

Synthesis of Novel Aromatic Core Zero Generation Dendrimers

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Abstract. Bromomethyl arenes used as polyfunctional core of dendrimers were derivatized with diethanolamine branches. The obtained compounds containing 4 or 6 hydroxyl terminal surface groups are highly water-soluble.

Keywords: dendrimer, bromomethyl arenes, diethanolamine

INTRODUCTION

The first dendrimer-like structure was presented in 1978 by Fritz Vögtle as a highly-branched macromolecule.¹ Dendrimers are typically symmetric around the core, mono-dispersed molecules, having a very well defined size and delimited shape, respectively. The core is derivatized with branching molecules, containing functional groups, organized in generations. A subunit of the dendrimer is called a dendron. Dendrimers can be obtained by divergent (construction of the molecule is progressing from the core to the surface) or by convergent (starting from the end-groups and stepwise progressing inwards and lately attaching the dendron to the core) routes.² The control over size, shape, and surface functionality makes dendrimers one of the “smartest” or customizable commercially nanotechnology products.³

Herein we report the synthesis of zero generation dendrimers using 1,4-bis(bromomethyl)benzene, 1,3,5-tris(bromomethyl)benzene and 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene as the core. Derivatization was made with diethanolamine and led to highly polar compounds.

Diethanolamine (DEA) is known for its application in several fields: as surface-active agent in cosmetics, agricultural products or pharmaceuticals.⁴ Biological testing proved that DEA derivatives show antibacterial, antifungal, anticancer and antioxidant properties.⁵

In the synthesis of some metallodendrimers 1,4-bis(bromomethyl)benzene has been used as a linking agent.⁶ Dendrimers constructed from 1,3,5-tris(bromomethyl)benzene core and derivatized with sodium tris(ethoxycarbonyl)methanide, 4-formylbenzoic acid,

triethyl phosphine, 2-(2-pyridyl)benzimidazole, tosylate or N-tosylated aminoisophthalate diester^{7–11} had been reported. Literature data regarding the use of 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene as central unit is related mainly to metallodendrimer synthesis.¹²

Since diethanolamine possesses the properties of secondary amines and alcohols due to the presence of both amino and hydroxyl functional groups, it undergoes different reactions. DEA reacts with acyl chlorides, cellulose derivatives or acids. It is also a suitable precursor for the morpholine synthesis.¹² Morpholine was first obtained by the dehydration of diethanolamine in the presence of sulfuric acid. Several methods have been tested in order to obtain the heterocyclic compound in higher yield.¹³ Morpholine derivatives have a large scale of applications: as sulfur dioxide absorbent,¹⁴ as catalyst,^{15,16} in biochemical applications,^{17,18} in different hydrogels preparation,^{19,20} in morpholine-based chemotherapeutic agent synthesis.^{21–23}

EXPERIMENTAL

Materials and Methods

The starting chemicals: 1,4-bis(bromomethyl)benzene, 1,3,5-tris-(bromomethyl)benzene, 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene, anhydrous potassium carbonate and diethanolamine were purchased from Sigma-Aldrich. Acetonitrile, ethanol, diethyl ether and 48 % aqueous hydrobromic acid were supplied from Merck. All chemicals and reagents were used as received.

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Thin layer chromatography (TLC) monitoring was carried out using Merck Kieselgel 60 F 254 sheets. Spots were visualized by the use of UV light at 254 nm and colored *via* treatment with 5 % ethanolic phosphomolybdic acid solution followed by heating. UV-Visible absorbance spectra were obtained using an Agilent 8453 spectrophotometer. Electrospray ionization mass spectrometry (ESI-MS) was involved for product characterization, the spectra were recorded on Agilent / Technologies 6320 spectrometer at room temperature; ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers operating at 400 and 100 MHz respectively at 600 and 150 MHz.

Synthesis of Compounds 3a–c

For the synthesis of the novel dendrimers 3 mmol of the aromatic core (**1a–c**) was dissolved in acetonitrile under continuous stirring at 40 °C. Separately, diethanolamine (6.3 mmol) was dissolved in acetonitrile and added to the reaction mixture. After homogenization, anhydrous potassium carbonate was added in excess in order to neutralize the formed hydrogen bromide. The resulted mixture was stirred for 24 h under reflux conditions. Completion of the reaction was monitored by TLC. Next, the mixture was allowed to reach room temperature. The unreacted potassium carbonate and the formed potassium bromide were separated by filtration. The filtrate was then evaporated using a rotary evaporator. The resulted products were purified by vacuum distillation. The obtained dendrimers were viscous, slightly yellowish liquids.

Synthesis of Compounds 4a and 5

2,2',2'',2'''-[1,4-phenylenebis(methylenenitrilo)]tetraethanol (1.6 mmol) was dissolved in aqueous hydrobromic acid, added in large excess under stirring. The resulted mixture was heated at 130 °C on a silicon oil bath. A Dean-Stark apparatus was attached to the flask and used for the continuous removing of the produced water in order to maintain the concentration of HBr in the reaction mixture. After the evacuation of water, the unreacted acid was removed by connecting the flask to vacuum. The resulted solid phase was dissolved in ethanol, active carbon was added and next filtered. The filtrate was evaporated on a rotary evaporator to half of its initial volume. Diethyl ether was added dropwise. The formed precipitate was filtered and dried overnight. The obtained morpholine derivative was a white solid.

The method described above was applied also for the synthesis of compound 5 using 9.5 mmol of substrate **2**. After the purification procedure a white crystalline product resulted.

NMR Spectra

3a. 2,2',2'',2'''-[1,4-Phenylenebis(methylenenitrilo)]tetraethanol ($\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_4$)

0.81 g (87 %); ^1H NMR (600 MHz, D_2O , 293 K) δ / ppm: 2.82 (t, 8H, $-\text{N}-\text{CH}_2-$), 3.71 (t, 8H, $-\text{CH}_2-\text{O}-$), 3.86 (s, 4H, aryl- CH_2-), 7.40 (s, 4H, aryl); ^{13}C NMR (150 MHz, D_2O , 293 K) δ / ppm: 54.74, 57.88, 62.49, 130.30, 135.45; MS m/z : 313 ($[\text{M}+\text{H}]^+$, 100 %).

3b. 2,2',2'',2''',2''''-[1,3,5-Phenylenebis(methylenenitrilo)]hexaethanol ($\text{C}_{21}\text{H}_{39}\text{N}_3\text{O}_6$)

1.17 g (91 %); ^1H NMR (400 MHz, D_2O , 293 K) δ / ppm: 2.68 (t, 12H, $-\text{N}-\text{CH}_2-$), 3.65 (t, 12H, $-\text{CH}_2-\text{O}-$), 3.70 (s, 6H, aryl- CH_2-), 7.25 (s, 3H, aryl); ^{13}C NMR (100 MHz, D_2O , 293 K) δ / ppm: 54.92, 58.14, 58.63, 130.34, 137.67; MS m/z : 430 ($[\text{M}+\text{H}]^+$, 100 %).

3c. 2,2',2'',2''',2''''-[2,4,6-Trimethyl-1,3,5-phenylenetrtris(methylenenitrilo)]hexaethanol ($\text{C}_{24}\text{H}_{45}\text{N}_3\text{O}_6$)

1.25 g (89 %); ^1H NMR (400 MHz, CD_3OD , 293 K) δ / ppm: 2.48 (s, 9H, $-\text{CH}_3$), 2.70 (t, 6H, $-\text{N}-\text{CH}_2-$), 3.52 (t, 12H, $-\text{CH}_2-\text{O}-$), 3.92 (s, 6H, aryl- CH_2-); ^{13}C NMR (100 MHz, CD_3OD , 293 K) δ / ppm: 17.37, 56.70, 60.20, 139.43; MS m/z : 472 ($[\text{M}+\text{H}]^+$, 100 %).

4a. 4,4'-[1,4-Phenylenebis(methylene)]dimorpholine ($\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$)

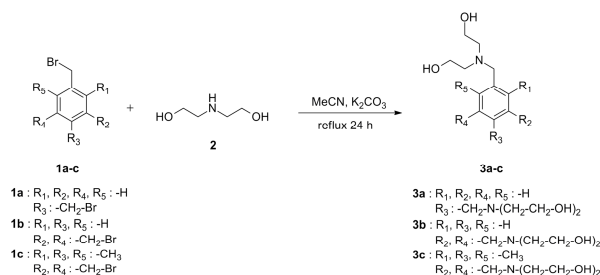
0.37 g (84 %); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 293 K) δ / ppm: 3.14 (t, 8H, $-\text{N}-\text{CH}_2-$), 3.78 (s, 4H, aryl- CH_2-), 4.43 (t, 8H, $-\text{CH}_2-\text{O}-$), 7.62 (s, 4H, aryl); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, 293 K) δ / ppm: 50.85, 58.47, 63.17, 130.61, 131.93; MS m/z : 277 ($[\text{M}+\text{H}]^+$, 100 %).

RESULTS AND DISCUSSION

Synthesis of the aromatic core (G[0]) of dendrimers was accomplished according to Scheme 1.

For compound **3a** we present a new method of synthesis while compounds **3b** and **3c** are newly synthesized. Since the surface functional groups are $-\text{OH}$, the dendrimers are highly soluble in polar solvents.

We tested different solvents, as reaction media, and acetonitrile proved to be the suitable for this



Scheme 1. Synthesis of dendrimers.

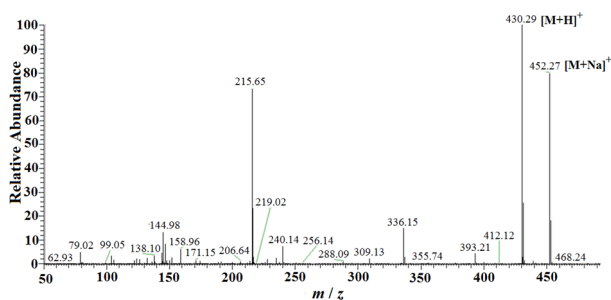


Figure 1. ESI-MS spectrum of compound **3b**.

purpose. Reactions were carried out also using triethylamine instead of potassium carbonate to remove the formed hydrogen bromide from the reaction mixture; unfortunately, we encountered difficulties in separation of the formed triethylammonium bromide, it being soluble in acetonitrile. For the purification of compounds **3a–c** column chromatography was first used but the separation of unreacted DEA from the dendrimer was not successful; vacuum distillation made this possible.

Mass Spectrometry

The ESI technique,²⁵ being useful in both low mass molecules and macromolecules characterization, was involved as characterization method. Methanolic solutions of the synthesized compounds containing 0.5 mg mL⁻¹ substrate per sample were analyzed. Figure 1 illustrates the recorded mass spectrum of compound **3b**. The peak at $m/z = 430$ corresponds to $[M+H]^+$. Also the peak for $[M+Na]^+$ is detectable at $m/z = 452$.

In the mass spectrum of compound **3c** (Figure 2) the peak for $[M+H]^+$ appears at 472 m/z value.

NMR Spectroscopy

All compounds were structurally characterized by nuclear magnetic resonance spectroscopy. In Figure 3 the ¹H-NMR spectrum for compound **3b** recorded in CD₃CN is depicted. Comparing the signals with the ones appearing on the spectrum recorded in D₂O, a new signal is present at 3.14 ppm assigned to the terminal

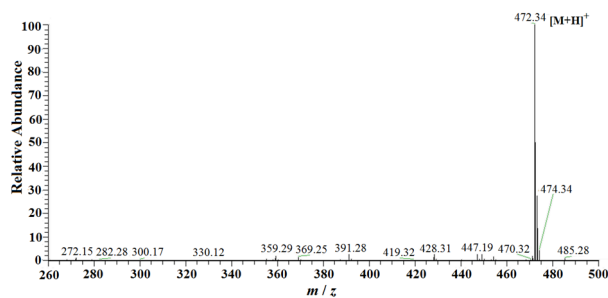


Figure 2. ESI-MS spectrum of compound **3c**.

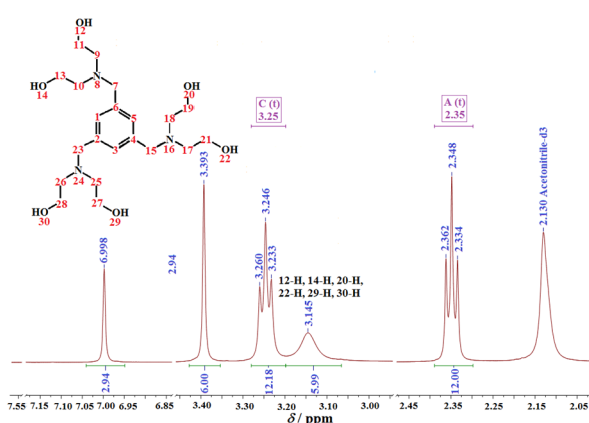


Figure 3. Fragment of the ¹H-NMR spectrum of compound **3b** [CD₃CN, 298 K, 400 MHz].

–OH protons. Based on these findings in order to differentiate the methylene protons from the diethanolamine chains, the corresponding quaternary ammonium salt of the product was formed by adding HCl to compound **3b**.

The spectrum recorded in DMSO-*d*₆ (Figure 4) shows a broad multiplet of four peaks at 3.28 ppm, 3.26 ppm, 3.22 ppm and 3.20 ppm assigned to the H-a, H-a' noted protons while another multiplet is detected, with four peaks at 3.79 ppm, 3.79 ppm, 3.78 ppm and 3.77 ppm assigned to protons noted by H-b, H-b'. This unexpected splitting of the signals suggests that the geminal H-a, H-a' and H-b, H-b' pairs are diastereotopic. In the aromatic zone, the splitting of the signal is also observed. A multiplet appears between 7.82–8.05 ppm, corresponding to the benzenic protons (1-H, 3-H, 5-H).

Forasmuch the diethanolamine branch methylene protons are differenced and the aromatic protons are not

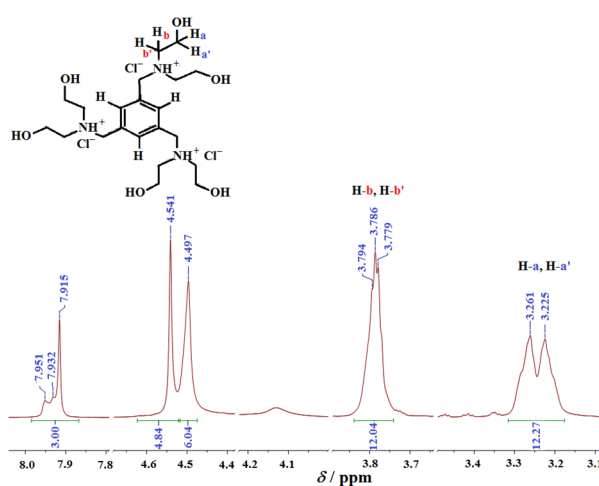


Figure 4. Fragment of ¹H-NMR spectrum of the quaternary ammonium salt of compound **3b** [DMSO-*d*₆, 298 K, 400 MHz].

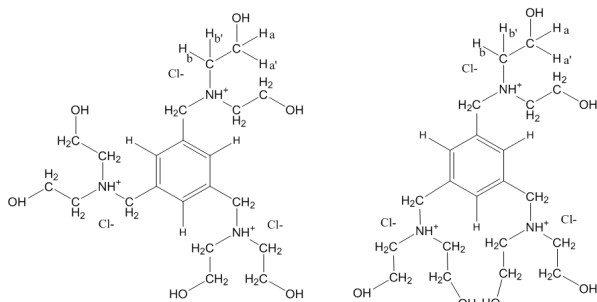


Figure 5. Suggested conformations for compound **3b**.

equivalent, one can conclude that compound **3b** has two isomers. The suggested conformations are shown in Figure 5.

UV Spectroscopy

The aqueous solution of the considered compounds shows no UV absorption changes in the range of 200–400 nm.

In order to grow the dendrimer by one generation, a new derivatization step with diethanolamine is required. For this purpose, the terminal hydroxyl groups must be halogenated first to allow the coupling of secondary amine branches, by adding concentrated HBr and heating at 160 °C. It is known that diethanolamine undergoes dehydration with sulfuric acid to form morpholine.¹³ In the presence of hydrobromic acid the compound **4a** was formed when 2,2',2'',2''''-[1,4-phenylenebis(methylenenitrilo)]tetra-ethanol was used.

CONCLUSION

In this paper we reported the synthesis of two new dendrimers, having as the core 1,3,5-tris(bromo-methyl)benzene and 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene, by derivatization with diethanolamine branches. The obtained compounds, with 4 or 6 hydroxyl terminal surface groups, show an increased water-solubility, in comparison with the parent molecules. 2,2',2'',2''''-[1,4-phenylenebis(methylenenitrilo)]tetra-ethanol in presence of aqueous hydrogen bromide led to the formation of 4,4'-[1,4-phenylene-bis(methylene)]-dimorpholine.

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