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Molecular simulations of dendritic molecules : a study of PAMAM and phenyl-acetylene dendrimers

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Molecular Simulations of Dendritic Molecules: a Study of PAMAM and Phenyl-Acetylene Dendrimers

by

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B.S., Computer Science, University of New Mexico, 2000

THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Masters of Science

Computer Science

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Dedication

To my parents, Mike and Laura, for their support.

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Abstract

Dendrimers are branched molecules that often have chemical properties similar to proteins and other large organic molecules. Dendrimers presently have applications as reactive surfaces for catalysis, and as hosts for drug delivery. Computer simulations of dendritic molecules are difficult due to their relatively large size and the tendency of atoms within a dendrimer to come within very close proximity to each other. The large number of steric interactions makes modeling of dendrimers difficult due to unphysically high energies that arise when a modeler attempts to construct a starting dendrimer from which to minimize its energy. Here we present Dendmol, a code that uses rigid body mechanics and a Monte Carlo method to set up the initial conditions for a dendrimer and present our findings. We found that this method is able to rapidly find conformations of dendrimers that can be readily placed into molecular mechanics, and molecular dynamics codes for further study of the dendrimer.

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Glossary

Å	Angstrom, $10^{-10}m$
dendrimer	A repeatedly branched molecule.
dihedral angle	The dihedral angle is the angle between the two planes formed by the three bond vectors between four consecutive atoms.
endocytosed	Endocytosis is the process by which cells absorb molecules from their environment.
fs	Femtosecond = $10^{-15}s$
hill climbing	Hill climbing is a mathematical technique often used for optimizing functions. Hill climbing allows the optimizer to search regions of the parameter space that have higher energies than those already explored. Hill climbing helps to prevent the optimizer from getting stuck in a local minimum.
moiety	Groups of atoms within a molecule that are responsible for a specific chemical functionality.
monodisperse	Having the same molecular weight.
Monte Carlo	A computational technique to sample high dimensional space using pseudo-random numbers.

Glossary

PAMAM	A type of dendrimer based on polyamidoamine groups.
PA	A type of dendrimer based on phenyl-acetylene groups.
ps	Picosecond = $10^{-12}s$
recursion	Recursion is a method that involves defining a function in terms of itself.

Chapter 1

Introduction

1.1 History

Dendritic architecture is common in biological systems. Trees, blood-vessels, neurons, and many other biological structures exhibit dendritic architecture. Dendritic architecture provides a means for providing high surface area to volume ratios. Although these structures are found at many different size scales in nature there are no known dendritic structures that occur in nature at the molecular scale.

Dendrimers are a class of synthetic polymers that exhibit dendritic architecture at the molecular scale. The first reported synthesis of a dendrimer was in 1985 by Vögtle and co-workers [1]. The term dendrimer is derived from Greek, "dendri" (tree like) and "meros" (part of). Traditional synthetic polymer solutions are usually composed of a mixture containing many different molecular weights. Dendrimers are unique from such polymers because unlike traditional synthetic polymers, dendrimers have a consistent molecular weight (i.e. they are "monodisperse"). Dendrimers are also unique among polymers because of their repetitive and regular branching.

Synthesis of dendrimers required a departure from traditional organic polymerization techniques and was accomplished by stepwise, repetitive reactions that guarantee monodispersity. The first dendrimers were synthesized from the core outwards using "cascade" synthesis; this technique is now known as divergent synthesis. Divergent synthesis techniques suffer from low yields and purification problems. In order to improve yields convergent synthesis was later developed in 1980 by Fréchet and coworkers. Convergent synthesis involves building the branching ends of a dendrimer first, then fusing branches together to form increasingly larger pieces of the dendrimer. Convergent synthesis is presently the preferred technique for the synthesis of dendrimers.

1.2 Structure of Dendrimers

Dendrimers are branched polymers that radiate from a central core. Figure 1.1 illustrates the general motif of a 2nd generation dendrimer. There are presently two conflicting nomenclatures for naming the generations of dendrimers. For this thesis we will use the nomenclature developed by Fréchet and Tomalia [2]. The first branching units that radiate from the core are termed the 0th generation. Subsequent branchings from these monomers are termed the $n+1$ generation where n is the generation from which the monomers have branched. The molecular group at the center of the dendrimer is referred to as the core, for PA dendrimers the center group is a benzene ring, for PAMAM dendrimers the center group is ethylene-diamine. Monomers radiate from the core, and each of these monomers is also capable of branching. The branching of the dendrimer is terminated after a certain generation with terminal ends represented by boxes in the figure.

Dendrimers are distinguished from other macromolecules by their well-defined branching properties, repeated subunits and consistent molecular weight. Because dendrimers branch with each generation, the number of atoms and molecular weight grow exponentially with the number of generations. Such exponential growth limits dendrimers from

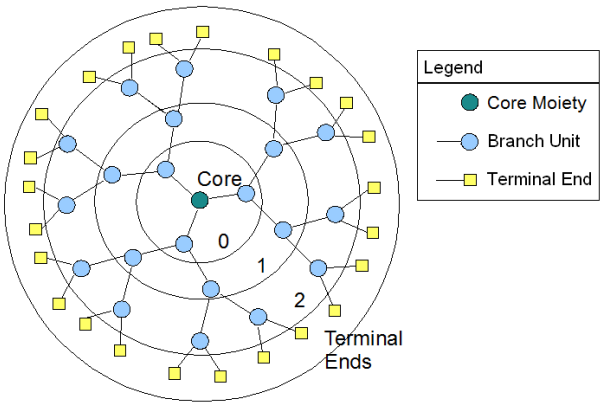


Figure 1.1: Dendrimer Motif

being constructed beyond a constant generation due to steric hindering of the outer atoms. This phenomenon is called de Gennes packing [3]; exponential growth of the number of atoms accompanied by only a cubic growth in available volume with each generation.

The general structure of a dendrimer consists of a core, the branching arm subunits, and terminating units. In Figure 1.1, the core has 3 branches. In general the core of a dendrimer may have any number of branches but typical dendrimers have between two and four branches on the core. The subunits each have two branches radiating from them. Although the majority of dendrimers have two branching units per subunit, in general they may have more than two. The yellow squares on the outer portion of the figure represent the terminating units. The 2-dimensional topology of the figure can be misleading since dendrimers are 3-dimensional and typically fold in on themselves. Dendrimers may also contain regions of empty space that are not well illustrated in 2D.

In a PAMAM (Polyamidoamine) dendrimer the most common core used is EDA (Ethylenediamine). This core allows for four branching arms to be placed on it for the construction of the 0th generation dendrimer. Branching units in PAMAM dendrimers are polyamidoamine. While branching units in PA dendrimers are phenyl-acetylene. The branching units are perhaps the most influential variable that determines the overall structural prop-

erties of a dendrimer.

The branching units serve largely as the architectural backbone of the dendrimer and hence contribute the most to the overall structure of a dendrimer. Long branching units are useful for making larger generation dendrimers. Rigid branching arms produce more crystalline dendrimers while flexible branching arms result in more globular dendrimers.

In this thesis the terminal units will always be hydrogen. In general, though, the terminal ends may be any functional group. Functionalizing the different terminal ends can modify both the inner and outer chemistry of a dendrimer.

Dendrimers contain voids often filled with solvent. The polarizability of the solvent, pH, and size of the solvent molecules effect the structure of a dendrimer to varying degrees.

1.3 Strategies for Synthesis

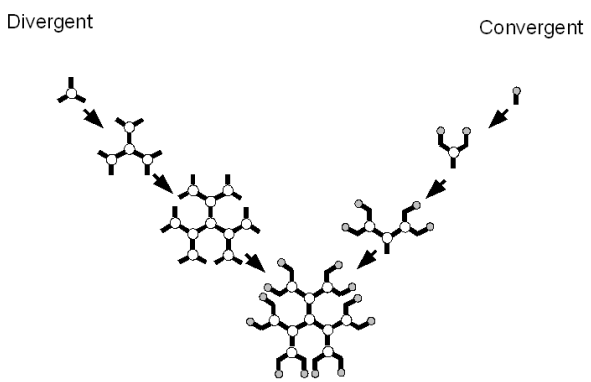


Figure 1.2: Convergent vs. Divergent Synthesis. Two ways to synthesize dendrimers.

Two approaches have been developed to synthesize dendrimers stemming from traditional organic chemistry. These two methods are known as divergent and convergent synthesis. The first synthesis of dendrimers performed by Vögtle in 1978 used “cascade”

synthesis which is presently known as convergent synthesis. This approach suffers from low yields and purification problems.

The Tomalia group developed the divergent method for dendrimer synthesis at Dow from 1979-1985. This approach allowed for the formation of (PAMAM) dendrimers of generations 1-13 in high yields [2].

1.4 Applications

Since dendrimers are an entirely new class of polymers it is expected that they will have many unique properties and hence many novel applications.

Dendrimers have been used for drug and gene delivery [4]. By encapsulating drug molecules, dendrimers can enhance aqueous solubility of host molecules, provided the terminal ends of the molecule are soluble in an aqueous environment. This can increase circulation time of host molecules and protect them from harsh environments therefore slowing drug metabolism. Dendrimers may also have functional groups attached to their periphery that enable them to target specific tissues and be selectively endocytosed. With selective endocytosis, a dendrimer could potentially be used to efficiently deliver toxins to cancer cells while preserving non-cancerous cell lines.

Dendrimers also have potential applications in solar energy conversion. Organic photovoltaic devices using dendrimers could provide an alternative route to bulk silicon photovoltaic devices [5]. Dendrimers may ultimately allow us to improve the efficiency and cost effectiveness of solar cells.

1.5 Approach

The goal of this thesis is to expand upon molecular simulation techniques to simulate dendrimers so that we can better understand their unique properties. Much of the difficulty with running atomistic simulations of dendrimers lies with setting up reasonable initial conditions that can be used by molecular mechanics and molecular dynamics programs. The problem is that most available techniques produce large degrees of unphysical steric crowding that cause the molecular mechanics, and molecular dynamics programs to fail. The current state of the art in setting up atomistic simulations of large dendrimers is to use continuous configuration biased Monte Carlo (CCBB MC) [6, 7].

We approach the problem of simulating dendrimers using multiple techniques. The first technique is to use a Monte Carlo method with rigid body dynamics. The Monte Carlo simulation creates a random initial conformation of a dendrimer with few bad contacts between atoms. Bad contacts are defined as atom pairs whose distances are close enough to facilitate the formation of a covalent bond that would change the structural formula of the dendrimer. Typically a bad contact happens any time two non-bonded atoms are within 1Å (0.1nm) of each other.

Our Monte Carlo algorithm utilizes a simplified discrete energy function that has many degeneracies (equivalent energies, but different conformations). The simplified energy calculation allows for quick evaluation of energies. The degeneracies allow us to explore a large conformational space without having to do any hill-climbing.

A molecular mechanics simulation is then run on the resulting initial conformation. In this simulation all degrees of freedom are allowed and we are no longer constrained to a rigid body system. Since there are few bad contacts, standard molecular mechanics techniques such as Quasi-Newton are able to further minimize the structure using a more realistic forcefield.

After the minimization is performed using molecular mechanics we evolve the system through time using molecular dynamics to simulate the molecule for 100ps with a temperature of 300K in gas phase. This is performed for both PA and PAMAM dendrimers. For the PA dendrimers we also insert solvent molecules to study solvent effects such as solvent penetration and conformational changes resulting from dendrimer-solvent interactions.

Once the molecular dynamics completes, we analyze the properties of the dendrimers including their radial density function, surface area, volume, solvent penetration and, radii of gyration and compare our results to those found in the literature.

Chapter 2

Constructing a Dendrimer for Simulation

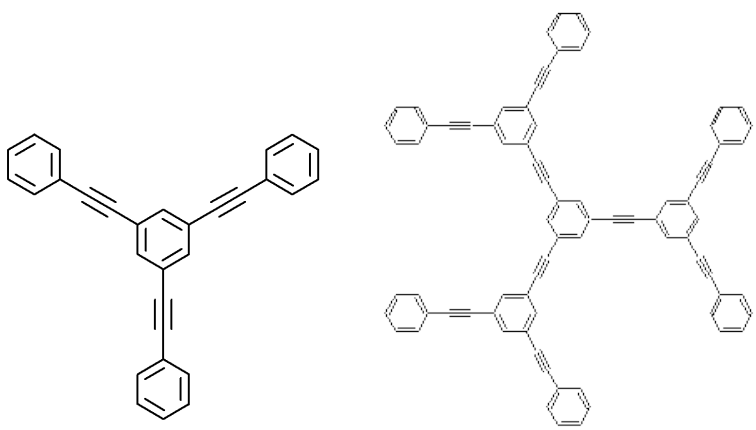
2.1 The Problem

The large sizes of dendrimers make it difficult to set up initial conditions required for molecular simulations. Because the number of atoms scales exponentially with the number of generations, the number of degrees of freedom also scales exponentially. Furthermore, because dendrimers are not linear polymers, they cannot easily be laid out in a spatial configuration that guarantees no steric overlaps.

In this thesis, we study two different classes of dendrimers. We study Phenyl-Acetylene (PA) dendrimers with benzene cores and Polyamidoamine (PAMAM) dendrimers with ethylenediamine cores. Skeletal formulas for PA dendrimers of generation 0 and 1 are shown in figure 2.1. Skeletal formulas for PAMAM dendrimers of generation 0-2 are shown in figure 2.2.

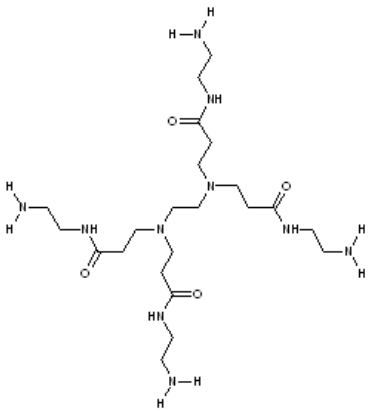
Three dimensional initial placement of atoms in a molecular simulation is often accom-

plished through a tedious process of constructing the molecule of interest using chemistry software packages that allow the user to connect bonds and place atoms in a 3 dimensional GUI environment. Unfortunately the construction of molecules using this technique leaves an unknown user bias that could place a dendrimer in a physically unrealistic local minimum. Perhaps more importantly, setting up simulations of dendrimers in this manner takes significant amounts of time because they require the placement of large numbers of atoms (147,396 in the case of PAMAM10). For these larger dendrimers, the task of constructing the dendrimer by hand becomes nearly impossible since the user cannot typically arrange atoms without resulting in molecule with significant steric overlaps.

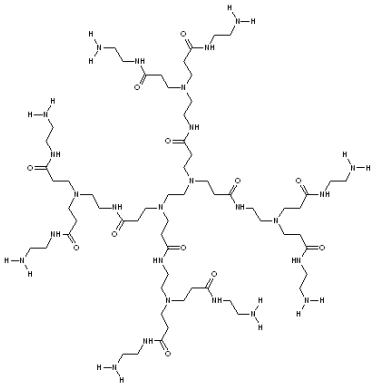


(a) Skeletal formula PA0 (b) Skeletal formula PA1

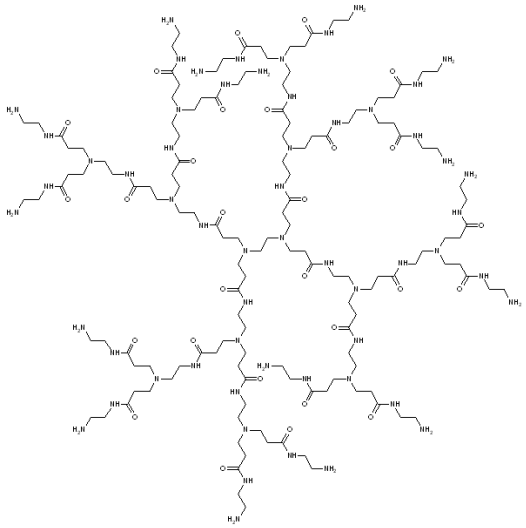
Figure 2.1: Skeletal formulas for PA dendrimers.



(a) Skeletal formula PAMAM0



(b) Skeletal formula PAMAM1



(c) Skeletal formula PAMAM2

Figure 2.2: Skeletal formulas for PAMAM dendrimers.

2.2 Approach

In this thesis, we initially construct both PA and PAMAM dendrimers based on a rigid bond-length and bond-angle model. In our model, only the dihedral angles of the dendrimers are permitted to vary as shown in figure 2.4.

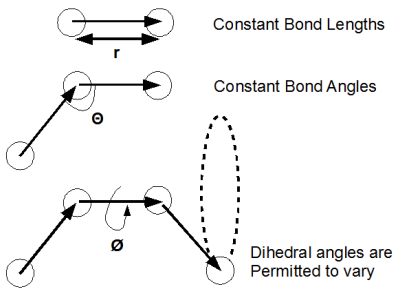


Figure 2.3: Atoms represented as circles are not permitted to change their distance between one another if they are bonded together, and may not change their angle with respect to one another if they share a bond angle. On the other hand, the atom on the dashed circle is permitted to move. In other words, r and θ are fixed, ϕ is free.

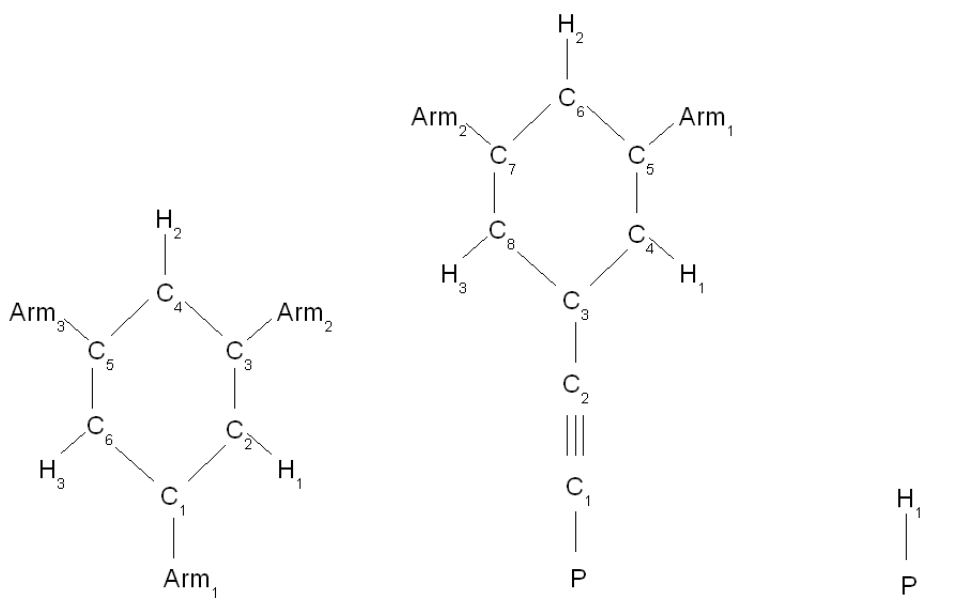
Figure 2.4: Bond angles and dihedral angles

The approach of constraining bond-angles and bond-lengths is frequently used with Monte Carlo methods and is used to study proteins and other macromolecules [8]. This approximation is justified by the fact that bond angles and bond lengths are well preserved in macromolecules. The preservation of bond lengths and bond angles in macromolecules is due to the relatively large energies required to change a bond angle or bond length compared to changing a dihedral angle. The differences in energies between bond-lengths and bond-angles are typically about an order of magnitude larger than the energy required to move the dihedral angles. By constraining the bond-lengths and bond-angles, the number of degrees of freedom for the system is reduced by approximately 3-fold simultaneously maintaining realistic ensembles of molecules.

Dendrimers as regularly branched molecules, can be constructed using recursion. In

general, we construct a dendrimer by starting with a core moiety and branching out recursively from its branch points. Branch points are bonded with a given arm appropriate for the dendrimer of interest. These arms have more than one branch point enabling continued divergent growth of the molecule. Dendrimers are then terminated with a terminal end group which does not have any branch points.

For PA dendrimers, we use a phenyl group as the core moiety as shown in figure 2.5(a). From it, we branch off with with phenyl-acetylene arms as shown in figure 2.5(b) to branch the dendrimer out. The terminal unit used in the PA dendrimers is simply a hydrogen as shown in figure 2.5(c) for the dendrimers we study here.

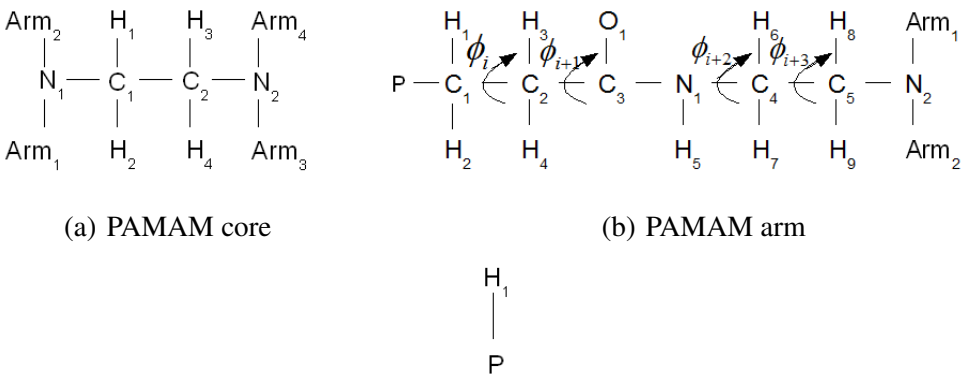


(a) PA core (b) PA arm (c) Terminal end

Figure 2.5: Parts of a PA dendrimer. The *P* ends are placeholders that bind to *Arm* ends. *P* ends may repeatedly bond to *Arm* ends so that the dendrimer branches out in a recursive manner. The terminal hydrogen can bind to the *Arm* ends to terminate the growth of the dendrimer.

For the PAMAM dendrimers, we use an EDA (Ethylenediamine) group as the core moiety and branch with polyamidoamine groups. Again, the terminal units we use for our

study of PAMAM dendrimers is simply a hydrogen.



(a) PAMAM core

(b) PAMAM arm

(c) Terminal end

Figure 2.6: Parts of a PAMAM Dendrimer. Ethylene-diamine (ETA) core, Polyamidoamine (PAMAM) arms, and terminal hydrogen.

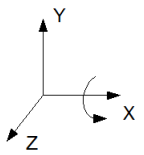
In order to construct a dendrimer for simulation we first declare variables in Eqn. (2.2.1) that describe bond lengths and bond angles found in PA and PAMAM dendrimers.

$$
\begin{aligned}
&r_{cn} = 1.471\text{Å (Carbon-Nitrogen single bond length)}\\
&r_{c3c3} = 1.531\text{Å } (sp^3 \text{ Carbon-Carbon single bond length})\\
&r_{ch} = 1.087\text{Å (Carbon-Hydrogen single bond length)}\\
&r_{co} = 1.23\text{Å (Carbon-Oxygen double bond length)}\\
&r_{aromatic} = 1.395\text{Å (Carbon-Carbon conjugated bond length)}\\
&r_{ccsp1} = 1.23\text{Å (Carbon-Carbon triple bond length)}\\
&\varphi_k = k\text{th dihedral angle}\\
&\psi = 109.5^\circ\text{Tetrahedral Angle}\\
&P = \text{Placeholder matrix representing the current position}\\
&I = 4\times 4 \text{ Identity matrix}
\end{aligned}
\tag{2.2.1}
$$

We make use of 4×4 matrices in figure 2.7 to form a homogeneous coordinate system that we can transform into 3-D Cartesian coordinates to place each atom in a dendrimer. Quaternions are often represented as 4×4 matrices with the following matrix operators to perform rotations, and translations.

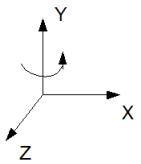
We also define a set of matrix transformations that are used to construct PA core in equations 2.2.3. The matrix transformations used to construct the PA arms are in equations 2.2.4.

$$R_x(\theta) = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos(\theta) & -\sin(\theta) & 0 \\ 0 & \sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$



(a) X Rotation Matrix

$$R_y(\theta) = \begin{pmatrix} \cos(\theta) & 0 & \sin(\theta) & 0 \\ 0 & 1 & 0 & 0 \\ -\sin(\theta) & 0 & \cos(\theta) & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$



(b) Y Rotation Matrix

$$T(x, y, z) = \begin{pmatrix} 1 & 0 & 0 & x \\ 0 & 1 & 0 & y \\ 0 & 0 & 1 & z \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

(c) Translation Matrix

Figure 2.7: 4×4 Translation matrix used to move atoms in their local coordinate system.

$$
\begin{aligned}
C_1 &= T(r_{cn}) \cdot P \\
C_2 &= R_x(\phi_i) \cdot T(r_{c3c3}) \cdot R_y(-\frac{\psi}{2}) \cdot C_1 \\
C_3 &= R_x(\phi_{i+1}) \cdot T(r_{c3c3}) \cdot R_y(\frac{\psi}{2}) \cdot C_2 \\
N_1 &= T(r_{cn}) \cdot R_y(-\frac{\psi}{2}) \cdot C_3 \\
C_4 &= R_x(\phi_{i+2}) \cdot T(r_{cn}) \cdot R_y(-\frac{\psi}{2}) \cdot N_1 \\
C_5 &= R_x(\phi_{i+3}) \cdot T(r_{c3c3}) \cdot R_y(-\frac{\psi}{2}) \cdot C_4 \\
N_2 &= T(r_{cn}) \cdot R_y(\frac{\psi}{2}) \cdot C_5 \\
H_1 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(\frac{\psi}{2}) \cdot C_1 \\
H_2 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(-\frac{\psi}{2}) \cdot C_1 \\
H_3 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(\frac{\psi}{2}) \cdot C_2 \\
H_4 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(-\frac{\psi}{2}) \cdot C_2 \\
H_5 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(-\frac{\psi}{2} - 180^\circ) \cdot N_1 \\
H_6 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(\frac{\psi}{2}) \cdot C_4 \\
H_7 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(-\frac{\psi}{2}) \cdot C_4 \\
H_8 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(\frac{\psi}{2}) \cdot C_5 \\
H_9 &= T(r_{ch}) \cdot R_y(180^\circ - \psi) \cdot R_x(-\frac{\psi}{2}) \cdot C_5 \\
O_1 &= T(r_{co}) \cdot R_y(\frac{\psi}{2}) \cdot C_3 \\
Arm_1 &= R_x(\frac{\psi}{2}) \cdot R_y(180^\circ - \psi) \cdot N_2 \\
Arm_2 &= R_x(-\frac{\psi}{2}) \cdot R_y(180^\circ - \psi) \cdot N_2
\end{aligned}
\tag{2.2.2}
$$

Equations for construction of a PA dendrimer core can be found in Equation 2.2.3.

$$
\begin{aligned}
C_1 &= P = I \\
Arm_1 &= R_y(-120^\circ) \cdot C_1 \\
C_2 &= T(r_{aromatic}) \cdot C_1 \\
H_1 &= T(r_{ch}) \cdot R_y(-60^\circ) \cdot C_2 \\
C_3 &= T(r_{aromatic}) \cdot R_y(60^\circ) \cdot C_2 \\
Arm_2 &= R_y(-60^\circ) \cdot C_3 \\
C_4 &= T(r_{aromatic}) \cdot R_y(60^\circ) \cdot C_3 \\
H_2 &= T(r_{ch}) \cdot R_y(-60^\circ) \cdot C_4 \\
C_5 &= T(r_{aromatic}) \cdot R_y(60^\circ) \cdot C_3 \\
Arm_3 &= R_y(-60^\circ) \cdot C_5 \\
C_6 &= T(r_{aromatic}) \cdot R_y(60^\circ) \cdot C_5 \\
H_3 &= T(r_{ch}) \cdot R_y(-60^\circ) \cdot C_6
\end{aligned}
\tag{2.2.3}
$$

Equations for construction of a PA dendrimer arm can be found in Equation **??**.

$$
\begin{aligned}
C_1 &= T(r_{cc}) \cdot R_x(\phi_i) \cdot P \\
C_2 &= T(r_{ccsp1}) \cdot C_1 \\
C_3 &= T(r_{cc}) \cdot C_2 \\
C_4 &= T(r_{aromatic}) \cdot R_y(60^\circ) \cdot C_3 \\
C_5 &= T(r_{aromatic}) \cdot R_y(-60^\circ) \cdot C_4 \\
C_6 &= T(r_{aromatic}) \cdot R_y(-60^\circ) \cdot C_5 \\
C_7 &= T(r_{aromatic}) \cdot R_y(-60^\circ) \cdot C_6 \\
C_8 &= T(r_{aromatic}) \cdot R_y(-60^\circ) \cdot C_7 \\
H_1 &= T(r_{ch}) \cdot R_y(60^\circ) \cdot C_4 \\
H_2 &= T(r_{ch}) \cdot R_y(60^\circ) \cdot C_6 \\
H_3 &= T(r_{ch}) \cdot R_y(60^\circ) \cdot C_8 \\
Arm_1 &= R_y(-60^\circ) \cdot C_5 \\
Arm_2 &= R_y(-60^\circ) \cdot C_7
\end{aligned}
\tag{2.2.4}
$$

We begin by constructing the core of the dendrimer. The first three rows of the last column correspond to x, y, and z Cartesian coordinates. Each 4×4 matrix represents an orientation and translation of the canonical Cartesian coordinates.

After building the core we branch out recursively off the "Arm" units and terminate them with hydrogen terminal units at the appropriate generation. At this point, all conformation of the dendrimer are uniquely specified by the vector $\vec{\phi}$. For our initial conformation, we simply choose random angles from -180° and 180°.

Chapter 3

Generating Low Energy Structures

3.1 Overview

The initial structure as constructed in chapter 2 is likely to have a significant number of bad contacts since we chose a random conformation. In order to remedy this problem we must change the conformation in such a way as to minimize the bad contacts or "energy" of the system.

Finding the minimum energy conformation of molecules is known to be NP-complete [9]. Since we cannot calculate the minimum energy conformation we need algorithms that can find conformations that can be used in existing molecular mechanics and molecular dynamics codes in reasonable amounts of time. We propose using a combination of Monte Carlo rigid body dynamics, molecular mechanics, and molecular dynamics to accomplish this task.

Typical molecular simulations using classical mechanics depend on bonded and non-bonded interactions. Bonded interactions involve bond-length, bond-angle, and torsion terms. These calculations are typically performed in $O(n)$ time where n is the number of

atoms. Non-bonded interactions involve electrostatic interactions and Van der Waals interactions. Non-bonded interactions are pair-wise interactions and hence have $O(n^2)$ interaction terms. Since the non-bonded energies drop off rapidly with distance, it is reasonable to not include interacting terms beyond some chosen cutoff radius. Spatial subdivision algorithms can be used to reduce the amount of computation needed to calculate the non-bonded interactions. Technically the asymptotic performance of the calculations in the worst case remains $O(n^2)$. However, in practice spatial subdivision algorithms reduce the computational complexity to $O(n)$. [8]

3.2 The Monte Carlo Method

Monte Carlo methods are a class of randomized computational methods. These methods are particularly useful for minimization of many-dimensional functions. In molecular mechanics calculations, Monte Carlo is typically employed by calculating the energy of a particular state the molecular system is in, then it randomly perturbs that state and recalculates the energy of the system. If the energy is less than the previous energy, it is always accepted, if the energy is greater than the previous energy it is accepted with some probability that is often a function of the temperature. We present a slight deviation from this strategy.

Using the spatial subdivision algorithm the energy of a molecule can be calculated in $O(n)$ time, where n is the number of atoms.

We use the Monte Carlo method to modify only the dihedral angles in the dendrimer. In order to simplify the calculation of the energy we use a step function to calculate energy. The step function allows us to compute the number of closely paired atoms that are likely to contribute to unrealistically high energies. By computing energies as a step function, our energy calculations are not approximations when we use the spatial subdivision algorithm.

We wrote a program called Dendmol. Dendmol is a rigid body mechanics Monte Carlo code. Since bond angles and bond lengths are constant, the conformation of a dendrimer is completely specified by its dihedral angles. Dendmol represents each dendrimer as a vector $\vec{\phi}$ of dihedral angles. Dendmol first initializes the elements of $\vec{\phi}$ to uniformly distributed random angles between -180 and 180 degrees. This creates a dendrimer with a random conformation. For small dendrimers (generation 0-3) this is often not a bad starting configuration, but with larger dendrimers, a random conformation typically places many atom pairs too close to each other to be physically reasonable.

Since all the bond lengths and bond angles are fixed, there is no need to calculate the energy of bonded interactions. The only interactions that need to be computed are the non-bonded interactions. For the purpose of constructing physically viable conformations, it is only necessary to consider non-bonded interactions that have high energy. We consider any pair of non-bonded atoms to have high energy if they are less than 1.08$\mathring{A}$ apart. This distance If all the non-bonded interactions have low energy, then it is likely that the dendrimer has a physically viable conformation.

A simplified energy function is used to compute the energy of the dendrimer. We simply count the number of non-bonded atom pairs that are within the cutoff distance.

$$E(r) = \begin{cases} 1, & \text{if } r \leq r_c \\ 0, & \text{if } r > r_c \end{cases}$$

$$E_{total} = \sum_{k}^{\text{all atom pairs}} E(r)_k$$

After the energy is calculated it is compared with the previous energy calculation. A random dihedral angle is chosen to turn a random amount weighted by a parameter an allowable torsional parameter. If the energy is larger than the previous energy it is

rejected. If the energy is less than previous energy it is accepted. It may sound as though this prevents hill-climbing which is an integral part of most Monte Carlo simulations, however since there are many conformations of the same energy in this scheme there is a vast configurational space in which to search.

3.3 Molecular Mechanics

Molecular mechanics is a time and temperature independent method to minimize the potential energy of a system of molecules using Newtonian mechanics. For this thesis we use the "minimize" sub-program in the TINKER [10] package to minimize the energy of the dendrimer using molecular mechanics.

TINKER supports several forcefields including MM3 [11–13]. A forcefield is a set of functional forms and parameters used to calculate the potential energy of a system of atoms. For this thesis we used the MM3 forcefield. However, since several interactions in the dendrimer are not included in MM3, we had to add them manually by estimating the interaction terms (see appendix).

First using Dendmol to reduce the number of close atoms pairs to a small number, the dendrimers are then saved in the TINKER XYZ file format. From here, we run TINKER molecular mechanics using the "minimize" program that is part of the TINKER package. The dendrimer is then minimized to an RMS (Root Mean Square) of 0.1 (kcal/mol)/Å. At this point, the dendrimer is ready to be run in TINKER's molecular dynamics code.

3.4 Molecular Dynamics

Molecular dynamics is a time and temperature dependent method used to calculate the trajectories of atoms using the same forcefields that are used in molecular mechanics. The

purpose of molecular dynamics is to capture the state of molecular systems with high spatial and temporal resolution. For this we also use the TINKER "dynamic" program and ran each dendrimer for 100ps at a temperature of 300K. 100ps gives the dendrimer sufficient time to get close enough to equilibrium to take meaningful measurements of radius of gyration and radial density functions. If we were interested in doing a more thorough molecular dynamics study of dendritic polymers, we would need to run the simulations to at least 20ns [14]. We could not do this due to limitations of available computing hardware and because TINKER has not been parallelized.

Since some of the molecular interactions that are necessary for the type of dendrimers we worked with are not available in the standard force fields provided with TINKER, we had to include a number of parameters based on similar interactions. The table of these interactions is provided in the appendix.

For the molecular dynamics, we used a modified MM3 potential [11–13]. Since the MM3 forcefield did not have several interactions that were needed to describe the dynamics of the molecules so these interactions were added by hand, and can be found in the appendix. Since the missing interaction terms were for energies of dihedral angles, and out of plane angles we set all these interactions to have 0 energy. This is a reasonable approximation since the Van der Waals forces dominate the energy terms of large dendritic polymers.

Simulations of PA and PAMAM dendrimers were run for 100ps in gas phase and simulations of PA dendrimers were run in a solvent droplets of dichloromethane for 20ps each. Attempts were made to run simulations of PAMAM dendrimers solvated in water, however it was found that TINKER does not handle large systems of water molecules [15]. Additionally the TINKER xyz file format dedicates 5 columns for atom identifiers limiting the number of atoms that can be properly simulated to 99,999.

(I need to discuss the creation of the 2 dichloromethane spheres that I used to submerge

the dendrimers. How large these spheres were, and how I minimized their structures and later submerged the dendrimer). I did this in a way to run the simulation at room temperature and pressure.

Chapter 4

Discussion and Results

Presently, the structure and chemical mechanisms for dendrimers remain poorly understood. There is a gap between experimental evidence and theoretical models that can be reliably compared. On one hand, we know quite a lot about the properties of dendrimers in certain solvents, their spectra, and other properties. But theoretical models of these properties have been difficult to establish because of the large size of most dendrimers and the complex environments they are typically exposed to.

In this work, our results for radius of gyration of PAMAM dendrimers agrees well with experimental evidence, and our studies of the radial distribution of monomers within both PA and PAMAM dendrimers suggest that there is extensive backfolding. This is in agreement with Maiti et al. [6]

It is likely that we have a good approximate understanding of the structure of dendrimers. We can safely conclude from experimental and theoretical results that dendrimers undergo significant back folding and some dendrimers have significant interior voids that allow them to function as hosts to smaller molecules.

A number of improvements that could be made to Dendmol are readily apparent. The

first would be to create a file format that will be read in by Dendmol that describes the internal coordinates of a dendrimer. From this file, Dendmol could be used to construct a much larger family of dendrimers and dendritic structures than were studied here. The second improvement would be to improve on how the dihedral angles are chosen for the Monte Carlo update. Presently these angles are chosen at random. However it is conceivable that with the right data structures, the angles to be modified could be selected based on which chain they belong to and the distribution of energy in that chain. This could speed up Denmol's performance. This was not necessary for this study since Denmol typically completed its run in under an hour even for large dendrimers.

Measurements of area and volume for PA dendrimers:

Generation	Area ($Å^2$)	Volume ($Å^3$)	Radius of Gyration (Å)	Gyration STD (Å)
PA1	480.7	415.3		
PA2	1182.2	1040.5	9.42	0.09
PA3	2578.4	2290.5	12.73	0.12
PA4	5259.2	4768.5	15.44	0.23
PA5	10682.5	9777.3	16.63	0.53
PA6	21208.3	19683.6	19.92	0.31
PA7	41767.6	39487.4	22.31	0.10
PA8	81824.6	78847.6	26.39	0.22
PA9	145534.7	154168.8	30.13	0.09

PAMAM Dendrimers:

Generation	Area (Å^2)	Volume (Å^3)	Radius of Gyration (Å)	Gyration STD (Å)
PAMAM2	2095.6	1907.4	8.06	0.42
PAMAM3	4628.7	4296.3	10.33	0.70
PAMAM4	9643.4	9069.2	13.06	0.57
PAMAM5	20625.1	18723.9	20.87	0.55
PAMAM6	41710.5	37929.4	25.97	1.03
PAMAM7	83091.5	76254.9	30.27	0.89
PAMAM8	42545.5	72781.4	20.48	1.54

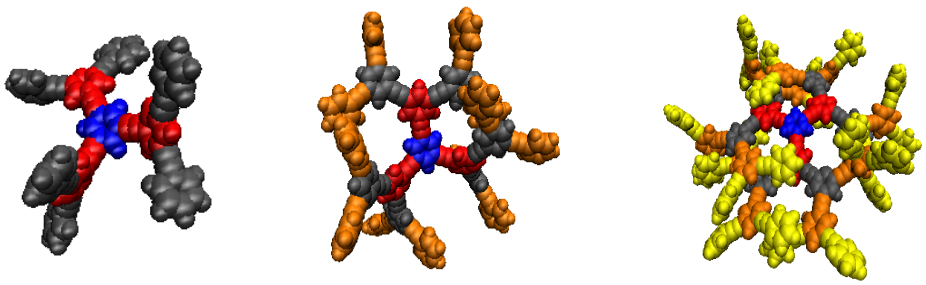
The number of atoms for each simulation differed. In the gas phase simulations, only the atoms of the dendrimer were considered. In solution phase I created a sphere of dichloromethane molecules to surround the dendrimer.

Generation	PA Atoms	PAMAM Atoms	PA + solvent Atoms
1	120	228	5925
2	264	516	5949
3	552	1092	5982
4	1128	2244	47433
5	2280	4548	47720
6	4584	9156	48619
7	9192	18372	50072

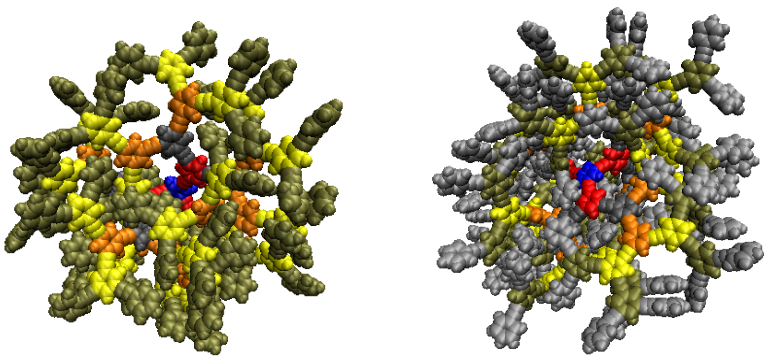
We can see in Table 4.1 the trends of convergence for PA dendrimers.

PA Generation	Time	Monte Carlo Steps	Close Pairs
7	less than 24 hours	266745	0
8	less than 48 hours	979815	0
9	96 hours	1050250	34
10	96 hours	605890	438
11	96 hours	323446	3600

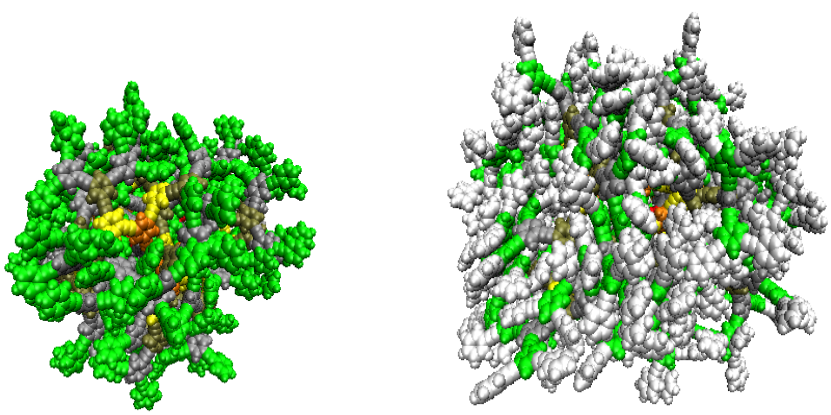
Table 4.1: Denmol runs to illustrate long term convergence with PA dendrimers.



(a) PA 1 (b) PA 2 (c) PA 3

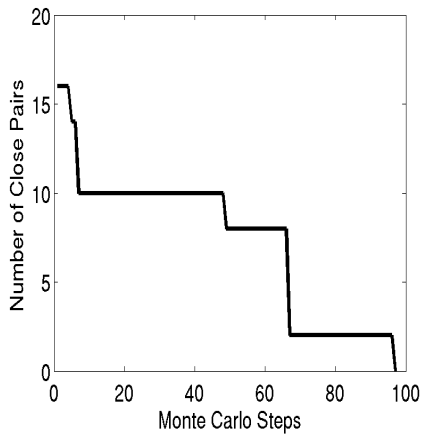


(d) PA 4 (e) PA 5

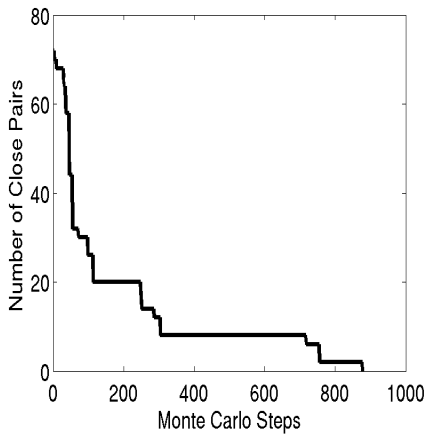


(f) PA 6 (g) PA 7

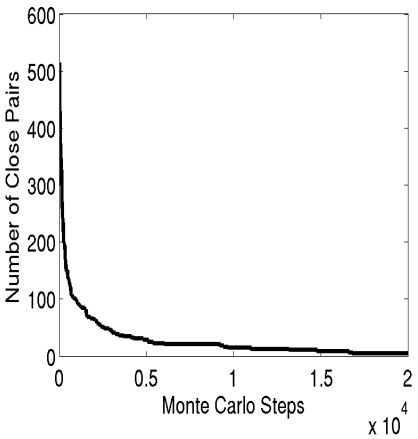
Figure 4.1: VDW Rendering of PA dendrimers with monomers colored by generation.



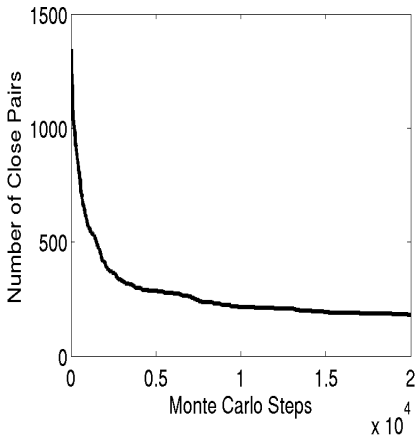
(a) PA 4



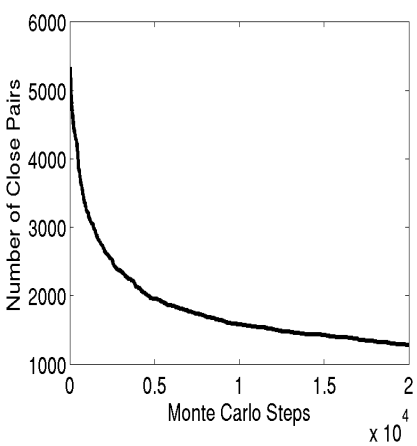
(b) PA 5



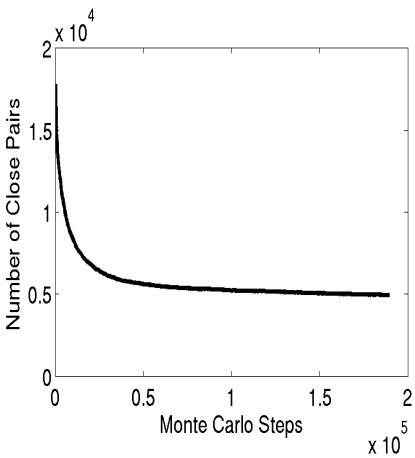
(c) PA 6



(d) PA 7



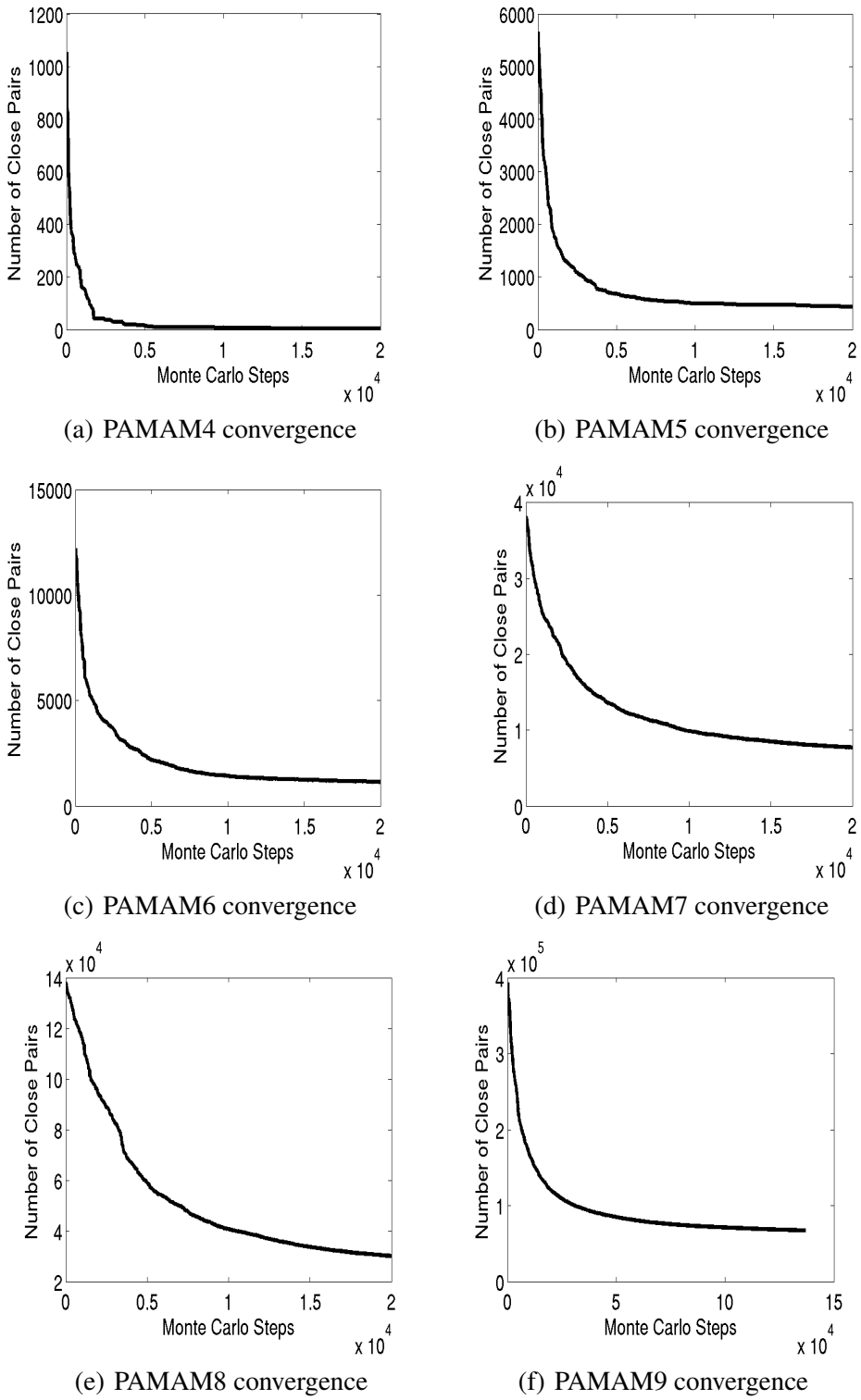
(e) PA 8



(f) PA 9

Figure 4.2: Convergence of Dendmol while constructing PA dendrimers.

PAMAM Generation	Time	Monte Carlo Steps	Close Pairs
5	24 hours	2108681	4
6	24 hours	1150436	6
7	24 hours	639563	176
8	96 hours	1238507	1116
9	96 hours	585331	4176
10	96 hours	252275	21064
11	96 hours	95442	104246



(a) PAMAM4 convergence

(b) PAMAM5 convergence

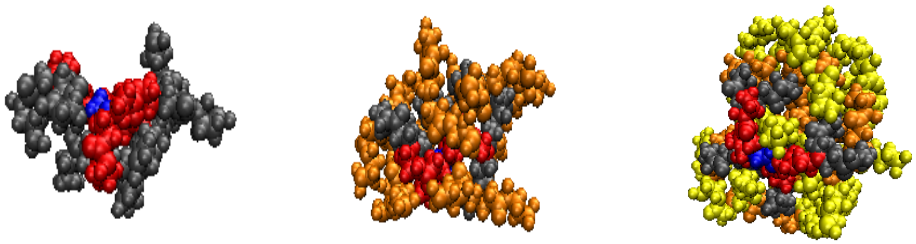
(c) PAMAM6 convergence

(d) PAMAM7 convergence

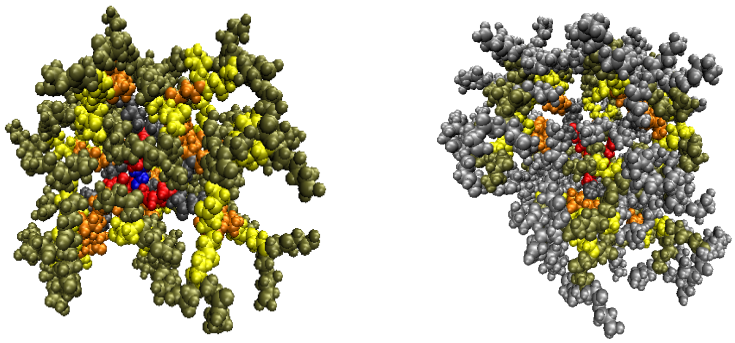
(e) PAMAM8 convergence

(f) PAMAM9 convergence

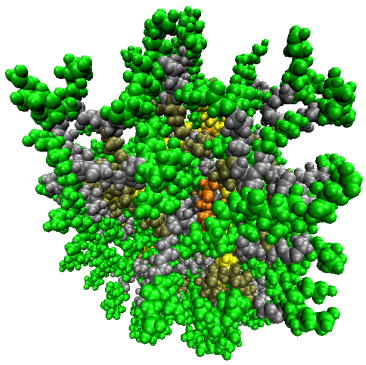
Figure 4.3: Convergence of Dendmol while constructing PAMAM dendrimers.



(a) PAMAM 1 (b) PAMAM 2 (c) PAMAM 3



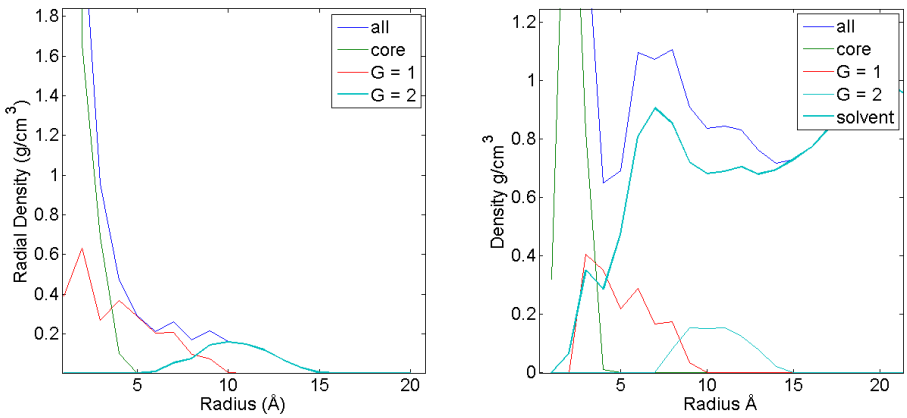
(d) PAMAM 4 (e) PAMAM 5



(f) PAMAM 6

Figure 4.4: VDW Rendering of PAMAM dendrimers with monomers colored by generation.

Radial distribution functions were calculated for PA dendrimers from generation 2 through 7.



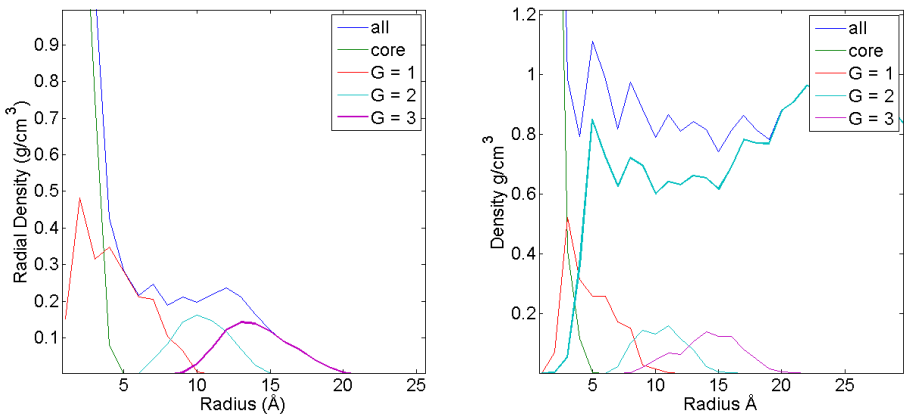
(a) PA2 RDF (b) PA2 solavted RDF

Figure 4.5: PA2 unsolvated and solvated radial distribution function.

In figure 4.5(a) we see that the first and second generation both are found in relatively high density near the core of the molecule. This implies backfolding even in early generations. The third generation has comparatively little backfolding. In figure 4.5(b) we see that there is little difference in the distribution of monomers when in gas phase. The dichloromethane penetrates through the interior of the dendrimer sharply reducing in concentration 7$\AA$ from the center.

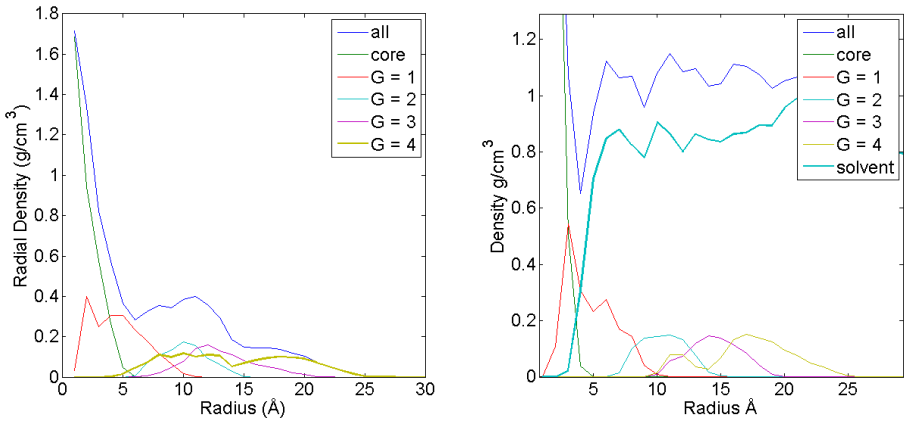
In 4.6(a) the first and second generation both are found in relatively high density near the center of the molecule. The third generation has comparatively little backfolding but it does overlap the second generation and even part of the first generation.

In 4.6(b) The distribution of the G3 atoms in PA3 are slightly affected by the presence of solvent which results in slight swelling of the dendrimer. The dichloromethane solvent penetrates through the interior of the dendrimer with a sharp decrease in concentration 5Åfrom the center.



(a) PA3 RDF (b) PA3 solvated RDF

Figure 4.6: PA3 unsolvated and solvated radial distribution function.

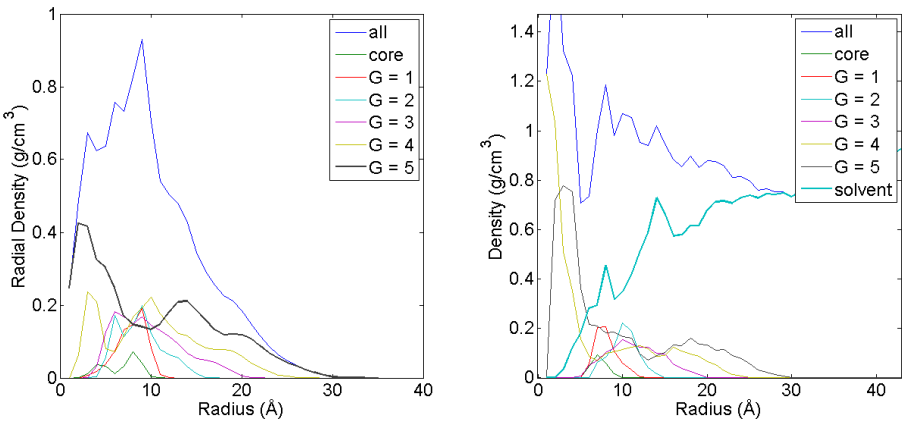


(a) PA4 RDF (b) PA4 solvated RDF

Figure 4.7: PA4 unsolvated and solvated radial distribution function.

In 4.7(a) the first and second generation both are found in relatively high density near the center of the molecule. The third generation has comparatively little backfolding but it does overlap the second generation and first generation. The fourth generation penetrates through to within 5Åof the center of the dendrimer with a nearly constant density of approximately $0.1 g/cm^3$.

In 4.7(b) There is no apparent swelling of the PA4 dendrimer the presence of solvent. The fourth generation is pushed further out of the dendrimer so that it only penetrates to within 10Åof the center.

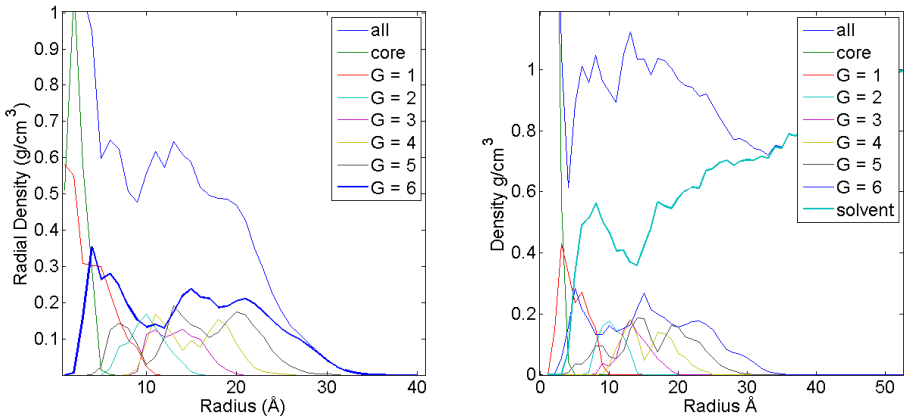


(a) PA5 RDF (b) PA5 solvated RDF

Figure 4.8: PA5 unsolvated and solvated radial distribution function.

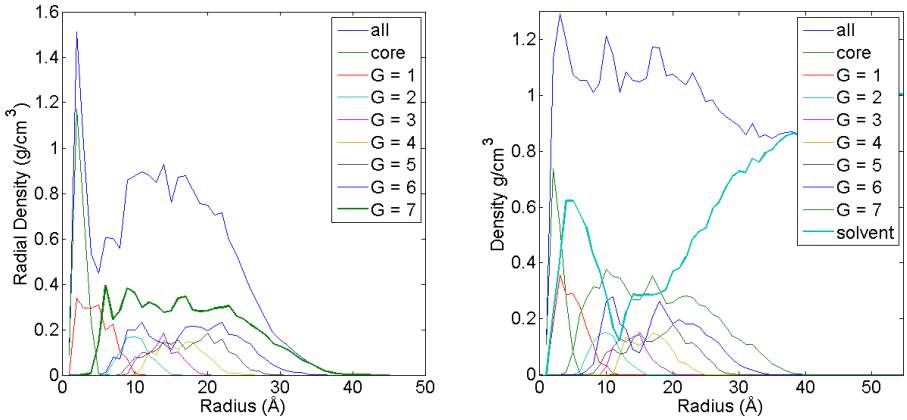
In 4.8(a) we also see a gradual increase in concentration with generation. Each of the generations tend to peak in concentration with approximately $0.2g/cm^2$. The last generation is peculiar in this case since it penetrates to nearly 1Åof the center. In the solvated case 4.8(b) we see nearly the same distribution of density with generation. The solvent penetrates near to the center of the molecule with a steady decline in concentration.

In 4.9(a) we see a gradual increase in concentration with generation. Each successive generation has slightly more concentration than the previous generation. The sixth generation has a bimodal distribution and penetrates deep into the interior of the dendrimer having a higher concentration than most other generations in most parts of the dendrimer. We see a similar pattern of distributions with generation in the solvated case with no apparent swelling of the dendrimer. The solvent penetrates deep into the interior of the dendrimer with a pronounced peak at 10Å. This peak suggests the presence of voids in the dendrimer that may be useful for containing a host molecule.



(a) PA6 RDF (b) PA6 solvated RDF

Figure 4.9: PA6 unsolvated and solvated radial distribution function.



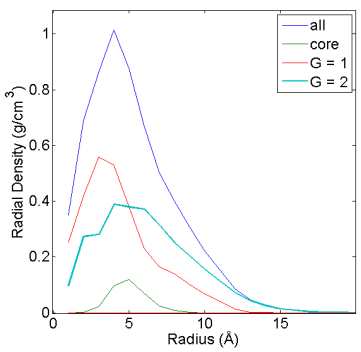
(a) PA7 RDF (b) PA7 solvated RDF

Figure 4.10: PA7 unsolvated and solvated radial distribution function.

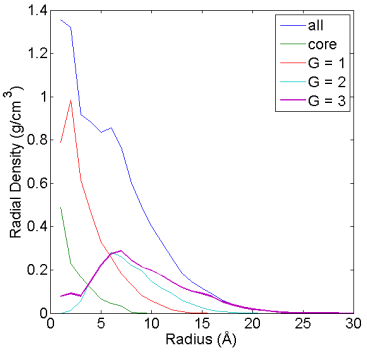
In 4.10(a) the concentration of atoms with each generation is noticeably flat for large intervals over the radius of the dendrimer. There is a slight increase of concentration with each generation with a large increase in concentration of the terminal end of the dendrimer. From 4.10(b) we observe a very similar pattern of density distribution with generation and a decreasing concentration of solvent down to about 10Åfrom the center.

At approximately 5$\mathring{A}$ there is a spike in solvent density suggesting a possible void where a host molecule could reside.

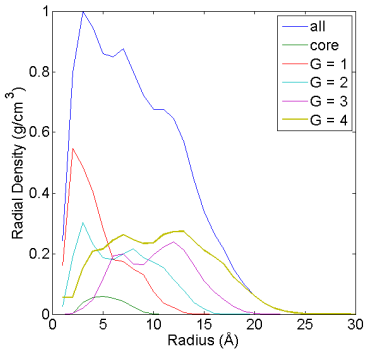
In 4.11(a) generation one and two have considerable overlap and penetrate near the center of the core. In 4.11(b) we see a similar pattern where the outer branches penetrate into the core and have considerable overlap with each other. At this stage in dendrimer growth we can see that the outer portions of the dendrimer tend to have higher concentrations of the outer arms. In 4.11(c) we can see that there is now a flattening out of the density distributions. All the generations have considerable overlap, but they also tend to have a more consistent distribution. In 4.11(d) it can be seen that all the generations tend to peak at the same concentration and still have significant backfolding with the terminal ends penetrating to within 5Åof the center.



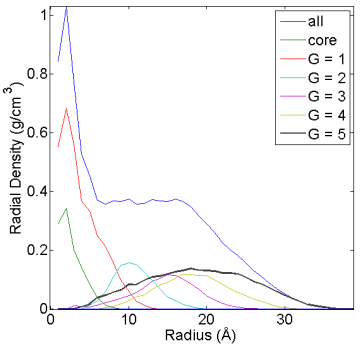
(a) PAMAM2 RDF



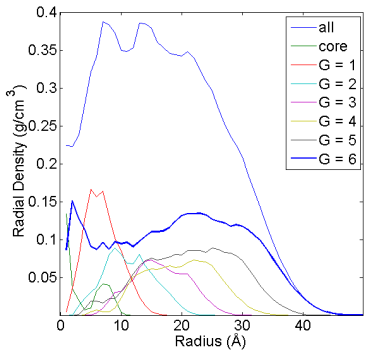
(b) PAMAM3 RDF



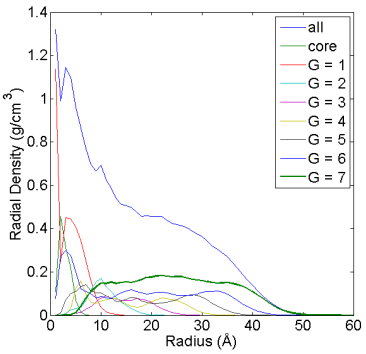
(c) PAMAM4 RDF



(d) PAMAM5 RDF



(e) PAMAM6 RDF



(f) PAMAM7 RDF

Chapter 5

Summary and Conclusion

Dendmol successfully creates initial conformations of PA dendrimers with no steric overlaps from generation 0-7 in less than 24-hours using a single core of an Intel® Xeon® 2.3GHz CPU. After 96-hours Dendmol is able to reduce the number of steric overlaps in PA8-10 to an extent where TINKER is capable of taking over.

(Here I should talk about PAMAM convergence)

One disadvantage to the rigid body technique is that molecules do not actually move this way because in physical systems atoms are permitted to move in all directions and bond lengths and bond angles are allowed to change. Although most realistic ensembles of molecules are represented with internal coordinates, it can be the case that a kinetic pathway is not easily reached in internal coordinates that may be accessible when using other coordinate systems. In molecules that are very flexible in their dihedral angles because the flexible nature of the dendrimer compensates for small local changes. However in the Phenyl-Acetylene dendrimers there are obvious differences in the structure when bond-lengths, and bond-angles are allowed to move about freely. Although they do not move a lot, a one-degree angle bend can have a significant global effect down the chain of the molecule.

Several obvious extensions to Dendmol can be made. The first is to create a file format that specifies the chemical structure of the dendrimer to be studied. This input file would specify the core molecule, branching units, and terminating units without specifying the dihedral angles. Once the file was read, Dendmol would proceed by modifying dihedral angles to untangle the structure.

Another improvement to Dendmol could be using a more intelligent criterion for choosing dihedral angles to rotate. An algorithm that was more likely to choose dihedral angles that directly impacted close pair atoms, would probably converge faster and may allow Dendmol to untangle larger dendrimers.

Appendices

Appendix A

Modifications to the MM3 Molecular Force Field

```
bond 50 4 15 1.2
angle 50 50 50 .4 120 120.5 0.0
angle 50 4 4 1.8 180 180.5 0.0
opbend 50 4 20.500
opbend 4 50 50 50 0.0
opbend 5 50 50 50 0.0

# Torsions for PA
torsion 50 50 50 4 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 50 50 4 4 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 4 50 50 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 50 4 4 50 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
opbend 3 8 0.0
opbend 5 8 0.0

# Torsions for PAMAM
torsion 1 1 8 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 1 1 8 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 1 3 8 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 1 1 3 8 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 1 3 8 1 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 3 8 1 1 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 3 8 1 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 5 1 9 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 5 9 1 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 5 1 8 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 5 1 3 8 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 7 3 8 1 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
torsion 7 3 8 5 0.0 0.0 1 0.0 180.0 2 0.0 0.0 3
opbend 1 8 1 1 0.0
opbend 8 3 1 7 0.0
opbend 7 3 1 8 0.0
opbend 1 3 7 8 0.0
opbend 1 8 3 5 0.0
opbend 1 8 5 5 0.0

angle          1    3    8      0.570     114.400       0.000       0.000
angle          7    3    8      1.070     124.800       0.000       0.000
angle          5    8    5      0.670     109.500     110.200     111.000
angle          3    8    5      0.670     109.500     110.200     111.000
angle          1    8    5      0.670     109.500     110.200     111.000
angle          1    8    3      1.620     121.100       0.000       0.000
bond           8    5           6.1000      1.6600
bond           8    3           6.1000      1.6600
```

Appendix A. Modifications to the MM3 Molecular Force Field

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