Tetrahedron 71 (2015) 1109–1116

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and properties of chiral internally branched PAMAM-dendrimers

Johannes F. Petersen [a], Christian G. Tortzen [a], Michael Pittelkow [a], Jørn B. Christensen [b,*]

[a] Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark
[b] Department of Chemistry, University of Copenhagen, Thorvaldsensvej 40, DK-1870 Frederiksberg, Denmark

ARTICLE INFO

Article history:
Received 12 July 2014
Received in revised form 15 December 2014
Accepted 22 December 2014
Available online 29 December 2014

Keywords:
Dendrimer
Amide coupling
Optical activity
Convergent synthesis
Internal branching

ABSTRACT

Improved synthetic methodology for the synthesis of internally branched chiral poly(amidoamine) (PAMAM) dendrons and dendrimers has been developed and the compounds have been characterized by NMR spectroscopy, IR spectroscopy, and optical rotation measurements. The dendrons and dendrimers show increased degree of internal hydrogen bonding upon increasing generation and the presence of different types of amide-protons in the compounds is indicative of the existence of a tertiary structure in these PAMAM-dendrimers.

1. Introduction

Dendrimers and dendrons are highly branched synthetic macromolecules. They breach the gap between small-molecule organic chemistry and polymer chemistry in the sense that they can be similar in size to polymers and can be synthesized in a controlled manner to yield monodisperse materials. A dendrimer is a structure that consists of a core, an interior, and a surface with a large number of surface groups, which is a consequence of the highly branched structure. Dendrons are the branched wings of the dendrimers.[1–4] Large dendrimers have a diameter of nanometer-dimensions and can, if designed properly, compartmentalize small molecules through non-covalent interactions either to the surface groups (*exo*-complexation)[5–7] or the interior (*endo*-complexation).[5–7] This is a feature they share with some globular proteins.[8]

exo-Complexation provides the opportunity for using dendrimers as quantized nano-scale building blocks[9] for use in supramolecular chemistry and medicinal chemistry (e.g., in tectodendrimers)[10,11] and in the case of dendrimer–protein conjugation, where the stochiometries for the composition of the tectodendrimers or the conjugates are dependant on the size and nature of the surface of the dendrimers.[12] *endo*-Complexation provides an opportunity for using the dendrimer for drug-delivery purposes[13–15] or for using the interior of the dendrimer as a microenvironment to facilitate reactions to take place under mild conditions.[16,17]

A strong driving force for the development of the field of dendrimer science is the potential application of dendrimers in different areas of chemistry, nanotechnology, biology, and medicine.[13,14,18,19]

Although a large number of papers describing the synthesis of dendrons and dendrimers are available[1,20–22] surprisingly few describe structures beyond the lowest generations (sizes). Only a few families of dendrimers are commercially available with the PAMAM (poly(amidoamine))-,[23] PPI (poly(propyleneimine))-,[24,25] poly(lysine)-,[26,27] Majoral-Caminade phosphorous-,[28] and Hult polyester-dendrimers[29] as the best-known classes. This reflects the general challenge in the area of dendrimer synthesis: The synthesis of large well-defined synthetic macromolecules is difficult. It is difficult to achieve full conversions in coupling reactions in either divergent or convergent synthesis schemes, as the reactions can be very slow. The purification of the products is also difficult due to issues with compartmentalization of small molecules (and solvents) inside the macromolecules, structural similarities between different sizes of polymers/oligomers and solubility issues.

Dendrimers having *endo* amino-groups as part of their interior structure may form complexes with transition-metal ions, and these complexes can in many cases be reduced with suitable reducing reagents to form dendrimer-encapsulated metal nanoparticles (DENs).[5,30,31] DENs have been prepared with a number of different types of metals, and they have been shown to be efficient catalysts for a variety of reactions including catalytic hydrogenations,[32] oxidation reactions,[33,34] and Heck-,[35,36] Suzuki-,[37,38] and Stille-reactions.[39,40] Our own work on catalysis with DENs lead us

* Corresponding author. Tel.: +45 35332452; e-mail address: jbc@chem.ku.dk (J.B. Christensen).

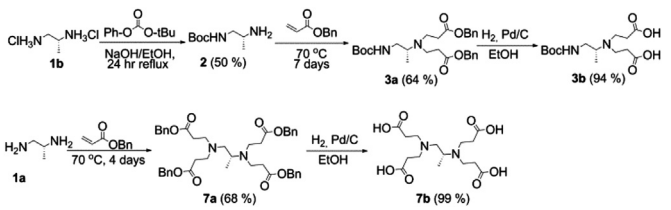
http://dx.doi.org/10.1016/j.tet.2014.12.080
0040-4020/

to consider the possibility of preparing chiral metal nanoparticles that might be used for catalyzing stereoselective reactions. We have previously reported a study on the convergent synthesis of internally branched PAMAM-dendrimers[41] and later a communication on chiral dendrimer-encapsulated metal nanoparticles of Pd and Rh.[42] Herein we describe our optimized synthetic protocols as well as the full characterization of a family of chiral PAMAM-dendrons and dendrimers based on chiral 1,2-diaminopropane.

2. Results and discussion

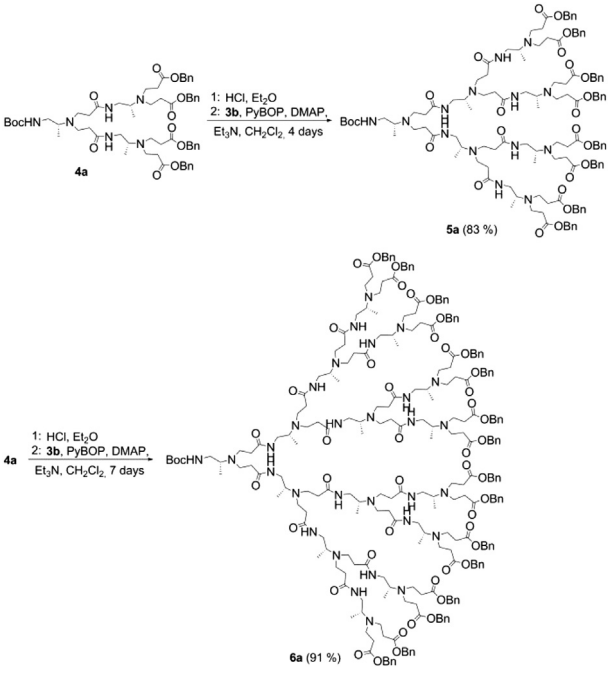
2.1. Synthesis

We chose to use 1,2-diaminopropane (**1a**) as the chiral element in the dendrons and dendrimers, because this keeps the PAMAM-skeleton of the dendrimers intact. 1,2-Diaminopropane (**1a**) is easily resolved on a large scale using classical resolution[43] with tartaric acid, and both enantiomers of the diamine were available. We have previously developed a methodology for the regiospecific carbamate monoprotection of polyamines[44] and in this case Boc-protection was chosen. We found it convenient to use the dihydrochloride of (2*R*)-1,2-diaminopropane (**1b**) instead of the free base for the synthesis of the mono Boc-protected amine (**2**). The hydrochloride was easily prepared by a simple ion-exchange reaction between the tartrate salt of the amine and KCl in water with formation of the poorly soluble potassium hydrogen tartrate as the driving force for the ion-exchange procedure. The mono Boc-protected diamine (**2**) was pure as seen by ^{1}H NMR spectroscopy with no signs of the opposite regioisomer. This regiochemistry was previously reported by our group in a study of the protection of diamines.[44] This material rearranges upon standing to give a mixture of the two regioisomers, and this was circumvented by performing the next step immediately after isolation of the mono protected diamine. The first step of the double Michael-addition in neat benzyl acrylate is a fast reaction giving the monoadduct. The second Michael-addition is slow, but can be driven to completion giving the building block (**3a**), which is stable and easily purified on large scale (>30 g) by dry column vacuum chromatography.[45] The Michael-additions proceed faster in hydroxylic solvents, but performing the reaction between the amine (**2**) and benzyl acrylate in either methanol or ethanol led to partial trans-esterification. Trans-esterification was not seen in 2-propanol, but in this case, the Michael-addition was slow. Deprotection of the Boc-group gives the primary amine (**3c**). This reaction may be performed using trifluoroacetic acid, but we found that using HCl in ether gave a cleaner product. Removal of the benzyl-esters was done by means of catalytic hydrogenation with Pd on C to give the di-carboxylic acid (**3b**) in 94% yield. Amide coupling of the two building blocks (**3c**) and (**3b**) with PyBOP as the coupling reagent gave the generation 0.5 dendron (**4a)** in 64% yield. The core was synthesized by quadruple Michael-addition between **1a** and benzyl acrylate (neat) to give the benzyl ester core (**7a**) in 68% yield. Removal of the benzyl-esters by catalytic hydrogenation using Pd/C gave the corresponding tetracarboxylic acid (**7b**) in 99% yield. The synthetic scheme is outlined in Scheme 1.



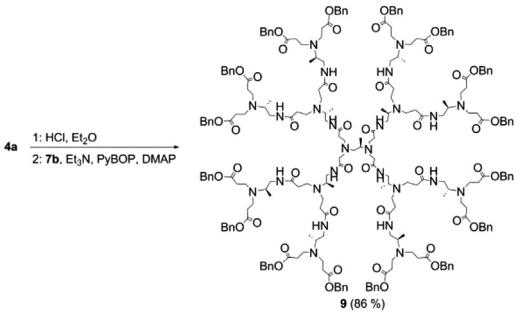
Scheme 1. The synthetic route to the building block for the dendrons (**3b**) and to the dendrimer core (**7b**).

Two strategies for synthesis of the higher generation dendrons were investigated; stepwise growth and accelerated growth as shown in Scheme 2. This is the first example of the use of accelerated growth in the synthesis of PAMAM-dendrons. Using accelerated growth gives access to higher generation dendrons more rapidly and the purification by size-exclusion chromatography turned out to be much easier than when using the stepwise growth process. It turned out that the coupling reaction was considerably slower requiring much longer reaction times (7 days vs 4 days) and we found that since the coupling reagent PyBOP slowly decomposes during the reaction, it was necessary to add additional amounts of fresh PyBOP to the reaction mixture during the coupling affording dendron **5a** in 83% and **6a** in 83% yield from dendron **4a**.



Scheme 2. Synthesis of dendrons **5a** and **6a**.

Coupling of the dendrons (**3a**, **4a**, **5**, **6**) to the core (**7b**) of the dendrimers was done as shown in Scheme 3. First the Boc-groups were deprotected with HCl in ether, then the carboxylic acid cores(**7b**)/dendrons (**3a**, **4a**, **5**, **6**) were added together with the amide coupling reagent and Et_3N. The dendrons and dendrimers synthesized are shown in Fig. 1.



Scheme 3. The synthesis of the final dendrimers was performed by coupling to the core **7b**. Here the coupling to form the G 2.5 dendrimer is illustrated.

2.2. Characterization

2.2.1. NMR spectroscopy. The full assignment of the ^{1}H and ^{13}C NMR spectra of **4**, **5**, **6**, **7**, and **8** was performed using different NMR