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Efficient synthesis of water-soluble, phosphonate-terminated polyester dendrimers

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ABSTRACT

Simple and effective syntheses of novel, water-soluble, phosphonate-terminated polyester dendrimers varying in size and structure are described. These macromolecular compounds, consisting of thiophosphoric and 1,3,5-benzenetricarboxylic ester building blocks may find potential applications in health sciences as microbicides and/or as useful macromolecular models for functional coatings of superparamagnetic iron oxides (SPIOs) nanoparticles intended for use in hyperthermal therapy and magnetic resonance imaging (MRI). The dendrimers, possessing free phosphonate functional groups on the surface, were prepared in high yields from previously synthesized phosphorus-based substrates with 3,5-bis (dimethoxyphosphonyl)-methyl]benzoic acid (**4**), being an essential precursor of the dendrimer polyanionic surface. In addition, an interesting example of virtual coupling between remote nuclei in the ^{13}C NMR spectrum of bisphosphonate monomer **3** was observed.

Dendrimers[1] have created a remarkable interest in areas ranging from materials science to biomedical applications. These macromolecules exhibit a high density of surface functional groups that can be easily tuned according to the field of application. Charged dendrimers are generally water-soluble compounds useful for biomedical applications, and polyanionic dendrimers are proven to be less toxic than polycationic ones.[2] Probably, the most important feature of polyanionic dendrimers is their significant antiviral activity, so they may serve as microbicidal drugs in their own right.[3] Antiviral dendrimers acting as non-natural imitations of the target cell surface are commonly designed with anionic surface groups. The polyanionic dendritic drug then competes with the cellular surface for virus binding, resulting in a lower cell-virus infection rate. On this matter, several dendrimeric frameworks terminated with carboxylic[4] and sulfonic[3a] acid functional groups, and to a lesser extent dendrimers,[5] and dendrons[6] capped with phosphonic and amino phosphonic[7] acids residues have been synthesized. But, none of these were polyester compounds. Interestingly, the 'smallest' dendrimer (generation one) terminated with amino phosphonic acid residues showed the most activity (compared with similar but higher generation structures), for example, multiplication of human natural killer cells.[8] These and other biological properties of organophosphorus dendrimers have been recently summarized comprehensively.[9]

However, phosphonic acids possess very strong binding affinity to the metal oxide surfaces. Consequently, this phenomenon sparked various studies and decorated magnetic metal oxide nanoparticles (NPs) with phosphonate terminated organic compounds have been synthesized.[10] Several research groups work on applications of superparamagnetic iron oxide (SPIO) NPs, including both diagnostics (MRI) and therapy (hyperthermic destroying of tumors). To make metal oxide NPs biologically tolerable,[11] suitable surface modifications applying compounds having free phosphonate groups as anchors are necessary.[12] Recently, the synthesis of small-sized phosphonated dendrons as potential organic coatings for iron oxide nanoparticles has been disclosed.[13]

On the other hand, polyphosphonate dendrimers, monodispersed entities whose relevant characteristics (size, hydrophilicity etc.) and polyfunctionality can be tuned as a function of their generation, should display much stronger binding to iron oxide NPs than monophosphonate or bisphosphonate dendrons.[13] Among dendrimers, polyesters have proved to be particularly important,[14] because they have biodegradability potential, and in the presence of enzymes can be hydrolyzed into small molecules, which are able to leave the body.

Recently, we developed a method for the synthesis of dendrimeric polyphosphates and their analogs.[15] We also have reported, the effective syntheses of new polyester dendrimers based on a trimesic acid framework derivative.[4b,16] In a continuation of these efforts, the straightforward and efficient syntheses of new, water-soluble, phosphonate terminated, polyanionic

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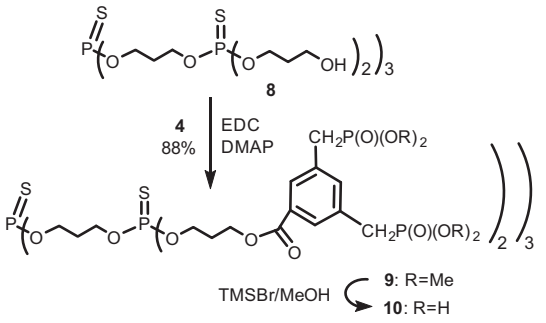
dendrimers composed of both thiophosphate and 1,3,5-benzenetricarboxylate units are reported herein.

Although the surface unit precursor, 3,5-bis[(dimethoxyphosphonyl)methyl]benzoic acid (**4**) is a known compound,[17] its synthesis required slight improvements. The synthesis commenced from a convenient starting material, methyl 3,5-bis(hydroxylmethyl)benzoate (**1**), which can be easily obtained from the parent trimesic acid.[16]

Bromination of diol **1** with phosphorus tribromide[18] in carbon tetrachloride provided dibromide **2** in 90% isolated yield. (Scheme 1) An Arbusov[19] reaction (90 °C, overnight) using an excess of trimethyl phosphite (neat) afforded the corresponding bisphosphonate **3** in high yield (84%). It is worth noting that bisphosphonate **3** cannot be obtained directly from diol **1** using recent methodology,[20] which does not work in the case of methyl phosphonates. The carboxylic ester functionality in bisphosphonate **3** was hydrolyzed using aqueous lithium hydroxide (1 M) to provide the key monomer, 3,5-bis[(dimethoxyphosphonyl)methyl]benzoic acid (**4**) in 86% yield. This compound represents an AB_2-type monomer. The A group (carboxyl) is active and the B groups (phosphonate) are protected such that the A group solely reacts with the B (active) groups in the prior generation of the dendrimer. Another monomer, this time, A_2B, **7** (in concordance to the above description) was obtained from trimesic acid dimethyl ester (**5**).[18,21] In this case the free carboxylic acid of compound **5** was reacted with di-*tert*-butyl-dicarbonate to yield the corresponding trimesic acid *tert*-butyl-dimethyl ester (89%).[22] Selective hydrolysis of both methyl groups in the triester was effectively achieved using aqueous lithium hydroxide to provide compound **6** in high yield (88%). Another highly chemoselective reaction was the reduction of the two carboxylate groups in diacid monoester **6** using borane-dimethyl sulfide complex, which furnished 3,5-bis(hydroxymethyl)benzoic acid *tert*-butyl ester (**7**) in a high isolated yield (83%).

The phosphorus-based dendrimers, used in this project as substrates were synthesized in a divergent manner from readily available, inexpensive chemicals, via an amidophosphite method. The detailed syntheses of thiophosphate dendrimers **8** and **11** have been described previously.[4b,15] It is worth noting that thiophosphate dendrimers turned out to be well tolerated by biological systems.[23] Hydroxy-terminated, first generation, thiophosphate dendrimer **8** was reacted with an excess of acid **4**, (Scheme 2) in the presence of the water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[24] (EDC), and 4-dimethylaminopyridine (DMAP) to afford the second generation dendrimer **9** in 88% isolated yield. Cleavage of the terminal methyl phosphonate esters in **9** was accomplished by applying, McKenna's method,[25] by means of a large excess of trimethylsilyl bromide (TMSBr) which transformed methyl phosphonate **9** into the

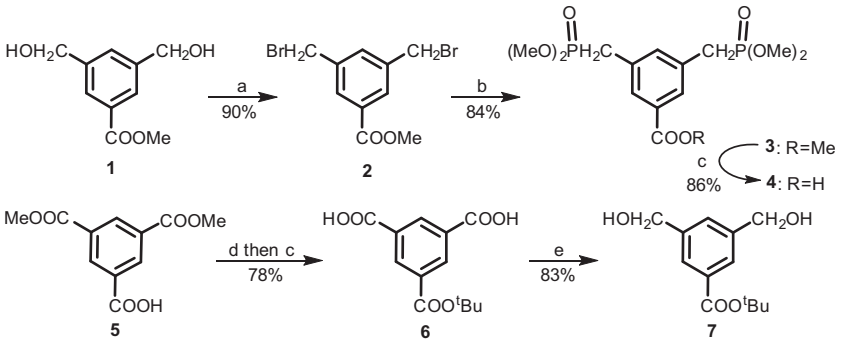


Scheme 2. Synthesis of dendrimer **10** with **12** phosphonate groups.

corresponding trimethylsilyl phosphonate ester intermediate that was swiftly hydrolyzed in situ to give phosphonic acids **10** in a protic solvent (MeOH). All of the deprotection stages were unambiguously evidenced by ^{31}P $\{^1H\}$ NMR. The presence of subsequent intermediates, bis-trimethylsilyl phosphonate esters (8 ppm) and even very unstable phosphonic acids trimethylsilyl esters (~17 ppm, broad singlet, most likely due to the existence of the *P*-epimeric isomers) were detected. These rather mild conditions did not cause cleavage of the other ester bonds present in the macromolecule and the integrity of the dendritic structure was preserved. Dodecaphosphonic acid **10** was further transformed into its dodecaanion (sodium hydrogen phosphonates) using aqueous sodium bicarbonate.

To demonstrate the usefulness of the presented synthetic approach, another, much larger phosphonate polyester dendrimer **13**, (theoretical mol. wt. 12096 D) was synthesized from dendrimeric substrate **11**.[4b] During this synthesis, the fully protected intermediate **12** was isolated, which was used to form novel polyanionic compound **13** (Fig. 1). Despite the fact that dendrimer **13** (generation four, the largest unprotected compound described here, overall yield 50%, from **11**) was composed of a lipophilic, thiophosphate-based interior (22 P = S functions), possessing 24 4-carbon chains, 21 3-carbon chains, and 24 aromatic rings, the effect of the surface polar phosphonate groups seemed to predominate. Free acid **13** was sparingly soluble in water, and in order to achieve reasonable solubility (50 mg/1 mL), it was necessary to convert a few (statistically three/four) of the 48 $P(O)(OH)_2$ groups into the corresponding sodium salts.

The presented methodology also enabled the convergent synthesis of phosphonate-capped polyester dendrimers. Moreover, depending on the nature of the substituents connected to both sides of the starting monomer or focal point, the interior of the macromolecule can be tuned accordingly. The synthesis of the



Scheme 1. Reagents and conditions: (a) PBr_3, CCl_4, rt; (b) $P(OMe)_3$, 90 °C; (c) LiOH aq, MeOH, 4 °C; (d) di-*tert*-butyl-dicarbonate, DMAP, CH_2Cl_2, rt; (e) $B_2H_6{\cdot}(CH_3)_2S$, THF, rt.