Synthesis and Characterization of a Chiral Dendrimer Derived from Pentaerythritol

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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 CD$_6$ and CD$_3$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 dendrimer 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 approach5,6 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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Scheme 1. Global Synthetic Scheme for Chiral Dendrimer 1; PG[4] Stands for Protecting Group
Number n

Scheme 2. Synthesis of 1a

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diethyl (ethoxymethylene)malonate (2) in eight steps, of which the first two steps were described previously, yielding diethyl (diethoxymethyl)(hydroxymethyl)malonate (4). The alcohol moiety of 4 was converted into the corresponding MEM ether 5 using a standard procedure. Lithium aluminium hydride reduction of the malonate diester 5 was transformed into diol 6. This diol was protected as the bis TBDMS-ether and subsequent reaction of the acetal functionality by treatment with a catalytic amount of p-toluenesulfonic acid in boiling ace tone for 15 min gave aldehyde 8. Sodium borohydride reduction of 8 afforded the corresponding alcohol 9, which was subsequently coupled to the first dendritic wedge ([G-0]) in a Williamson synthesis, using sodium hydride and benzyl bromide ([G-0]-Br), to give the desired achiral 10.

In order to synthesize a dendrimer with four different generations attached to the core, it was necessary to 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 enantioselectivity 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[3-(heptafluoropropyl)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, 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, butyl-lithium/hexane at -78 °C followed by Hg(OAc)2 and (i-PrS)B10), either no reaction took place or substantial degradation of the substrate occurred. Eventually deprotection, furnishing 15, was accomplished in good yield (76%) with 8-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 techniques 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 benzyl 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 18:8:8:4:4:4 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 benzyl protons of the largest dendritic wedge ([G-3]), being the only signal with

Figure 2. The ether region of the 400.13 MHz 1H-NMR spectrum of 1 in CDCl3, CD6D, and CD3OD, respectively.

An interesting feature of the 1H-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 250 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. 1H-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: bp 0.02 136-138°C. Yield: 133.6 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, 61.4, 63.2, 100.9, 166.0.

Diethyl (Diethoxyethyl)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: bp 0.07 107-109°C. Yield: 111.4 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, 61.3, 61.5, 63.4, 66.9, 103.2, 167.3.

Diethyl (Diethoxymethyl)(I2-methoxyethoxy)ethoxymethyl)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: bp 0.04 136-138°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, 56.9, 61.1, 63.7, 66.8, 66.6, 67.2, 71.6, 95.8, 103.0, 167.6.

2-(Diethoxymethyl)(I2-methoxyethoxy)ethoxy)methyl]-1,3-propanediol (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 (15.5 mL), aqueous sodium hydroxide (2.3 g of sodium hydroxide in 15.5 mL of water) and, again, water (46.5 mL) were
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A solution of p-toluene-sulfonic acid monohydrate (9.0 g; 47 mmol) and crude 7 (69.4 g; 0.132 mol) in acetonitrile (900 mL) was boiled under reflux for 15 min. After cooling down of the reaction mixture to room temperature, aqueous sodium bicarbonate (5% w/v; 150 mL) was added and the mixture was evaporated in vacuo. Addition of diethyl ether (3 x 200 mL), washing of the organic phase with water (6 x 150 mL), drying (MgSO4), and evaporation of the solvent yielded the bis-silyl derivative 8 (44.7 g; 67.2 mmol), which was used in the next reaction without further purification. Yield (for the crude product): 70.2 g (87%).

2,3-Bis[(tert-butyldimethylsilyl)oxymethyl]-3-(2-methoxyethoxy)methoxy)propane (8). A solution of p-toluene-sulfonic acid monohydrate (9.0 g; 47 mmol) and crude 7 (69.4 g; 0.132 mol) in acetonitrile (900 mL) was boiled under reflux for 15 min. After cooling down of the reaction mixture to room temperature, aqueous sodium bicarbonate (5% w/v; 150 mL) was added and the mixture was evaporated in vacuo. Addition of diethyl ether (3 x 200 mL), washing of the organic phase with water (6 x 150 mL), drying (MgSO4), and evaporation of the solvent yielded the bis-silyl derivative 8 (44.7 g; 67.2 mmol), which was used in the next reaction without further purification. Yield (for the crude product): 70.2 g (87%).

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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 (s, 2H), 3.56 (br s, 6H), 4.39 (s, 4H), 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, 127.8, 127.9, 128.2, 128.5, 136.7, 136.8, 138.8, 139.1, 139.3, 141.3, 141.4, 141.5, 159.7, 159.8, 159.9, 160.0, 160.1.

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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.