

# The Structure of PAMAM DAB-*dendr*(NH<sub>2</sub>)<sub>4</sub> – the First Crystal Structure of a PAMAM-dendrimer.

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ABSTRACT. The first crystal structure of an amino terminated PAMAM-dendrimer (DAB-*dendr*(NH<sub>2</sub>)<sub>4</sub>) is reported. The structure features a compact dendrimer conformation without voids, held together by intermolecular hydrogen bonds between dendrimers.

Talking about crystallinity and dendrimers usually makes people smile, because the vast majority of dendrimers are more or less oily or sticky materials. On the other side, the relatively

symmetrical nature of most dendrimers should provide for efficient crystalline packings.”Dendrimers are the name for a molecular architecture characterized as a structure emanating from a core by repetitive branching, so it is expectable that the properties of a dendrimer are given by the nature of the branch cell units and the core as shown in figure 1.

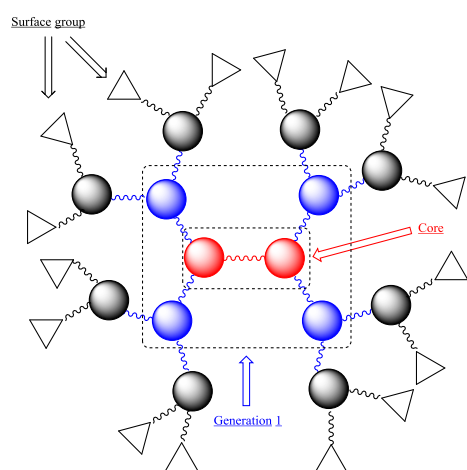


Figure 1: Structure of a hypothetical dendrimer built from  $AB_2$ -units from a tetravalent core.

Dendrimers can be classified in different ways: According to the chemical linkages between the branch-cell units like in PolyAmidoAMine- (PAMAMs), Poly(PropyleneImine)- (PPI-), Phosphorous-, Silane-, Siloxane-, Polyester- or Triazine-dendrimers, after the discoverer of the specific type of dendrimer or dendron (Tomalia-dendrimers, Newkome-dendrimers, Frechét-dendrons...) <sup>1</sup> or by baptizing a new dendrimer-family a unique name like Arborols <sup>2</sup> and so on.

A more informative way of classification of dendrimers has been used by Newkome <sup>3-5</sup> and Percec <sup>6</sup>, where the dendrimers are classified according to the nature of the branch-cell ( $AB_2$ ,  $AB_3$ ,  $A_2B_2$ ,...), which is important because much of the interest in dendrimers and dendrons

deals with using the multivalent surface for enhancing interactions like binding to biological targets and so on<sup>7, 8</sup>.

Searching the literature reveals a small number of crystal structures for dendrimers, but the majority of these are built from rigid branch cell units like Frechét-dendrons<sup>9-11</sup>, polyphenylene-dendrimers<sup>12</sup>, pyridine carboxamide dendrons<sup>13</sup>, benzene-1,3,5-tris(carboxamide) dendrimers<sup>14</sup>, aromatic sulfonimides<sup>15</sup>, porphyrin-cored silane dendrimers<sup>16</sup> and a Mo<sub>2</sub>-cored poly(3,5-dihydroxybenzoate) dendrimer<sup>17</sup>. Fewer are known for less rigid dendrimers with the structure of the tetrakis BOC-derivative of DAB-core poly(propyleneimine) G1 (Meijer-nomenclature but G0 according to the Tomalia-nomenclature) as a prominent example<sup>18</sup>. The structure (figure 2) is unusual in the sense that the four carbamates are backfolding to form a pretzel-like structure with hydrogen bonding across the dendrimer assembling the branch termini on one side of the backbone.

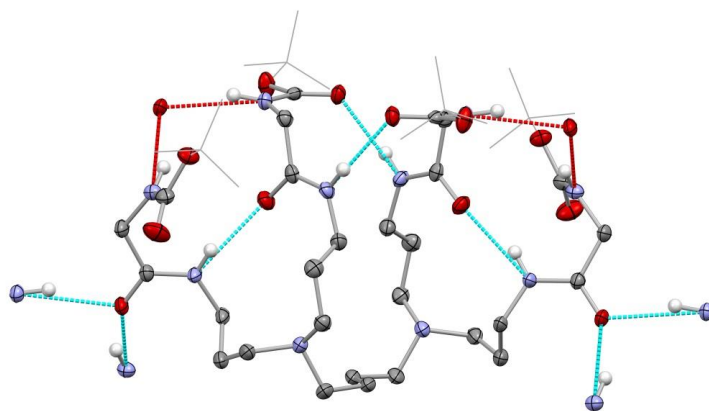


Figure 2, rendering of the folded molecular structure of DAB-dendr-(NH-glycine-t-BOC)<sub>4</sub> adapted from ref. 18 emphasizing both intra- and intermolecular hydrogen bonds. Hydrogens not involved in hydrogen bonding are

omitted for clarity. Terminal tertiary butyl groups are shown in wire-frame style for clarity. Color coding: carbon: grey; oxygen red; nitrogen: blue; hydrogen: white.

Flexible dendrimers can crystallize together with other molecules acting as templates, where the flexible dendrimer adapts to the conformation of the template like a lectin<sup>19, 20</sup> or a virus giving rise to crystalline dendrimer-virus assemblies<sup>21, 22</sup>.

Reproducibility, Scalability and Batch-to-Batch (RSB-to-B) consistency are key factors in bringing any compound from “bench to bedside” and it is a key issue in bringing nanoparticles such as dendrimers from the lab and into the clinic<sup>23</sup>. We have previously reported protocols for the synthesis of 1,4-diamino-butane core (DAB-core) PAMAM-dendrimers under RSB-to-B conditions<sup>24</sup> and found that DAB-core PAMAM-dendrimers are stable when pure and can be stored for years at -20°C without any signs of decomposition. The commercial products are sold as solutions in methanol. By serendipity a sample of G0 DAB-core PAMAM (figure 3) crystallized in storage and this has been used as seed crystals for facile crystallization of subsequent batches as illustrated on figure 4.

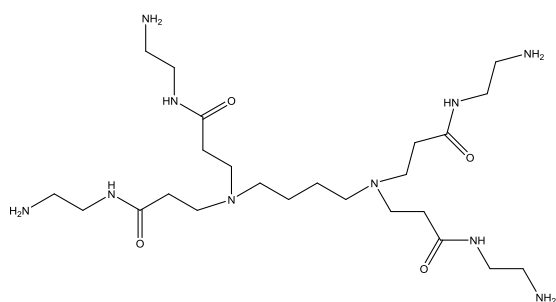


Figure 3. Structure of PAMAM DAB-*dendr*(NH<sub>2</sub>)<sub>4</sub>.



Figure 4: Left: Pure DAB-core PAMAM G0 a couple of hours after seeding. Right: After 24 hours at RT.

The crystal structure was determined by single-crystal X-ray diffraction and the molecular unit is depicted in Figure 5a. The overall conformation differs distinctly from the pretzel-fold of DAB-dendr-(NH-glycine-t-BOC)<sub>4</sub> (Fig. 2). The Z-shape of G0 DAB-core PAMAM is not adapted at the expense of hydrogen-bonding, but in this system hydrogen-bonding is exclusively intermolecular as shown in Figures 5b and 5c.

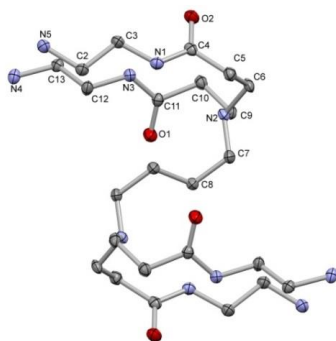


Figure 5a: Molecular structure of the G0 DAB-core PAMAM with thermal ellipsoid probabilities at 50% probability. The molecule crystallizes in the monoclinic space group  $P2_1/c$  with the molecule located on a center of inversion; only the asymmetric unit is labeled in the figure. Hydrogens are omitted for clarity.

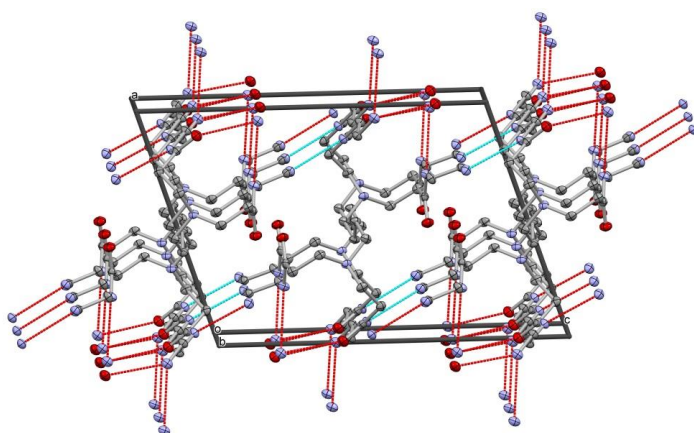


Figure 5b: View approximately along the crystallographic c-axis emphasizing the intermolecular hydrogen bonds engaged by a single molecule. Hydrogens from neighboring molecules acting as hydrogen-bond donors have been omitted for clarity, only the nitrogen atoms involved are shown.

As observed for DAB-dendr-(NH-glycine-t-BOC)<sub>4</sub> the tertiary amines are buried and do not partake in the hydrogen bonding pattern. The hydrogen-bonding in G0 DAB-core PAMAM produces a 2D-network in the ac-plane of the crystals as shown in Figure 4c, but this is not directly evident in the block-shape crystal morphology and cleavage properties of the crystals.

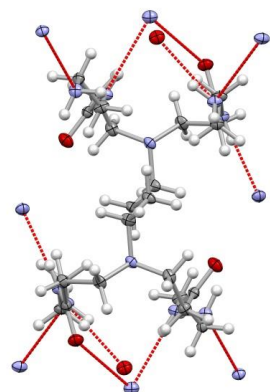


Figure 5c: The unit cell and packing of G0 DAB-core PAMAM viewed approximately along the b-axis emphasizing the 2D hydrogen bonding pattern.

The hydrogen bonds in G0 DAB-core PAMAM are all longer (N1-N4: 3.007 Å; N3-N5: 3.061 Å; O2-N5: 3.086 Å) than the intermolecular hydrogen bonds (average 2.94 Å) and the intramolecular hydrogen bonds (average 2.85 Å) in DAB-dendr-(NH-glycine-t-BOC)<sub>4</sub>. However, despite the weaker hydrogen bonding, the resulting packing is more dense for G0 DAB-core PAMAM with a calculated density of 1.251 g/cm<sup>3</sup> compared to 1.214 g/cm<sup>3</sup> for the dichloromethane solvate of in DAB-dendr-(NH-glycine-t-BOC)<sub>4</sub>. The Z-shape folding thus provides for a packing with no internal or external voids leading to a solvent-free structure. The absence of internal voids is contrary to the common belief that all generations of PAMAM-dendrimers have internal voids<sup>25</sup>.

De Gennes<sup>26</sup> predicted that a dendritic architecture without back-folding would eventually lead to a spherical shape of a dendrimer with an upper limit to the size (depending on the branch cell) due to the increased density of end-groups at the surface and Maciejewski<sup>27</sup> predicted possibility

of topological trapping inside a dendrimer. In the present case, the dendrimer is flexible enough to stretch out and form hydrogen-bonded networks that keep the structure together. It could therefore be expected that there will be a size-range of DAB-core PAMAM-dendrimers that are too bulky to form a hydrogen-bonded network in the solid state but not big enough to have a spherical shape that would allow a simple cubic close packing or hexagonal close packing.

## CONCLUSION

The first crystal structure of an amino terminated PAMAM-dendrimer (DAB-*dendr*(NH<sub>2</sub>)<sub>4</sub>) has been determined and the structure is compact without voids and held together solely by intermolecular hydrogen bonds.

## SUPPLEMENTARY INFORMATION

The crystallographic data have been deposited at the CCDC/FIZ Karlsruhe under deposition number 2016809.

**Formateret:** Skrifttype: Fed,  
Skriftfarve: Tekst 1

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