Synthesis and Characterization of a Chiral Dendrimer Derived from Pentaerythritol

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Received April 4, 1994

The synthesis and characterization of chiral dendrimer 1 in its racemic form is reported. The chirality of this macromolecule, with a molecular weight of 2831, is based on a pentaerythritol core, acting as a stereocenter with four dendritic substituents of different generation. The synthesis is making use of a newly developed, general route to a multisubstituted pentaerythritol derivative. Resolution of 1 is hampered by conformational flexibility. The latter, however, allows detailed $^1$H-NMR characterization indicating the stratified structure of the dendrimer. Considerable resolution of the $^1$H-NMR signals of the inner protons in C$_6$D$_6$ and C$_6$D$_3$N suggests that 1 adopts an overall chiral shape in solution.

Introduction

Recently, dendritic macromolecules have received considerable interest due to their unique hyperbranched polymeric structure and their well-defined three-dimensional architecture.1 Dendrimers emanate from a central core and have a well-defined number of generations and end groups. They are synthesized in a stepwise way via a repetitive reaction sequence. The syntheses described so far are either convergent or divergent of character.2 Polyamineamide dendrimers as introduced by Tomalia et al., using the divergent method, represent the first reported class and well-defined spherical shapes have been synthesized up to molecular weights of 700.000.1a The convergent route of Fréchet et al. is based on the synthesis of aromatic-ether dendritic wedges that are joined together in the last step of the dendrimer synthesis.2f Various other dendrimers based on one of these approaches have been disclosed, including a large scale synthesis3 and dendrimers using chiral building blocks.4

In almost all examples presented today, the overall shape of the dendrimer is symmetrical of nature, i.e., the dendritic wedges attached to the core are of the same generation. In this paper we present the synthesis and characterization of chiral dendrimer 1 in its racemic form. The chirality is based on a pentaerythritol core with four dendritic substituents of different generation (Figure 1). Dendrimer 1, with a molecular weight of 2831, should offer us detailed insight into the conformational flexibility of this new type of molecules.

Results and Discussion

A global synthetic scheme is given in Scheme 1. The aromatic-ether dendritic wedges [G-1]-Br, [G-2]-Br, and [G-3]-Br have been synthesized using the Hawker-Fréchet convergent approach5,7 and the step-by-step introduction of these dendritic wedges is performed by a newly developed method for the selective deprotection of a multisubstituted pentaerythritol derivative. The multisubstituted pentaerythritol derivative 10 (see Scheme 2) was synthesized from commercially available

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Figure 1.
deprotect only one of the two equivalent TBDMS groups. In this reaction the stereocenter was introduced and a method accomplishing this, using anhydrous ZnBr₂ in dichloromethane, was found by accident in our attempts to remove the MEM protecting-group.⁷ Spectral elucidation of the product by ¹H- and ¹³C-NMR spectroscopy unambiguously revealed that chiral alcohol 11 was formed. The introduction of enantiocentricity in this reaction using a variety of chiral auxiliaries failed so far, as was demonstrated by ¹H-NMR experiments with a chiral shift reagent (europium(III) tris[(heptafluoropropanyl)hydroxymethylene]-d-camphorato)).

The remaining part of the synthesis of the chiral dendrimer was realized by alkylating the alcohol moiety of 11 in a Williamson synthesis with sodium hydride and the bromide of the second dendritic wedge ([G-1]-Br), thus providing 12. In the next step the remaining TBDMS-groups was smoothly removed using tetrabutylammonium fluoride in THF,⁸ after which a next coupling step, using sodium hydride and the bromide of the third dendritic wedge ([G-2]-Br) in another Williamson synthesis, produced 14.

The cleavage of the MEM ether of 14 was not as straightforward as we anticipated. Using a host of various cleavage reagents (e.g., ZnBr₂, TiCl₄, butyllithium/hexane at −78 °C followed by Hg(OAc)₂ and (i-Pr)₂S)B₂), either no reaction took place or substantial degradation of the substrate occurred. Eventually deprotection, furnishing 15, was accomplished in good yield (76%) with B-chlorocatecholborane in anhydrous CH₂Cl₂.¹¹ The last step in our synthesis consisted again of a Williamson coupling, this time using sodium hydride and the bromide of the fourth dendritic wedge ([G-3]-Br), yielding racemic chiral dendrimer 1 in a yield of 74%. After chromatographic purification the dendrimer was obtained in a purity of >99% as determined by means of HPLC with silica Lichrosorb 60 as stationary phase. Solvent-free samples of 1, as determined by NMR spectroscopy, could be obtained after extended drying under reduced pressure. Dendrimer 1 proved to be very susceptible to Claisen rearrangements, yielding polar (phenolic) impurities; storage at temperatures as low as −40 °C was necessary to prevent degradation. Hence, HPLC in combination with ¹H-NMR spectroscopy should be regarded as optimal technique to determine the purity of this type of dendrimers. Elemental analysis and mass spectroscopy were not suitable techniques in this case. An overall yield of 4.6% is obtained in the 13-step synthesis of 1 from diethyl (ethoxymethylene)malonate (2).

Dendrimer 1 as well as all the intermediates are fully characterized. The ¹H-NMR spectrum of 1 in CDCl₃ shows an interesting feature for the resonances of the benzylic protons, revealing the stratified structure of the dendrimer. As can be seen in Figure 2, these resonances consist of a set of six singlets, centered around δ = 4.9 ppm, with an intensity ratio of 18:8:4:4:4 and of a set of four partially overlapping singlets near δ = 4.4 ppm with an intensity ratio of 2:2:2:2. The strongest signal (a) arises from the outermost benzylic protons of the largest dendritic wedge ([G-3]), being the only signal with


[Scheme 1. Global Synthetic Scheme for Chiral Dendrimer 1; PGⁿ Stands for Protecting Group Number n]
[Scheme 2. Synthesis of 1]
an intensity of sixteen protons. The two singlets with an intensity of eight (b, c) are interpreted as originating from the outermost benzylic protons of the one but largest dendritic wedge ([G-3]). Furthermore, the three singlets with an intensity of four (d, e, f) are ascribed to the benzylic protons in the next, more inwardly positioned, layer of the dendritic wedges [G-3], [G-2], and [G-1]. Finally, the benzylic protons directly attached to the pentaerythritol core appear as the four partially overlapping singlets near δ = 4.4 ppm (g). Moreover, the pentaerythrityl protons appear as an ill-resolved resonance at δ = 3.5–3.6 ppm (h). By recording the 1-H-NMR spectrum in C6D6 and C6D6N, respectively, a remarkable difference in chemical shift was observed (see Figure 2); both signals appear as four resolved singlets in a 2:2:2:2 ratio in the abovementioned solvents. The difference in structure of the two largest substituents in 1, i.e., [G-2] and [G-3], is 17 α-bonds apart from the pentaerythrityl protons and 15 α-bonds apart from the most inner benzylic protons, being too far from the core to differentiate between the CH2-groups in electronic properties. Therefore, we propose that dendrimer 1 can adopt an overall chiral shape in solution, which structure strongly depends on the solvent and/or complexation of 1 with solvent.

Another interesting feature of the 1-H-NMR spectrum is the sharpness of the peaks, compared to the size of the molecule. The reason for this is found in the substantial conformational freedom present in the molecule; considerable peak broadening appears only at temperatures below 230 K. However, no evidence has been found for the existence of a preferred conformational rotamer, and no diastereotopic protons could be detected.

The significant flexibility of the molecule at room temperature is also demonstrated in our attempts to resolve 1 in its enantiomers by means of HPLC with chiral stationary phases. In all cases we have observed a single Gaussian peak for racemic 1, while no resolution was obtained.

It is foreseen that reduction of the conformational freedom may facilitate the resolution of a chiral dendrimer. This decrease in flexibility can be obtained by increasing the crowding of the different groups in the molecule. In order to realize this, the possibility of synthesizing a chiral dendrimer with higher generations attached to the core is available. At the moment the synthesis of these compounds is an important goal in our further research on chiral dendrimers. Moreover, in this paper we have presented a new method for the selective deprotection of a multisubstituted pentaerythritol core, which, more generally, can find use in the synthesis of quaternary compounds containing four different substituents.

**Experimental Section**

Anhydrous dichloromethane was prepared by distillation from K2CO3, anhydrous DMF by vacuum distillation after standing on BaO for 72 h, and anhydrous THF by distillation from lithium aluminum hydride. Dry diethyl ether was prepared by standing on CaCl2 and subsequent drying with sodium wire. 1-H-NMR spectra were measured on a Bruker AM 400 spectrometer at 400.13 MHz. 13C-NMR spectra were run at the same apparatus at 100.62 MHz with proton noise decoupling. All NMR samples were routinely dissolved in CDCl3 and all δ values are given in ppm downfield from tetramethylsilane. The dendritic wedges used in the synthesis of the dendrimer were prepared according to the literature procedure of Hawker and Fréchet.

**Diethyl (Diethoxymethyl)malonate (3).** To a stirred solution of diethyl (ethoxymethylene)malonate (2) (129.5 g; 0.60 mol) in absolute ethanol (1 L) was added sodium metal (2.0 g; 88 mmol) in small pieces. The sodium was allowed to react completely, after which the mixture was brought to 45 °C and stirred at that temperature for 3 h. The mixture was neutralized with glacial acetic acid and the ethanol was evaporated in vacuo, after which the residue was taken up in dichloromethane (500 mL). Washing of the organic phase with water (3 × 250 mL), drying (MgSO4), and evaporation of the solvent gave crude 3, which was purified by distillation in vacuo: bp0.01 79–81 °C. Yield: 136.5 g (87%). 1H NMR: δ 1.19 (t, 6H), 1.27 (t, 6H), 3.58–3.78 (m, 5H), 4.21 (q, 4H), 5.11 (d, 1H). 13C NMR: δ 13.9, 15.2, 57.1, 64.3, 100.9, 166.0.

**Diethyl (Diethoxymethyl)(hydroxymethyl)malonate (4).** A solution of 3 (122.1 g; 0.47 mol), paraformaldehyde (23.9 g; 0.79 mol), and potassium carbonate (7.2 g; 0.072 mol) in anhydrous DMF (400 mL) was stirred for 48 h, after which water was added (1 L). Extraction with dichloromethane (3 × 500 mL) washing of the organic phase with water (5 × 500 mL), drying (MgSO4), and evaporation of the solvent gave crude 4. Purification was accomplished by distillation in vacuo: bp0.01 107–109 °C. Yield: 111.1 g (82%). 1H NMR: δ 1.21 (t, 6H), 1.26 (t, 6H), 3.21 (t, 1H), 3.70–3.92 (m, 4H), 4.17–4.25 (m, 6H), 5.19 (s, 1H). 13C NMR: δ 13.9, 15.2, 57.1, 64.3, 100.9, 166.0.

**Diethyl (Diethoxymethyl)([(2-methoxyethoxy)methoxymethyl])malonate (5).** A solution of MEM chloride (47.1 g; 0.38 mol), compound 4 (98.2 g; 0.34 mol), and diisopropylamine (70 mL) in anhydrous dichloromethane (500 mL) was stirred until TLC analysis showed complete conversion (ca. 6 h, eluent hexane/ethyl acetate 2:1 v/v). Washing of the reaction mixture with aqueous, saturated sodium bicarbonate (3 × 300 mL), drying of the organic phase over MgSO4, and evaporation of the solvent gave the crude product. Purification was accomplished by vacuum distillation: bp0.01 136–138 °C. Yield: 98.3 g (77%). 1H NMR: δ 1.20 (t, 6H), 1.26 (t, 6H), 3.40 (s, 3H), 3.54–3.84 (m, 8H), 4.11 (s, 2H), 4.18–4.26 (m, 4H), 4.71 (s, 2H), 5.04 (s, 1H). 13C NMR: δ 13.9, 15.1, 55.9, 61.1, 63.3, 66.9, 66.6, 67.2, 71.6, 95.8, 103.0, 167.6.

**Diethyl (Diethoxymethyl)(2-[[methoxymethoxy]methoxy]methyl)]malonate (6).** To a suspension of lithium aluminum hydride (15.6 g; 0.41 mol) in anhydrous diethyl ether (500 mL) was added dropwise compound 5 (95.4 g; 0.25 mol) at such a rate that gentle reflux of the diethyl ether was maintained during the reaction. The mixture was allowed to stir at room temperature for another 1 h, after which water (15.6 mL), aqueous sodium hydroxide (2.3 g of sodium hydroxide in 15.5 mL of water) and, again, water (46.5 mL) were
added carefully. Filtration and evaporation of the solvent yielded 61.4 g of the pure product (83%) as a colorless liquid. 

$^1$H NMR: $\delta$ 15.2, 48.2, 58.7, 61.9, 66.2, 66.8, 67.2, 71.5, 95.4, 105.8.

A solution of 6 (45.6 g; 0.154 mol), imidazole (63.3 g; 0.93 mol), and TBDMOS disulfide (67.2 g; 0.45 mol) in anhydrous DMSO (150 mL) was stirred for 24 h and subsequently the reaction mixture was taken up in water (400 mL). Extraction with diethyl ether (3 x 200 mL), washing of the organic phase with water (6 x 150 mL), drying (MgSO$_4$), and evaporation of the solvent yielded the bis-silyl derivative 7 as an oil (contaminated with tert-butyldimethylsilanol), which was used in the next reaction without further purification. Yield (for the crude product): 70.2 g (87%).

1,1-Diethoxy-2,2-bis([(tert-butylidemethylsilyloxy)methyl]-3-[2-(methoxyethoxy)oxy]methoxy)propane (7). A solution of 6 (45.6 g; 0.154 mol), imidazole (63.3 g; 0.93 mol), and TBDMOS disulfide (67.2 g; 0.45 mol) in anhydrous DMSO (150 mL) was stirred for 24 h and subsequently the reaction mixture was taken up in water (400 mL). Extraction with diethyl ether (3 x 200 mL), washing of the organic phase with water (6 x 150 mL), drying (MgSO$_4$), and evaporation of the solvent yielded the bis-silyl derivative 7 as an oil (contaminated with tert-butyldimethylsilanol), which was used in the next reaction without further purification. Yield (for the crude product): 70.2 g (87%).

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oxy[benzyl]oxy[benzyl]oxy[propane] (1). Chiral dendrimer 1 was obtained in the racemic form by reaction of 15 (0.48 g; 0.38 mmol) with [G-3]-Br (0.75 g; 0.45 mmol) as described for 11 in a yield of 0.80 g (74%). Purification was accomplished by means of preparative HPLC (eluent dichloromethane/acetonitrile 99:1 v/v) with Silica Lichrosorb SI-60 5 μm (column dimensions 100 × 16 mm i.d.); detection with UV light at λ = 254 nm) as stationary phase. 1H NMR: δ 3.54 (e, 2H), 3.56 (br s, 6H), 4.39 (s, 2H), 4.40 (s, 4H), 4.44 (s, 2H), 4.80 (s, 4H), 4.82 (s, 4H), 4.85 (s, 4H), 4.87 (s, 8H), 4.91 (s, 8H), 4.96 (s, 16H), 6.41–6.61 (m, 25H), 6.63 (d, 8H), 7.18–7.40 (m, 75H). 13C NMR: δ 45.7, 69.3, 69.4, 69.7, 69.8, 69.9, 70.0, 73.1, 73.2, 100.8, 101.4, 101.5, 106.0, 106.3, 106.4, 127.1, 127.2, 127.5, 127.7, 127.9, 128.2, 128.5, 136.7, 136.8, 138.8, 139.1, 139.3, 141.3, 141.4, 141.4, 159.7, 159.8, 159.9, 160.0, 160.1.

Acknowledgment. We wish to thank Mr. J. L. J. van Dongen for his chromatographic contributions and Dr. J. A. J. M. Vekemans for valuable discussions. DSM Research is acknowledged for an unrestricted grant.

Supplementary Material Available: 1H- and 13C-NMR spectra of 1, 6, and 8–15 (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.