Improved Synthesis of an Ethereal Tetraamine Core for Dendrimer Construction

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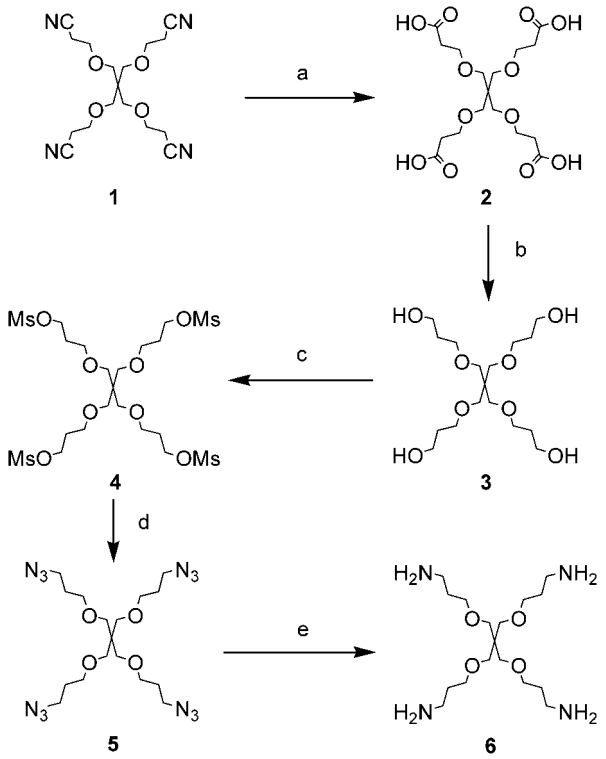
Abstract: A new route to a pentaerythritol-based tetraamine is delineated and subsequently contrasted to a previous report. Access to the pure tetraamine is facilitated by the smooth reduction of its tetraazide precusor. Characterization includes the preparation of a 4:1 Zn-tetraphenylporphyrin/tetraamine complex.

Protocols for precise molecular cores and branched monomers[1−13] underpinning the desired perfection, or pursuit thereof, in subsequent dendritic constructs have been reported;[14] however, if these cores are not absolutely perfect, subsequent dendritic growth will be limited to the degree of initial defects. In a recent publication,[15] Hukkamäki and Pakkanen described the preparation of a tetraamine core **6** (Scheme 1), which was accessed from the tetranitrile precursor **1** (prepared via a simple Michael-type addition of acrylonitrile to pentaerythritol). Subsequent nitrile reduction afforded the tetraamine **6**, which was obtained "pure enough to proceed to polyamine **8**"; however, based on their analytical and NMR data,[15] their sample of the initial core was contaminated due presumably to a retro-Michael reaction[16] or secondary amine formation[17] (or a combination the two) during the reduction of the starting tetranitrile. Previously, Lellek and Stibor[18a] had delineated a procedure to prepare the tetraamine via a BH_3·THF reduction of its tetranitrile precusor; however, extended reaction times (i.e., 2 months) preclude efficient use of this method. We herein report a high-yield synthesis of the pure ethereal tetraamine core **6** and subsequent reaction with acrylonitrile, followed by catalytic reduction, to give the polyamine dendrimer **8**. Supportive and comparative data demonstrate the advantage of this route to this useful core.

Scheme 1[a]



[a] Key: (a) concd HCl, MeOH/H_2O; (b) BH_3·THF, dry THF, 25 °C, 24 h; (c) MsCl, Et_3N, 25 °C, 12 h; (d) NaN_3, DMF, 60 °C, 8−9 h; (e) 10% Pd−C, H_2, 25 °C, 7 h.

It is worth noting that considering the multifunctional and commercial attributes of the pentaerythrityl starting point, it is understandable that it has been employed in a variety of rolls related to dendritic materials. These include its use as a core component for chiral[18a−d] and nonchiral[18e−m] constructs as well as its use for both a core and/or branch junctures.[18n−q] It has also found utility in the metallodendrimer arena.[18r−v]

Thus, pentaerythritol has been shown[19,20] to react with acrylonitrile to generate tetranitrile **1**, which following hydrolysis, (HCl_{concd}) gives (98%) tetraacid[21] **2** confirmed (^{13}C NMR) by the appearance of peaks at δ 35.14 (CH_2-CO_2H) and 173.25 (CO_2H) and the disappearance of peaks at δ 19.0 (CH_2CN) and 118.39 (*C*N). Facile reduction (**(**BH_3·THF) of tetraacid **2** afforded (97%) the colorless tetraol **3**, which was supported (^{13}C NMR) by the loss of

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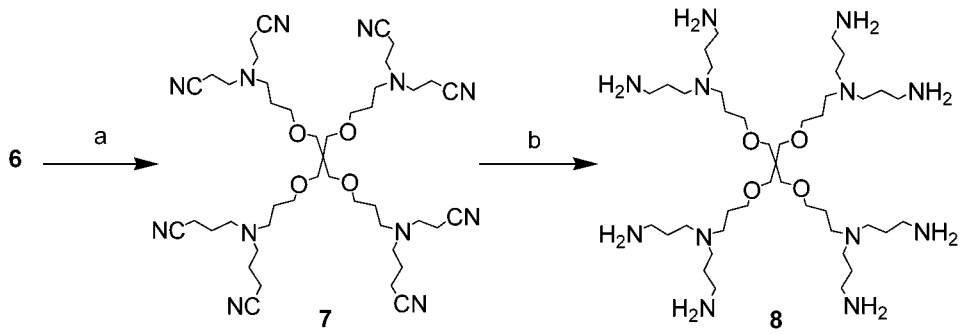
Scheme 2[a]



[a] Key: (a) 12 equiv of acrylonitrile, MeOH, 0.1 equiv of H_2O, 0 → 80 °C; (b) Raney Co, EtOH, 600 psi, 60 °C, 12 h.

the signals assigned to the carboxyl moieties and the appearance of a new signal at δ 58.09 (CH_2OH). This tetraol was readily converted (CH_3SO_2Cl, Et_3N, >90%) to the corresponding mesylate **4** as confirmed (^{13}C NMR) by the new signals at δ 66.49 (CH_2O) and 37.06 (CH_3). Subsequently, the tetramesylate **4** was converted (NaN_3, DMF; 100%) to azide **5**; transformation was supported by loss of the mesylate signals (^{13}C NMR) and a new absorption at δ 48.45 attributed to the CH_2N_3 group as well as the expected signal in the IR (2152 cm^{-1}) for the azide moiety and its mass spectrum (*m*/*z* 491 for M^+ + Na). Catalytic hydrogenation of azide **5** (10% Pd/C, H_2, MeOH) gave (> 95%) the corresponding tetraamine **6** as a colorless liquid. Shift (^{13}C NMR) of the CH_2N peak to δ 39.42, loss of the characteristic azide absorption in the IR, and the mass spectrum confirmed the formation of tetraamine **6**. Thus, this five-step sequence (75% overall) progressing from the tetranitrile **1** to the desired tetraamine **6** afforded a final product purity of 95%, or greater, based on NMR data.

To make comparisons to the literature, this amine core was treated[25] with an excess (50%) of acrylonitrile to generate (95%) the colorless, oily octanitrile **7** (Scheme 2), which was confirmed by the appearance (^{13}C NMR) of resonance peaks at δ 17.07 and 118.93 corresponding to CH_2CN and CN, respectively. Reduction[25] (Raney Co, 600 psi, 60 °C; 95%) of this octanitrile to the comparative octaamine **8** was confirmed by the appearance (^{13}C NMR) of new peaks at δ 39.19 and 25.17 assigned to the α- and β-aminomethylene groups, respectively. Thus, in contrast to the previously published[15] ^1H NMR spectrum (Figure 1a) of polynitrile **7**, our spectrum (Figure 1b) is devoid of extra peaks in the region of 3.4−3.7 ppm attributed to tetraamine impurities.

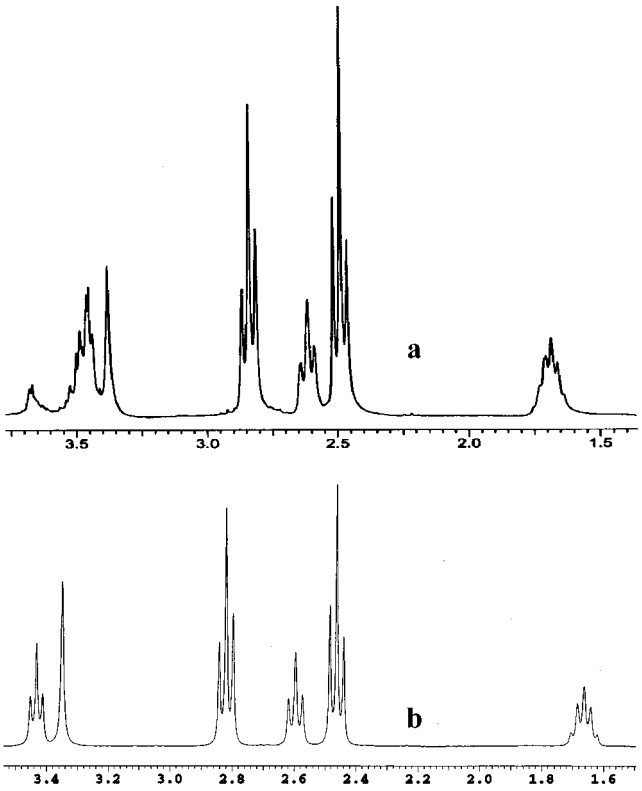


Figure 1. Proton NMR spectra of (a) the originally reported octanitrile (reproduced with permission from Elsevier Science: Hukkamäki, J.; Pakkanen, P. T. *J. Mol. Catal. A*: *Chem*. **2001**, *174*, 205−211), and (b) octanitrile **7**.

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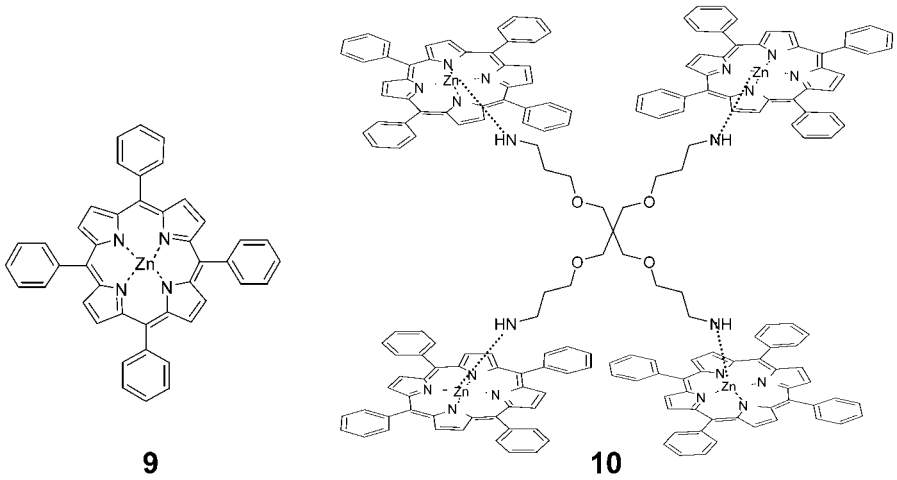

Figure 2. Idealized representation of the 1:4 complexation of tetraamine **6** with the Zn-tetraphenylporphyrin **9**.

An ideal way to evaluate the purity of such amino cores and subsequent dendrimers is to utilize a Zn-tetraphenylporphyrin shift reagent, as reported by Reek and co-workers.[22] Hence, treatment of tetraamine **6** with Zn-tetraphenylporphyrin[23] **9** (1:4 ratio) in $CDCl_3$ for 5 min generated complex **10** (Figure 2), which exhibited significant upfield shifts [^{1}H NMR δ −2.13 (CH_2N), −1.82 ($CH_2CH_2CH_2$), 0.96 (OCH_2CH_2), and 1.05 ($^tCCH_2$)] of all the pertinent absorptions related to **6**. Notably, for complexed **6**, the α-aminomethylene moiety signal appears further upfield than the adjacent β-aminomethylene group in contrast to that observed for uncomplexed **6**. A similar switch in ^{1}H NMR chemical shift position for the resonances attributed to the ethereal methylenes was also observed. Employing COSY[24] NMR on adduct **10** allowed easy assignment of the tetraamine-related ^{13}C NMR absorptions: δ 27.9 ($CH_2CH_2CH_2$), 34.86 (CH_2N), 42.95 (^tC), 67.56 (OCH_2CH_2), 68.13 ($^tCCH_2$).

In conclusion, it is essential to have pristine cores and branched monomeric building blocks in order to ensure the structural precision demanded for dendritic macromolecules.

Experimental Section

General Methods. The melting points were determined in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, unless otherwise stated.

Tetrakis(5-carboxy-2-oxabutyl)methane (2). Tetranitrile[16,17] **1** (5 g, 14.0 mM) was refluxed for 2 h in dry HCl saturated MeOH (20 mL) solution. The solvent was evaporated and dried to give the methyl ester of tetraacid as yellowish oil, which was hydrolyzed with NaOH at 70 °C for 24 h. The crude material was then crystallized from acetonitrile to afford (90%) the tetraacid **2**, as white solid: mp 107−109 °C (lit.[18] mp 104−106 °C); ^{13}C NMR (DMSO-d_6) δ 35.14 (CH_2CO), 45.55 (^tC), 67.23 (OCH_2CH_2), 69.47 ($^tCCH_2$), 173.25 (CO_2H); ^{1}H NMR (DMSO-d_6) δ 2.4 (8*H*, t), 3.24 (8*H*, s), 3.52 (8*H*, t), 12.14 (4H, br, s); IR 1125, 1745, 2845, 2956 cm^{-1}.

Tetrakis(5-hydroxy-2-oxapentyl)methane (3). To a stirred solution of tetrakis(5-carboxy-2-oxabutyl)methane[19] (**2**; 10 g, 23.6 mM) in THF (100 mL), under N_2, was added a BH_3·THF solution (1 M; 110.42 mL, 113.7 mM) dropwise at 0 °C for 1 h. After the mixture was stirred for 12 h, MeOH (20 mL) was added to quench the reaction, followed by water. The solvents were evaporated in vacuo, aqueous HCl was added, and the mixture was warmed to 60 °C for 1 h. The solution was concentrated to dryness and extract with warm absolute EtOH to give (95%) **3**, as colorless viscous liquid: 7.7 g; ^{13}C NMR (CD_3OD) δ 32.66 ($CH_2CH_2CH_2$), 45.04 (^tC), 58.09 (CH_2OH), 67.98 (OCH_2CH_2), 69.22 ($^tCCH_2$); ^{1}H NMR (CD_3OD) δ 1.62 (8*H*, q), 2.0 (4*H*, s), 3.3 (8*H*, s), 3.37 (8*H*, t), 3.53 (8*H*, t); IR 1125, 2845, 2956, 3464 cm^{-1}; ESI-MS *m*/*z* 391 (M + Na)$^+$ (calcd $C_{17}H_{36}O_8$ 368.467).

Tetrakis(5-mesyloxy-2-oxapentyl)methane (4). To a stirred solution of tetraol **3** (5 g, 14.2 mM) in THF/CH_2Cl_2 (1:1, 50 mL) at 0 °C were added a solution of mesyl chloride (7.28 g, 63.9 mM) and Et_3N (6.45 g, 63.92 mM) over 1 h, and then the mixture maintained at 25 °C for 12 h. The mixture was filtered, giving a filtrate that was evaporated to dryness, and the residue was dissolved in CH_2Cl_2, washed sequentially with water, 10% HCl, $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a white solid. This crude tetramesylate was column chromatographed (SiO_2) eluting with EtOAc/CH_2Cl_2 (1:1) to afford (90%) **4**, as white solid: 8.7 g; mp 68−70 °C; ^{13}C NMR δ 28.79 ($CH_2CH_2CH_2$), 36.49 (CH_3), 44.82 (^tC), 66.12 (CH_2CH_2O), 67.31 ($^tCCH_2$), 69.2 (CH_2OCH_2); ^{1}H NMR δ 1.65 (8*H*, q), 2.94 (12*H*, s), 3.29 (8*H*, s), 3.36 (8*H*, t), 3.52 (8*H*, t); IR 1124, 1174, 1348, 2863, 2929 cm^{-1}; ESI-MS *m*/*z* 703 (M + Na)$^+$ (calcd $C_{21}H_{44}O_{16}S_4$ 680.831).

Tetrakis(5-azido-2-oxabutyl)methane (5). To a mixture of mesylate **4** (5 g, 7.35 mM) dissolved in anhydrous DMF (50 mL) was added excess NaN_3 (3 g, 46.1 mM). The mixture was warmed at 60 °C for 5 h and then cooled. After concentration in vacuo, the damp residue was washed with brine to remove residual DMF and then extract with CH_2Cl_2. The crude tetraazide **5** was column chromatographed (SiO_2), eluting with EtOAc/hexane (5:95) to give (98%) **5** as a colorless viscous liquid: 3.27 g; ^{13}C NMR δ 29.02 ($CH_2CH_2CH_2$), 45.35 (^tC), 48.46 (CH_2N), 67.81 (OCH_2CH_2), 69.6 ($^tCCH_2$); ^{1}H NMR δ 1.5 (8*H*, q), 2.81 (8*H*, t), 3.29 (8*H*, s), 3.38 (8*H*, t); IR 1121, 2152, 2871, 2964 cm^{-1}; ESI-MS *m*/*z* 491 (M + Na)$^+$ (calcd $C_{17}H_{32}O_4N_{12}$ 468.523).

Tetrakis(5-amino-2-oxapentyl)methane (6). The tetraazide **5** (2 g) with 10% Pd/C (1 g) in MeOH (50 mL) was reduced in basic condition to give (100%) the desired amine **6**, as a colorless liquid: 1.5 g; ^{13}C NMR δ 33.08 ($CH_2CH_2CH_2$), 39.42 (CH_2N), 44.81 (^tC), 69.16 (OCH_2CH_2), 69.5 ($^tCCH_2$); ^{1}H NMR δ 0.95 (2*H*, s), 1.37 (8*H*, q), 2.47 (8*H*, t), 3.06 (8*H*, s), 3.15 (8*H*, t); IR 1125, 2867, 2982, 3320 cm^{-1}; ESI-MS *m*/*z* 365 (M + H)$^+$ (calcd $C_{17}H_{40}O_4N_4$ 364.531). The tetraamine was stored under an inert atmosphere under refrigeration, until use.

Synthesis of the First-Generation Octanitrile 7. To a solution of tetraamine **6** (200 mg, 549 μmol) in MeOH (3 mL) and water (1−2 drops) at 5 °C was added acrylonitrile (349 mg, 6.59 mM) dropwise. After being stirred for 1 h at 5 °C, the resulting mixture was heated at 80 °C for 6 h. After cooling, the solvent and the excess acrylonitrile were removed in vacuo to give a residue that was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The crude material was column chromatographed (SiO_2), eluting with EtOAc/hexane (80:20), to afford (90%) the colorless octanitrile **7**: 410 mg; ^{13}C NMR δ 17.07 (CH_2CN), 27.68 ($CH_2CH_2CH_2$), 45.4 (^tC), 49.76 (CH_2CH_2CN), 49.95 (NCH_2), 68.65 (CH_2CH_2O), 70.07 ($^tCCH_2$), 118.93 (CN); ^{1}H NMR δ 1.66 (8*H*, q), 2.46 (16*H*, t), 2.59 (8*H*, t),

2.82 (16*H*, t), 3.35 (8*H*, s), 3.43 (8*H*, t); IR 1095, 1365, 1461, 2244, 2852, 2919 cm^{-1}; ESI-MS *m*/*z* 811 $[M + Na]^+$ (calcd $C_{41}H_{64}N_{12}O_4$ 788).

Synthesis of the First-Generation Octaamine 8. A stirred MeOH/H_2O (9:1) suspension of octanitrile **7** (100 mg, 127 μM) and Raney Co (H_2, 600 psi) was maintained at 65 °C for 7 h. The solution was filtered and evaporated in vacuo and then extracted with CH_2Cl_2 to give (95%) octaamine **8**: 95 mg; ^{13}C NMR (D_2O) δ 25.17 ($CH_2CH_2NH_2$), 28.21 (CH_2CH_2N), 39.19 (CH_2NH_2), 44.98 (^tC), 50.15 and 50.88 (CH_2NCH_2), 69.45 (CH_2CH_2O), 70.22 ($^tCCH_2$); ^1H NMR δ 1.63 (16*H*, m), 1.75 (8*H*, br m), 2.53 (24*H*, m), 2.64 (16*H*, t), 3.41 (8*H*, s), 3.52 (8*H*, t); IR 1106, 1330, 1484, 1575, 2805, 2861, 2940, 3343 cm^{-1}; ESI-MS *m*/*z* 821.8 $(M + H)^+$ (calcd $C_{41}H_{96}N_{12}O_4$ 820.77).

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