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Viologen-based benzylic dendrimers: selective synthesis of 3,5-bis(hydroxymethyl) benzylbromide and conformational analysis of the corresponding viologen dendrimer subunit

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ABSTRACT

Convergent and divergent strategies for the synthesis of viologen dendrimers with 1,3,5-tri-methylene-branching units are discussed. The title compound is easily transformed into 1-[3,5-bis(hydroxymethyl)benzyl]-4-(pyridin-4-yl)pyridinium hexafluorophosphate, which is used in sequential growth and activation steps as a CB_2 compound in the cascade-type dendrimer synthesis (B = –OH, activation = –OH → Br). Analysis of the dendrimer structure reveals that three torsional angles, that is, τ_1 between the two pyridinium units, τ_2 between the methylene and pyridinium and τ_3 between the methylene and phenyl, determine the conformational space of the dendrimers. We report here the crystal structure of 1-[3,5-bis(hydroxymethyl)benzyl]-4-(pyridin-4-yl)pyridinium as PF_6^- salt which represents the smallest subunit of the dendrimer that shows the same three torsional angles. The crystal structure together with the results from PM3 calculations opens an avenue to judge the structure of benzylic viologen-based dendrimers.

1. Introduction

In the last three decades, a number of methods have been reported concerning the cascade synthesis of dendrimers with trifold core using different branching units. These syntheses require a trifunctional CB_2- or BC_2-type building block as the branching units with B representing a latent functionality and C representing a reactive functionality which reacts with A, where A is available by the activation of B. Depending on the synthesis (divergent or convergent) either CB_2- or BC_2-branching units are required. A representative example for the divergent approach is the synthesis of the propyl amine dendrimer from acrylonitrile (CB_2-type branching unit) with –C≡C– representing C and the nitrile function representing B_2 which can be activated to A_2, A representing an amine nitrogen which can undergo double alkylation.[1] A representative example for the convergent approach is the synthesis of the poly(benzyl ether) dendrimer from 3,5-dihydroxybenzyl alcohol (C_2B-type branching unit) with B representing the benzylic alcohol that can be transformed into the corresponding bromide (A) and the phenolic OH groups representing C_2.[2] A decade ago, we have introduced the synthesis of viologen dendrimers[3] via a divergent approach using CB_2-type branching units, the corresponding convergent approach using BC_2-branching units was reported by Balzani and co-workers[4] (Scheme 1). The divergent approach of the viologen dendrimers[3] emanates from the 1,3,5-tris(bromomethyl)benzene core and the step-wise use of CB_2-branching units, where C represents the reactive pyridyl nitrogen and B_2 represents two OH groups which can be transformed into the benzylic bromide (A). The corresponding BC_2 dicationic compound is a potential branching unit for the convergent approach.

The selective monoalkylation of 4,4′-bipyridine with 1,3,5-tris(bromomethyl)benzene is possible but its further transformation to the corresponding bis(hydroxymethyl)-4-(pyridine-4yl)pyridinium salt cannot be achieved because under the typical basic condition necessary for this reaction, the bipyridinium is irreversibly attacked by OH^-. Selective double substitution of 1,3,5-tris(bromomethyl)benzene by two bipyridines is not possible as the product is prone to polymerize. Thus both 'viologen'-branching units CB_2 and BC_2 require the specific synthesis of the corresponding benzylic bromides **1c** and **1d**, respectively. The procedures have been reported but the yields are not satisfactory.[5,6]

2. Results and discussion

Possible routes for the synthesis of **1c** are presented in Scheme 2. These include (I) the hydrolysis approach using 1,3,5-tris(bromomethyl)benzene **1e**, (II) the Appel method, (III) the Frechet-type synthesis of **2d** followed by reduction and (IV) the bromination of diethyl 5-methylisophthalate.

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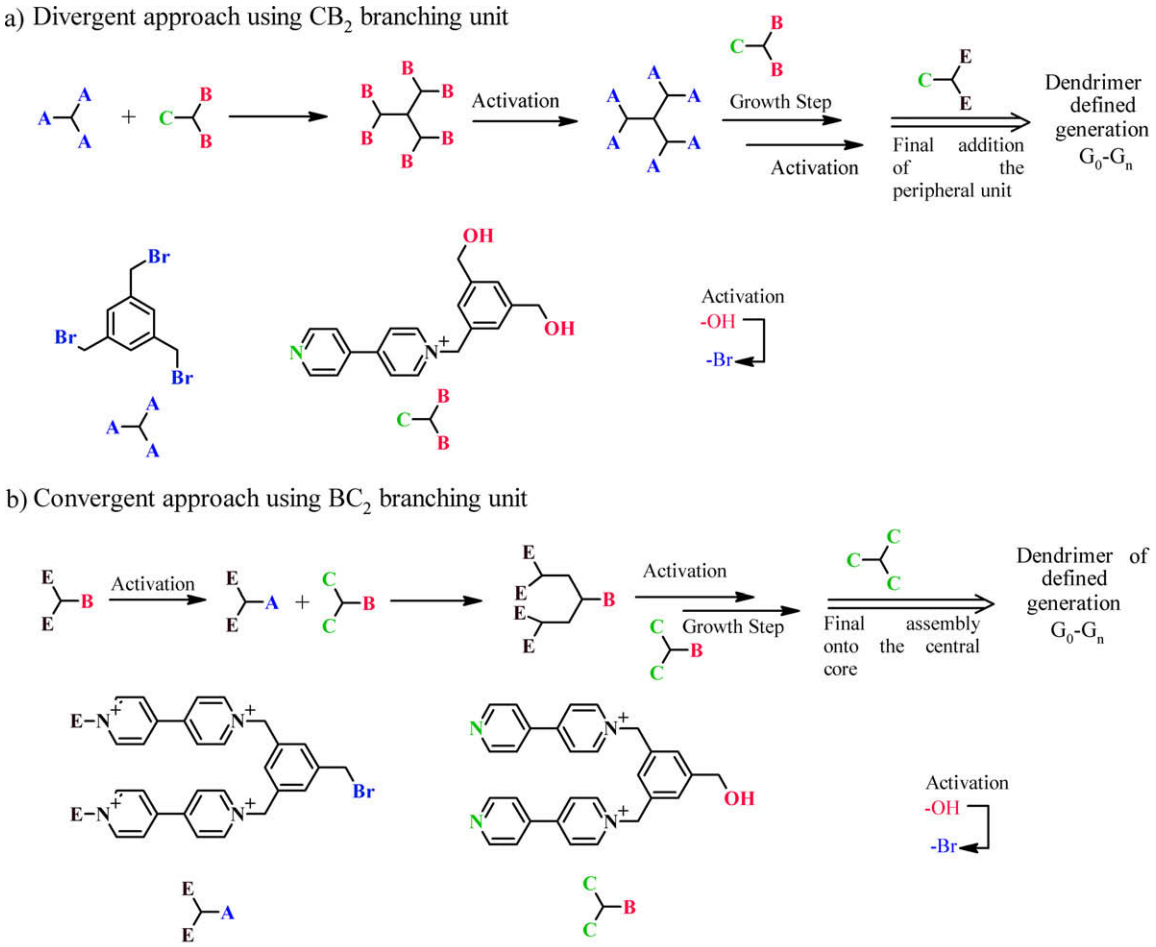
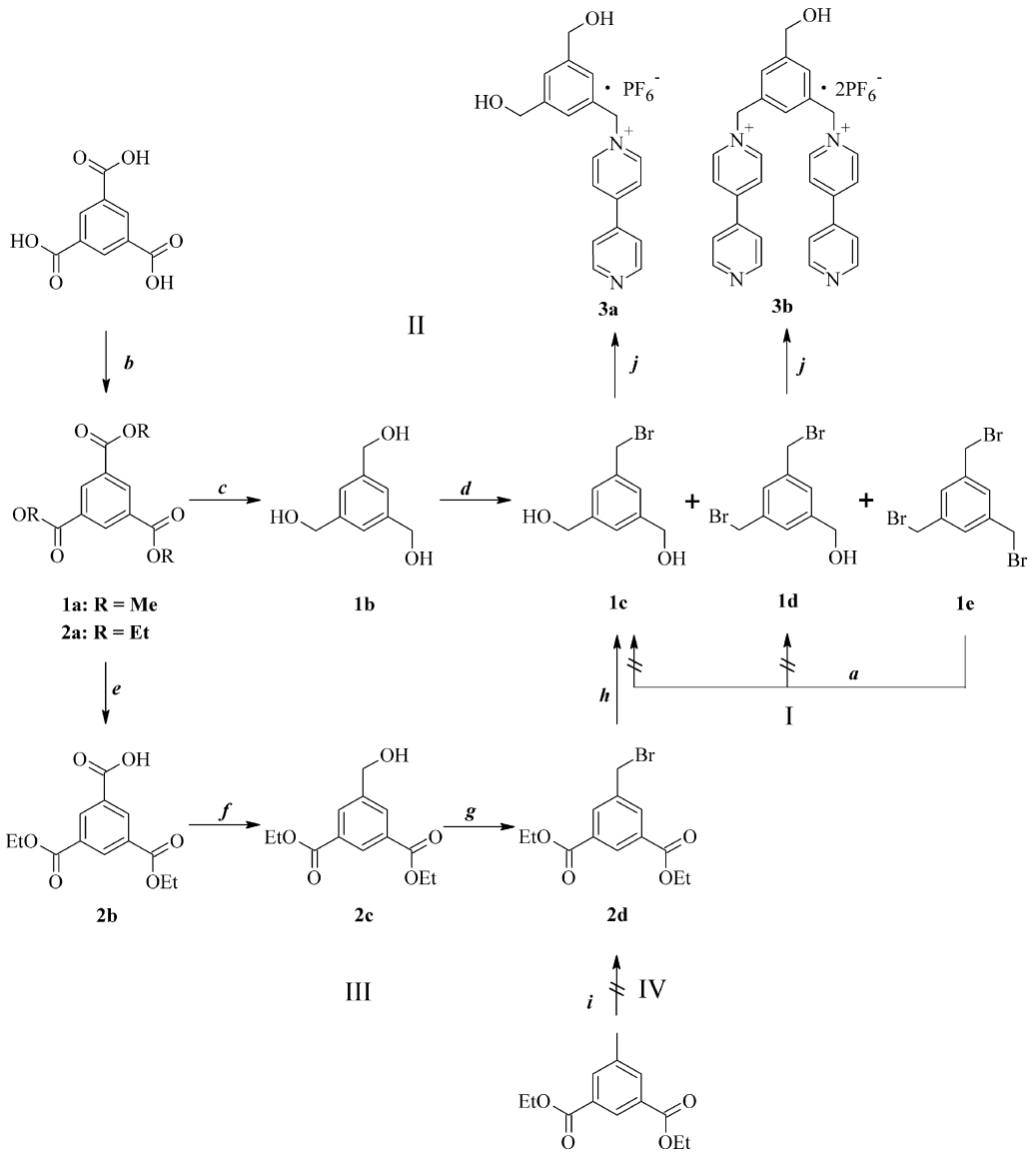


Scheme 1. Divergent and convergent strategies for benzylic viologen dendrimers.

(I) Hydrolysis of 1,3,5-tris(bromomethyl)benzene using different equivalents of strong or weak bases was not successful as the reaction yielded either mixture of ethers along with hydroxyl derivatives or completely hydrolyzed products, as reported for other benzylic bromide derivatives using different basic conditions.[7–9] (II) Since our first report on viologen dendrimer synthesis,[3] we use the Appel method to synthesize **1c** and **1d**. The synthesis starts with the conversion of trimesic acid to trimethyl **1a** or triethyl ester **2a** (90% in both cases), followed by the reduction of the triester **1a** with $LiAlH_4$ to yield the triol **(1b)** in 76% yield. The triol is then brominated using 1 equiv of Appel reagent to yield a mixture of the products **1c**, **1d** and **1e** which must be separated by tedious column chromatography [**1c** (36%) and **1d** (12%)]. There are two other methods tailored for higher yields of **1d**[10] (a well-known linker possessing two reactive and a latent site) by Stoddart and co-workers[6] and by Diez-Barra et al.[5] where the former used 3 equiv of the Appel reagent in THF and the latter used 1.1 equiv of Appel reagent in CH_3CN with 43% and 52% yields, respectively, after column chromatography. No reports are available on Appel conditions favouring high yields of **1c**. The limitations of Appel method are obvious: the reaction is not specific and the necessity of separation using column chromatography which limits the work-up to few hundred milligram scale. In order to overcome these problems and remembering that DIBAL-H is known to selectively reduce the ester functionality in the presence of primary or benzylic halides,[11,12] we propose route **IV** involving 5-bromomethyl diethylisophthalate[13] as the key intermediate. Its reduction with 1 M DIBAL-H in DCM gave **1c** in ca. 70% without the need of any column separation. We carried out the same reduction using $LiAlH_4$ at 0 °C as it is reported that $LiAlH_4$ selectively reduces ester functionality at lower temperature without reducing alkyl halides,[14–16] however, this reaction does not give reproducible results. Path **III** follows a route described earlier by Frechet[13] (**2a–d**), we followed the same route with some modifications. The method is based on the selective hydrolysis of 1,3,5-triethyltrimesic ester **2a** to 5-carboxy diethylisophthalate **2b** in 75% yield. The monocarboxy diester is then reduced to 5-hydroxymethyl-diethylisophthalate **2c** in 90% yield using 1 M BH_3–THF complex (lit.[13] 78% using 1 M BH_3–$(CH_3)_2S$). Bromination of the hydroxyl precursor using 5.6 M HBr in HOAc gave 5-(bromomethyl)diethylisophthalate **2d** in 95% (lit.[13] 90%, PBr_3 as brominating agent) which is then reduced to 3,5-bis(hydroxymethyl)benzylbromide **1c** 70% using 1 M DIBAL-H in DCM following the reported procedure.[17] Notably, all these steps



Scheme 2. Synthesis of hydroxymethyl- and bis(hydroxymethyl)benzylic bromides—the precursors of CB_2- and BC_2 viologen-branching units. Reagents and conditions: (a) hydrolysis under different basic conditions; (b) ROH, H_2SO_4, reflux, 24 h; (c) LAH, THF, reflux, 24 h; (d) CBr_4/PPh_3, THF, 0 °C to rt, 3 h; (e) KOH, EtOH–THF, reflux, 24 h; (f) 1 M BH_3–THF, 0 °C to rt, 6 h; (g) 5.6 M HBr–HOAc, rt, 36 h; (h) 1 M DIBAL-H/DCM, 0 °C to rt, 6 h; (i) NBS, Bz_2O_2, CCl_4, reflux; (j) (1) 4,4′-bipyridine, CH_3CN, 80 °C, 24 h; (2) 3 M NH_4PF_6/H_2O.

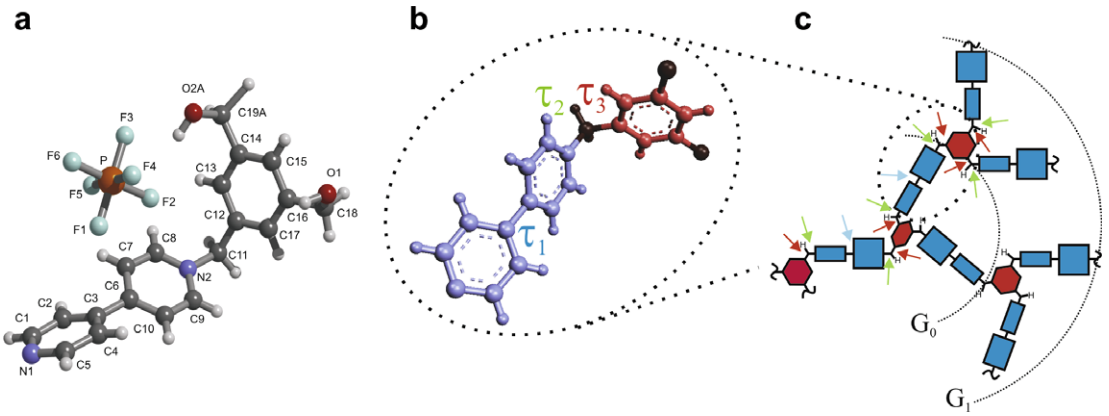


Figure 1. (a) X-ray structure of **3a** with torsions τ_1 (37.8° (C_4–C_3–C_6–C_{10})), τ_2 (87.3° (C_8–N_2–C_{11}–C_{12})) and τ_3 (−80.8° (N_2–C_{11}–C_{12}–C_{13})); (b) dendrimer subunit (based on **3a** X-ray conformation); (c) section of dendrimer consisting of **3a** subunits.

lead to the desired intermediates in good yield using simple recrystallization steps without column purifications. (For detailed synthetic procedures, see Supplementary data). (IV) The intermediate **2d** can also be synthesized by brominating 5-methyldimethylisophthalate using NBS as shown in route IV but this reaction proceeds with low yield because of the electron-withdrawing effects of the two ester groups.[18]

The mono- or di-alkylation of 4,4′-bipyridine is highly influenced by the solubility of the products in the solvent media. Dialkylation can be prevented by choosing a solvent in which the starting materials are soluble and the monoalkylated product is insoluble. In our case, we suppress the double alkylation by adding 1 equiv of **1c** slowly to 5 equiv excess of 4,4′-bipyridine in CH_3CN. The precipitated product is then filtered, washed with CH_3CN, dissolved in water and precipitated as hexafluorophosphate salt. The pale yellow powder thus obtained is again dissolved in water, heated to 80 °C and then cooled to yield pale yellow crystals. (Note: the pale yellow crystals became light green upon exposure to air). **3b** is synthesized using the same procedure, that is, 1 equiv of **1d** is added slowly to 10 equiv of 4,4′-bipyridine in CH_3CN and the resulting product is precipitated as hexafluorophosphate. The detailed synthetic procedures, CV and UV–vis characterizations are given in the Supplementary data.

3. X-ray crystallography, cyclic voltammetry and modelling

Viologen dendrimers[3,4,19] and dendrons[20] have been prepared extensively from 4,4′-bipyridine and **3a** using sequential substitution and activation reactions discussed in the prior paragraph. The geometry of the resulting dendritic structure has a large impact on the pimerization of viologen subunits,[20] the diffusion coefficient of the dendrimer, which in turn depends on the hydrodynamic radius,[3,19] and the size of the internal voids which is responsible for the pickup of large counter ions.[4,21]

A closer look at the dendrimer structure III shown in Figure 1 reveals that the overall conformational space available for the branches is given by only three torsional angles, that is, τ_1, τ_2 and τ_3, assuming that all the bending angles do not deviate much from their equilibrium value. The three torsional angles are located between the two pyridine moieties (τ_1), the methylene H and the pyridine (τ_2) and between the same methylene and the phenyl group (τ_3) (II in Fig. 1). Obviously, the salt **3a** (I in Fig. 1) exhibits the same set of angles. We were able to grow crystals of **3a** and to resolve its structure by X-ray analysis[22] (Fig. 1 I). The X-ray structure reveals that there are two molecules in a triclinic unit cell and the existence of an intermolecular hydrogen bond between O(1A)–H(1A) and N(1) (see Supplementary data). The torsional angles found in **3a** can be used as a reasonable starting point for the discussion of the dendrimer conformation. The torsional angles τ_1 in other bipyridinium systems cover the range from 20 to 50° in case of mono- and dialkylated viologens[6,23–29] with no large influence of the counter ion. However, the oxidation state is of importance, thus a diphenyl viologen shows dihedral angle (τ_1) of 37° and 1° for the dicationic and the radical cationic state, respectively. The other two torsions τ_2 and τ_3 have been reported for dibenzyl viologen by Inoue et al.[30] and by Garcia et al.[31] The former found three different τ_3 and τ_2 within a single crystallographic cell, the latter found τ_3 = -88.2° and τ_2 = 168.8°. These findings indicate no torsional angle preference, that is, a low torsional energy profile for τ_1, τ_2 and τ_3 planes.

Semi-empirical PM3 calculations were performed using Arguslab 4.0.1[32] and Hyperchem 8.0.6.[33] When the X-ray structure is used as a starting point for geometry optimization, a local minimum is found with only minor deviation from the solid state structure (except for a lateral shift of PF_6^-), indicating that PM3 is delivering reasonable values. If the PF_6^- counter ion is omitted in the same calculation, the lowest energy torsional angles τ_{1-3} do not change, indicating that the counter ion is not governing the torsional angles, rather the organic structure governs the position of PF_6. The torsional energy barriers related to a 360° rotation around τ_1,τ_2 and τ_3 have been judged from single point energy calculations at 10° increments without further geometry optimization (see Supplementary data). For a 360° rotation around τ_1 (with the τ_2 and τ_3 values fixed at their X-ray values) a fourfold barrier with a height below 1 kcal/mol was found, with one of the minima identical to the X-ray value (37.9°). PM3-based Wiberg atom–atom bond order calculations[34] reveal a bond order of only 1.02 between C3 and C6 for the minimum conformation in agreement with the observed low-energy torsional profile.

Rotation along τ_2 (with the τ_1 and τ_3 values fixed at their X-ray values) shows again a low-energy barrier (2–3 kcal/mol) but twofold, as expected for the methylene–pyridinium interaction. Finally for the rotation around τ_3 showed a low-energy barrier but twice as that of τ_2 (5–6 kcal/mol) and twofold as expected for the methylene–phenyl interaction.

^{1}H NMR spectra of the viologen dendrimers with the **3a** subunit show high symmetry indicating fast conformational changes.[3] Furthermore, cyclic voltammetry studies on **3a** and **3b** show slow fast electron transfer rates, which is again typical for redox couples with low activation barriers.

In summary, the conformational analysis of **3a**, based on X-ray, cyclic voltammetry and NMR data, representing a structural subunit of benzylic viologen dendrimers, reveals high flexibility with respect to the three torsional angles that play a role for the dendrimers shape.

4. Conclusions

The synthesis of viologen dendrimers with 1,3,5-trimethylene-branching units requires facile access to the CB_2-type synthon, 1-[3,5-bis(hydroxymethyl)benzyl]-4-(pyridin-4-yl)pyridinium hexafluorophosphate (Scheme 1). It is available according to Scheme 2 from **1c** and 4,4′-bipyridine. So far the synthesis of **1c** followed route II (Scheme 2) involving tedious chromatographic separation. The synthetic route III given in Scheme 2, explored in this work, allows the production of **1c** without the need of chromatography. The X-ray analysis of 1-[3,5-bis(hydroxymethyl)benzyl]-4-(pyridin-4-yl)pyridinium hexafluorophosphate combined with PM3-modelling studies gives a first time access to the sound estimate of the viologen dendrimer conformation.

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Supplementary data

Supplementary data (detailed experimental procedures, ^{1}H and ^{13}C NMR spectra of **1c**, **3a** and **3b**, cyclic voltammograms, UV–vis spectra of **3a** and **3b** and PM3 calculations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.097.

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