **9**, feature the resonances due to the ether moiety CH_2OCH_2 in addition to the resonances observable for **9**: a multiplet signal at 3.45 ppm for the methylene protons and signals at 68.72 and 71.45 ppm for the two carbon atoms neighboring the ether oxygen atom. The MALDI-TOF mass spectrum of **11** displays the expected alkali ion adduct signal at *m*/*z* 2559 corresponding to $[M + Na]^+$.

An increase in hydrophilicity was shown to improve the tolerance of dendrimeric X-ray contrast agents containing triiodobenzenes in mice.[6] Accordingly, the additional ether group in **11** is expected to lower the toxicity as compared to dendrimer **9** or **6**. Yet, due to

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the small amounts synthesized, **11** and **9** have not been studied in vivo.

Conclusion

Utilizing the high reactivity of the 12 Sn−H bonds in the hydride-substituted organotin dendrimer $Si(CH_2CH_2SnH_3)_4$ toward activated double bonds, we were able to functionalize the dendrimer surface hydrophilically. The 12-fold hydrostannation reaction of acrylic acid derivatives constituted the key step in the synthesis of the various carboxylate-, hydroxy-, ester-, or amide-terminated tin-based metallodendrimers $Si(CH_2CH_2SnR_3)_4$. The shielding of the hydrophobic metallorganic dendrimer backbone by the ionic or nonionic polar end groups R brings about the water solubility observed. Our special attention was directed to the 2-[*N*-(2-hydroxyethyl)carbamido]ethyl-functionalized dendrimers; an in vivo study revealed a reasonable tolerance in mice.

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