

Study on catalytic hydrogenation in synthesis of four-directional amine-terminated dendritic molecules

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Abstract

The syntheses of four-directional dendritic molecules derived from pentaerythritol are described. Amine functionalized molecules were synthesized in a two-step reaction sequence which involved cyanoethylation followed by catalytic hydrogenation of the cyano groups to the amine groups with H₂ and Raney nickel as catalyst. Two generations starting from pentaerythritol were synthesized. The products were characterized mainly by ¹H and ¹³C NMR as well as by IR. Yields were high in the syntheses of cyanoalkoxy-pentaerythritols **1N** and **2N** as well as in the synthesis of aminoalkoxy-pentaerythritol **1A**, but significantly lower in the case of aminoalkoxy-pentaerythritol **2A**. Factors affecting hydrogenation process as well as separation of side products and purification methods for the products are discussed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Aminoalkoxy-pentaerythritols; Hydrogenations; Low molecular weight dendrimers; Raney nickel

1. Introduction

The first synthesis of simple dendritic structures via divergent methodology was reported by Vögtle et al. in 1978 [1,2]. These low molecular weight polyamine dendritic systems were described as “cascade molecules”. Divergent methodology of dendritic molecules involves repetitive synthesis steps starting from a core molecule. The number of reactive terminal groups increases in each reaction cycle depending on the building block valency. In Vögtle’s procedure new generations of dendritic polyamines were synthesized by Michael-type addition of acrylonitrile to primary amines followed by chemical reduction of nitriles to corresponding primary amines. By using

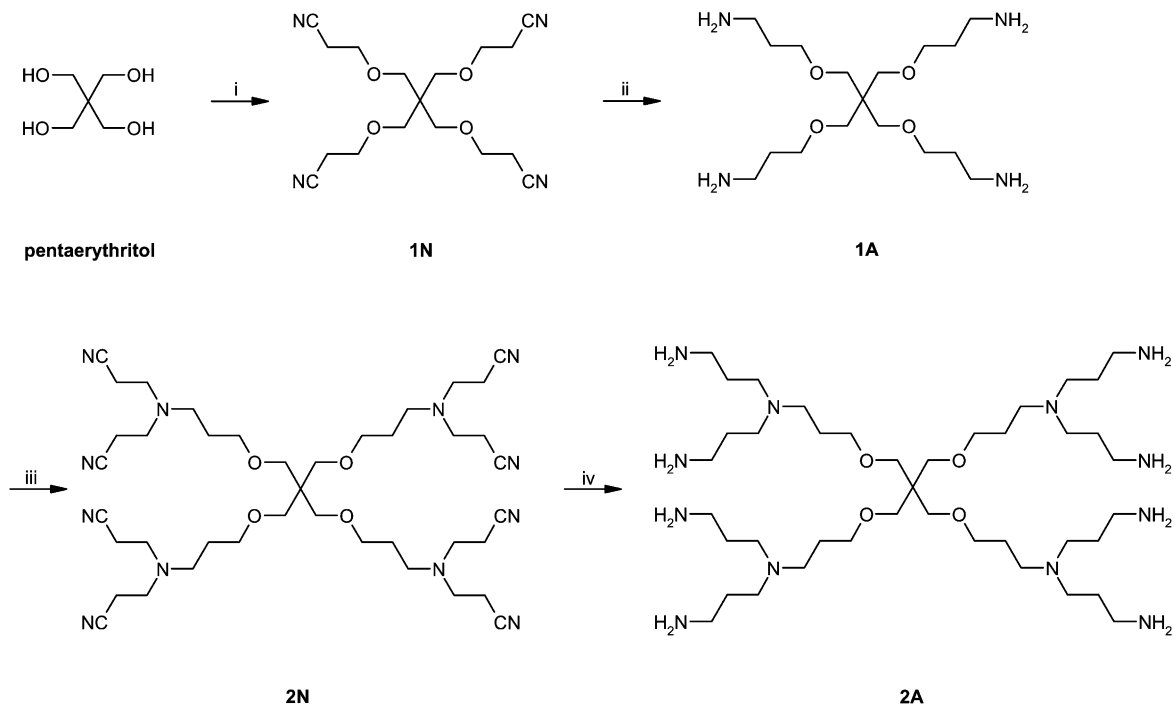
Raney nickel in the nitrile reduction and with some other synthetic modifications to the Vögtle’s procedure Wörner and Mülhaupt [3] have synthesized fifth generation nitrile. Since Vögtle’s original paper the field of cascade synthesis has expanded and new types of cascade molecules have appeared just to mention pioneering works of research groups of Denkwalter [4], Newkome [5] and Tomalia [6] among others.

Newkome and Lin [7] have used pentaerythritol as a core molecule in the synthesis of symmetrical, three-dimensional, ball-shaped cascade structures. The key building blocks were synthesized starting from tris(hydroxymethyl)aminomethane. Aminoalkoxy-pentaerythritols, e.g. **1A**, where the number indicates generation and the letter stands for terminal group, have been previously synthesized in patent literature, named as tetra(3-aminopropoxy)-pentaerythritol, and used as curing agents for epoxy resins [8].

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Scheme 1. Reagents: (i), H₂C=CHCN (5.0 equiv.), KOH, 1,4-dioxane; (ii), Raney nickel, H₂, MeOH/H₂O (1:1, v/v); (iii), H₂C=CHCN (20.0 equiv.), MeOH; (iv), Raney nickel, H₂, MeOH/H₂O (5:1, v/v).

In the present paper we report the syntheses of four-directional dendritic molecules using pentaerythritol as a core molecule (see Scheme 1). At full generations these molecules possess terminal amine groups at equal distance from the molecule center. Terminal amine groups can react further with two monomers or building blocks. The two-step synthesis of amine-terminated molecules consists of cyanoethylation and catalytic hydrogenation of the nitrile groups to corresponding amine groups with H₂ and Raney nickel as catalyst. According to our experiments the composition and protic nature of the used solvent mixture are important factors affecting the progress of hydrogenation. Formation of secondary amines or other side products were not observed in these hydrogenations. Although, the synthesis of aminoalkoxypentaerythritols, e.g. **1A** is previously known [8], to our knowledge the synthesis of **2N** and **2A** has not been previously reported in the literature. A straightforward

purification of synthesized compounds is also discussed.

2. Experimental

2.1. General

Pentaerythritol and acrylonitrile were obtained from Aldrich and Fluka, respectively. Raney nickel catalyst (50% slurry in water, active catalyst) used in hydrogenation was obtained from Aldrich and it is analogous to Raney 28 or W-2 grade. All chemicals were used as received.

¹H and inverse gated ¹H decoupled ¹³C NMR spectra were recorded on Bruker AM-250 and Bruker Avance 250 (250 and 62.9 MHz, respectively) spectrometers. IR spectra were recorded on Nicolet Magna 750 FT/IR spectrophotometer. Elemental analyses were carried out with Carlo Erba 1106 CHN + O/S and Carlo Erba EA 1110 CHNS-O analyzers. Melting

points were measured on Gallenkamp melting point apparatus.

2.2. Synthesis of 3-[3-(2-cyanoethoxy)-2,2-bis-(2-cyanoethoxymethyl)propoxy]propionitrile **1N**

Pentaerythritol (3.9 g, 28.7 mmol), 1,4-dioxane (19.5 ml) and 40% KOH were placed in a reaction flask equipped with a reflux condenser, a dropping funnel and a magnetic stirring bar. Acrylonitrile (9.45 ml, 0.144 mol) was added slowly through dropping funnel to the reaction mixture. The resulting mixture was maintained at room temperature for an additional 24 h. The reaction mixture was dissolved in CH_2Cl_2 (100 ml) and extracted several times with small amounts of deionized water. Organic layer was dried with Na_2SO_4 and the solvent, dioxane and excess of acrylonitrile were evaporated in vacuum. The crude product was purified either column chromatographically or by dissolving the impurities in deionized water. In chromatographic method the progress of the separation was followed by thin layer chromatography (thin layer plates were sprayed by Dragendorff reagent) or by ^1H NMR. The latter purification method gave **1N** (7.8 g, 78%) as white waxy solid product; mp 45–46.5°C (Found: C, 58.47; H, 7.11; N, 16.31; O, 18.61. Calc. for $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_4$: C, 58.59; H, 6.95; N, 16.09; O, 18.38%); $\nu(\text{KBr})/\text{cm}^{-1}$ 2254.5 ($\text{C}\equiv\text{N}$); δ_{H} (250 MHz; CDCl_3) 2.61 (8H, t, $\text{OCH}_2\text{CH}_2\text{CN}$), 3.49 (8H, s, CCH_2O), 3.66 (8H, t, $\text{OCH}_2\text{CH}_2\text{CN}$); δ_{C} (62.9 MHz; CDCl_3) 19.53 ($\text{OCH}_2\text{CH}_2\text{CN}$), 46.31 (CCH_2O), 66.31 ($\text{OCH}_2\text{CH}_2\text{CN}$), 69.39 (CCH_2O), 118.94 (CN).

2.3. Synthesis of 3-[3-(3-aminopropoxy)-2,2-bis-(3-aminopropoxymethyl)propoxy]propylamine **1A**

The hydrogenation was carried out in 100 ml stainless steel autoclave. **1N** (1.0 g, 2.9 mmol) was dissolved in $\text{MeOH}/\text{H}_2\text{O}$ (30 ml, 1:1, v/v). Raney nickel catalyst (2.0 g, wet-weight) was added to the mixture. The resulting mixture was hydrogenated at 50 bar hydrogen pressure at 70°C for 24 h. Stirring speed was 1000 rpm. After cooling the reaction mixture was centrifuged, filtered and the solvents were evaporated from the filtrate at reduced pressure to give **1A** (0.78–0.96 g, 74–91%) as light yellow viscous oil; δ_{H} (250 MHz; CDCl_3) 1.46 (8H, s, NH_2),

1.63 (8H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 2.73 (8H, t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 3.31 (8H, s, CCH_2O), 3.40 (8H, t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$); δ_{C} (62.9 MHz; CDCl_3) 34.13 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 40.52 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 45.86 (CCH_2O), 70.26 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 70.60 (CCH_2O).

2.4. Synthesis of 3-[[3-(3-{3-[bis(2-cyanoethyl)amino]propoxy}-2,2-bis{3-[bis(2-cyanoethyl)amino]propoxymethyl}propoxy)propyl]- (2-cyanoethyl)amino]propionitrile **2N**

Acrylonitrile (1.07 ml, 16.2 mmol) was added slowly to a solution of **1A** (0.296 g, 0.812 mmol) in methanol (10 ml) in a reaction flask equipped with a reflux condenser and a magnetic stirring bar. The resulting mixture was heated at 50°C for 48 h to complete the addition of acrylonitrile to **1A**. Finally, the excess of acrylonitrile and solvent were evaporated in vacuum to give **2N** (0.52 g, 81%) as yellow–orange viscous oil (Found: C, 61.07; H, 8.46; N, 20.53. Calc. for $\text{C}_{41}\text{H}_{64}\text{N}_{12}\text{O}_4$: C, 62.41; H, 8.18; N, 21.30%); $\nu(\text{KBr})/\text{cm}^{-1}$ 2249.3 ($\text{C}\equiv\text{N}$); δ_{H} (250 MHz; CDCl_3) 1.69 (8H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.49 (16H, t, $\text{NCH}_2\text{CH}_2\text{CN}$), 2.62 (8H, t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.84 (16H, t, $\text{NCH}_2\text{CH}_2\text{CN}$), 3.38 (8H, s, CCH_2O), 3.45 (8H, t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$); δ_{C} (62.9 MHz; CDCl_3) 17.22 ($\text{NCH}_2\text{CH}_2\text{CN}$), 27.73 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 45.46 (CCH_2O), 49.85 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$), 68.67 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 70.19 (CCH_2O), 119.03 (CN).

2.5. Synthesis of N^1 -(3-aminopropyl)- N^1 -[3-(3-{3-[bis(3-aminopropyl)amino]propoxy}-2,2-bis{3-[bis(3-aminopropyl)amino]propoxymethyl}propoxy)propyl]-propane-1,3-diamine **2A**

2N (0.38 g, 0.482 mmol) was dissolved in $\text{MeOH}/\text{H}_2\text{O}$ (30 ml, 5:1, v/v) and placed in a 100 ml stainless steel autoclave. Raney nickel catalyst (1.0 g, wet-weight) was added to the hydrogenation vessel and the resulting mixture was hydrogenated at 50 bar hydrogen pressure with stirring speed of 1000 rpm at 70°C for 168 h. The cooled reaction mixture was centrifuged, filtered and the solvents were evaporated at reduced pressure. The crude product was dissolved in deionized water and extracted several

times with small amounts of chloroform. After the phase separation the water layer was evaporated in vacuum to give **2A** (0.20 g, 51%) as light yellow very viscous oil; δ_{H} (250 MHz; D_2O ; DSS as external standard) 1.69–1.75 (40 H, br m with two maxima, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2)_2$), 2.42 (8H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.54 (16H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 2.69 (16H, br m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 3.42 (8H, s, CCH_2O), 3.55 (8H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$); δ_{C} (62.9 MHz; D_2O ; DSS as external standard) 27.62 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 30.45 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 41.42 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 42.02 (CCH_2O), 48.68 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 53.23 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 72.22 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 72.61 (CCH_2O).

3. Results and discussion

3.1. Cyanoethylation of pentaerythritol

In the first reaction step exhaustive addition of acrylonitrile to pentaerythritol takes place. Reaction is catalyzed by 40% potassiumhydroxide solution [7,9]. A small amount of 1,4-dioxane is needed as a solvent in order to control the temperature of the reaction mixture and to prevent very exothermic polymerization of acrylonitrile. Reaction was best performed at room temperature using 5 mol of acrylonitrile per 1 mol of pentaerythritol. The temperature of the reaction mixture increased by about 10°C during addition of acrylonitrile. Additional cooling was not used. The solubility of pentaerythritol in dioxane is poor, but in this case it dissolved completely when the whole amount of acrylonitrile was added.

Hydracrylonitrile ($\text{HOCH}_2\text{CH}_2\text{CN}$), the hydration product of acrylonitrile, was formed as a side product, similar to observations of de Brabander-van den Berg and Meijer [10]. Despite the water solubility of hydracrylonitrile and several extractions with water, traces of hydracrylonitrile remained in the crude product according to ^1H NMR. Also some unreacted pentaerythritol was observed.

Product impurities can be separated with column chromatography by using neutral SiO_2 column and dichloromethane/methanol (100:2) as an eluent. This method proved quite time consuming due to slow elution rate of the product. The progress of the separation process also had to be followed by thin layer chro-

matography (TLC) or by ^1H NMR due to the colourless product molecule and impurities.

An alternative method takes advantage of water solubility of product impurities. Nitrile **1N** is soluble in methanol and common organic solvents, but also slightly soluble in water, the reason why continuous extraction was not used. In this method, water was added to the crude product and the mixture was heated. If solid the product was heated until it melted. The mixture was stirred and slowly cooled to room temperature. The pure product separated as solid while impurities remained in water phase. In the end the product was filtered, washed with small amount of deionized water and dried on a filter paper at room temperature to give white waxy solid. The yield reported in the experimental part is from latter purification method. In column chromatographic purification the yields were considerably lower.

Pure **1N** was identified by elemental analysis and by ^1H , ^{13}C NMR and IR. The results of elemental analysis for **1N** are in good agreement with theoretical values. All spectroscopic data is consistent with the proposed structure. Total of three signals, one singlet and two triplets, with equal integrals are observed in the ^1H NMR spectrum of **1N** (Fig. 1a). The triplet of $\text{OCH}_2\text{CH}_2\text{CN}$ is the most downfield signal at 3.66 ppm. The singlet at 3.49 ppm is assigned to the protons of CCH_2O group. Methylene group next to the cyano group, $\text{OCH}_2\text{CH}_2\text{CN}$, gives the most upfield triplet at 2.61 ppm. In the ^{13}C NMR spectrum of **1N** five nonequivalent resonances are observed. Central carbon atom gives signal at 46.31 ppm, the intensity of one-fourth compared to other signals. Carbon resonances at 66.31 and 69.39 ppm are assigned to $\text{OCH}_2\text{CH}_2\text{CN}$ and CCH_2O , respectively. The most downfield resonance as well as the most upfield resonance are both very characteristic. Carbon atoms of the cyano groups give a signal at 118.94 ppm, while the signal at 19.53 ppm is assigned to methylene carbon beside the cyano group. The IR spectrum of **1N** shows a $\text{C}\equiv\text{N}$ stretch at 2254.5 cm^{-1} .

3.2. Hydrogenation of nitrile **1N**

The second reaction step includes hydrogenation of **1N** with H_2 and Raney nickel as catalyst in methanol/water (1:1) mixture. In our previous experiments we have observed that hydrogenations with

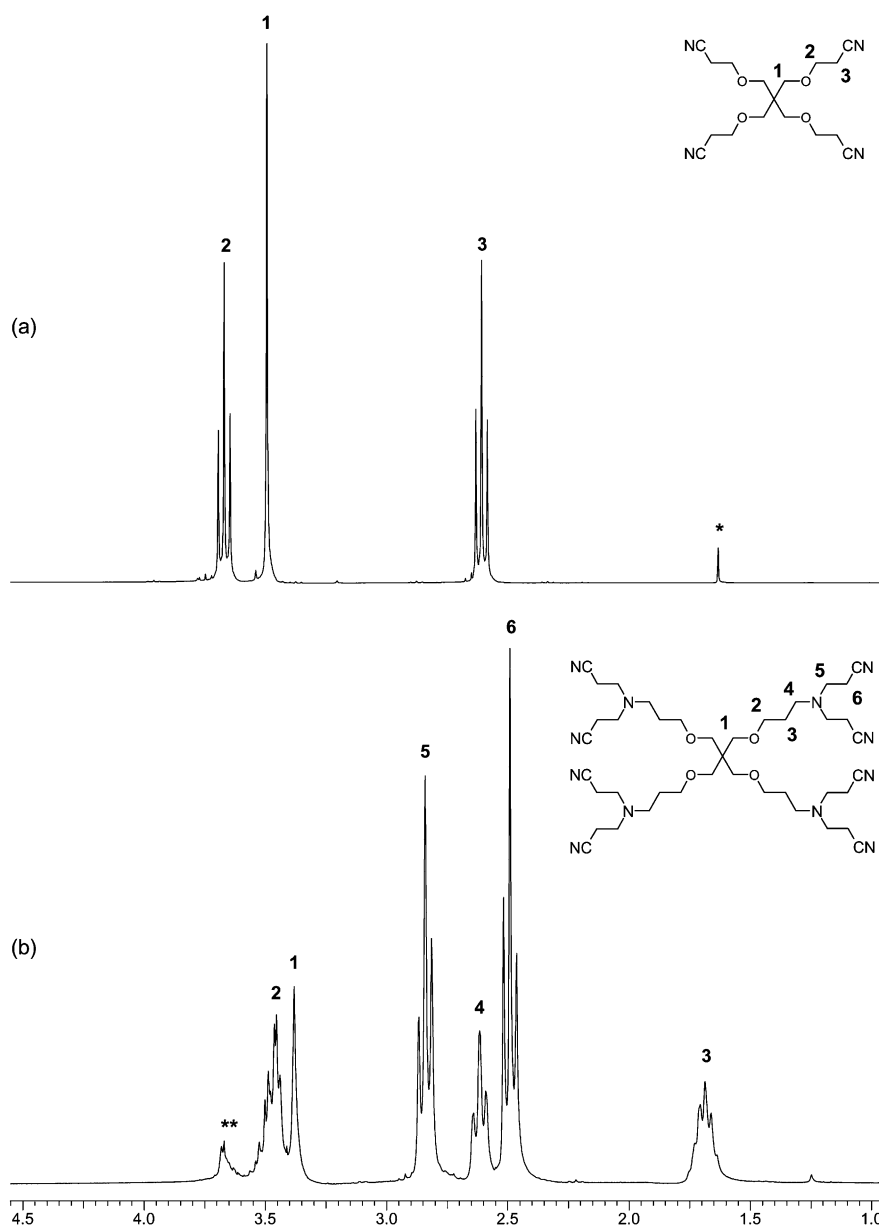


Fig. 1. ^1H NMR spectra (250 MHz, CDCl_3) of (a) **1N** (* solvent moisture) and (b) **2N** (** impurity).

Raney nickel are best performed in protic solvents, preferably in water. Hydrogenations of nitriles in methanol yielded less product than in methanol/water mixture using the same reaction times. In aprotic solvents, e.g. THF no product was formed. Methanol was added to improve solubility of **1N**.

The hydrogenation product **1A** as light yellow viscous oil was isolated by centrifuging and filtering the Raney nickel and by evaporating solvents. Since Raney nickel was wet-weighed, the total amount of catalyst varied slightly in the hydrogenation experiments affecting the yields reported in the

experimental section. Co-catalysts, especially water soluble co-catalysts, e.g. NaOH, should not be used in hydrogenation due to difficulties in separating them from product.

^1H , ^{13}C NMR and IR were used in the characterization of **1A**. Five signals were observed in the ^1H NMR spectrum. The two most downfield resonances, triplet for $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ and singlet for CCH_2O , remain almost unchanged at 3.40 and 3.31 ppm, respectively. In the course of the hydrogenation the resonance of $\text{OCH}_2\text{CH}_2\text{CN}$ at 2.61 ppm disappears and a multiplet of $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ appears at 1.63 ppm. Two new resonances are observed, a very characteristic broad resonance of NH_2 group at 1.46 ppm and triplet of $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ at 2.73 ppm. Integrated peak areas are in good agreement with proposed structure. In the ^{13}C NMR spectrum of **1A** the signal of cyano group at 118.94 ppm disappears and the signal of OCH_2CH_2 has moved downfield to 34.13 ppm. New signal of $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ appears at 40.52 ppm. Changes in the ^1H and ^{13}C NMR spectra as well as the absence of $\text{C}\equiv\text{N}$ stretch in the IR spectrum clearly indicate completeness of the hydrogenation process.

In the hydrogenation of nitriles secondary amines can be formed in a reaction of intermediate imines with primary amines [11,12] which in the hydrogenation of **1N** would lead to intramolecular cyclization or intermolecular bridging. The formation of secondary amines can be suppressed by using ammoniacal alcohol solutions in the reductions of nitriles [11,12]. However, our NMR data is consistent with the proposed structure for **1A** and shows no evidence of such side reactions. Selective hydrogenation experiments also showed that at this synthesis scale the use of ammonia is not necessary to maintain high yields of primary amines. More critical factor is the amount of wet-weighed catalyst.

3.3. Cyanoethylation of amine **1A**

The third reaction step includes exhaustive addition of acrylonitrile to **1A**. In this stage of synthesis two acrylonitrile molecules react with every amine group of **1A**. Methanol was used as a solvent. Reaction was performed by using 20 mol of acrylonitrile per mol of **1A** and completed by heating the reaction mixture at 50°C for 48 h. No side product formation occurred and pure **2N** was obtained simply by evaporating the

solvent and excess of acrylonitrile at reduced pressure.

Spectroscopic data for **2N** correlates very well with the proposed structure. Six discrete resonances are observed in the ^1H NMR spectrum of **2N** (Fig. 1b). The ^1H NMR spectrum of **2N** indicates appearance of two new triplets due to attached vinylcyanides at 2.84 and 2.49 ppm assigned to $\text{NCH}_2\text{CH}_2\text{CN}$ and $\text{NCH}_2\text{CH}_2\text{CN}$, respectively as well as the absence of amine proton resonance compared to the ^1H NMR spectrum of **1A**. In the ^{13}C NMR spectrum of **2N** the resonance of $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$ has moved upfield to 27.73 ppm while the resonance at 40.52 ppm assigned methylene group next to the amine group has moved downfield during the cyanoethylation and appears now at 49.85 ppm with the resonance of the $\text{NCH}_2\text{CH}_2\text{CN}$. Integrated peak areas support this interpretation. The resonances at 119.03 and 17.22 ppm are assigned to carbon atoms of the cyano groups and methylene carbons beside the cyano groups, respectively. The IR spectrum of **2N** shows a $\text{C}\equiv\text{N}$ stretch at 2249.3 cm^{-1} .

3.4. Hydrogenation of nitrile **2N**

The second generation nitrile **2N** was hydrogenated with H_2 and Raney nickel as catalyst in methanol/water (5:1) mixture. The portion of methanol is bigger due to poor solubility of **2N** in water. We have earlier stated out that hydrogenations are best performed in protic solvents, preferably in water and when the amount of methanol is increased amine yields stay lower. Hydrogen consumption in hydrogenation of **2N** was very slow and reaction was not complete even after 7 days reaction time.

The mixture of hydrogenation product and reactant was isolated by centrifuging and filtering the Raney nickel and by evaporating solvents. Deionized water was added to the mixture and the solution was extracted several times with small amounts of chloroform to separate the reactant from the hydrogenation product **2A**. After the phase separation water was evaporated and **2A** was obtained as light yellow very viscous substance.

^1H and ^{13}C NMR spectra were recorded in D_2O using 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an external standard. Signals in ^1H NMR spectrum are quite broad. The resonances due to the molecule centre remain almost unchanged while the resonance of NCH_2CH_2 protons moves upfield to 1.69–1.75 ppm

and a new resonance $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ occurs at 2.69 ppm. The appearance of NH_2 resonance in the field of 1.69–1.75 ppm is not quite clear due to broadness of the resonance and D_2O solvent. However, in the ^{13}C NMR spectrum of **2A** the signal of cyano group at 119.03 ppm is absent and the resonance of methylene carbon next to the cyano group has moved downfield to 30.45 ppm. The signal of $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ appears at 41.42 ppm. Changes in the ^1H and ^{13}C NMR spectra correspond well with proposed structure of **2A** as well as the absence of $\text{C}\equiv\text{N}$ stretch in the IR spectrum. Due to the hygroscopic nature of **2A** elemental analysis data differed from the theoretical values.

4. Conclusions

We have described a straightforward method for the syntheses of four-directional amine-terminated dendritic molecules derived from pentaerythritol. The first generation amine possesses four primary amine groups as reactive terminal groups, each of which reacts further with two new monomers and after end group modification the number of reactive amine groups at the periphery has duplicated. Synthesis procedure consists of cyanoethylation with acrylonitrile followed by hydrogenation with H_2 and Raney nickel as catalyst. In the synthesis of first generation nitrile unreacted pentaerythritol and hydracrylonitrile as side product are easily removed due to their excellent water solubility. Also, unreacted second generation nitrile is easily removed from the second generation amine by extracting with chloroform. The progress of hydrogenation process is strongly dependent on the protic

nature of solvent even so that in the aprotic solvents the formation of hydrogenation products is prevented. Hydrogenation of second generation nitrile proved to be the most time consuming synthesis stage probably due to unfavorable solvent composition and also in some extent due to steric effects. Based on these results huge problems could be expected in the synthesis of the third generation and especially in hydrogenation. On the other hand, if the hydrogenation of second generation nitrile is merely sterically restricted the use of longer spacers could lead to better results. Due to four-directional branching more symmetric and spherical molecules are achievable even at lower generations.

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