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Tecto-Dendrimers: A Study of Covalently Bound Nanospheres.

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ABSTRACT

We present a computational and theoretical study of the size, shape, and solution properties of tecto-dendrimers. This class of polymer, composed of a central dendrimer with multiple dendrimers attached at its periphery, holds promise for multi-drug delivery and environmental remediation applications. We find i) that the maximum number of tecto-units that may be attached to the central core varies logarithmically with the ratio of the sizes of the dendrimers, ii) that their density profiles display a minimum near the junction of the tecto-units with the core, iii) that a simple expression captures their radius of gyration, iv) that their intrinsic viscosity will display a maximum as a function of the number of tecto-units attached, and v) that their sphericity increases with increasing number of attached tecto-units. These results should bear upon both the synthesis and application of these materials.

Dendrimers, with their well-defined structure and large number of potential reactive sites, hold promise as molecular building elements. Synthetic chemists have employed clever schemes for producing a number of nano-structures derived from these basic units, including dendronized polymers¹, “dumbbell” configurations self-assembled with DNA links², and tecto-dendrimers^{3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13}. Tomalia and coworkers recently produced the latter by the synthetic coupling of peripheral dendrimers to a

central dendritic core. The potential for multi-drug delivery agents, Janus catalysts, and heavy metal remediation agents motivates efforts to produce this class of molecule. In particular, one can easily imagine combinations such as an anti-tumor/anti-capillary cocktail delivered in a single tecto-dendrimer, as was accomplished with the polymer/lipid “nanocell” devised by Sengupta¹⁴ and coworkers. The tecto-dendrimers, with their multiple modular components, should permit an expansion of this elegant idea.

However, several questions regarding their physics remain outstanding and potentially limit one’s ability to characterize, apply, and even synthesize them. In particular, we need to understand how their detailed topological structure affects their physical properties and sets them apart from other synthetic polymers. Tecto-dendrimers may be characterized not only by their overall mass, but (like their dendrimer predecessors) the generation of growth of the dendritic units and the number of peripheral dendrimers attached to the central core. Moreover, the peripheral, “tecto-units” need not be of the same generation of growth as the central dendrimer. Herein, we examine how these topological parameters dictate the number of peripheral units that can be attached, the mass distribution within the molecule, their size, their viscosity, and their sphericity.

We obtained our results from a combination of analytical and computational tools. Following our previous studies^{15, 16, 17, 18}, we applied Brownian dynamics¹⁹ to coarse-grained models of tecto-dendrimers in good solvents. The details of the simulation algorithm and model are found in reference 18; other than the topology, the model and algorithm are identical to that which we used previously in the study of dendronized polymers. We employed our freely available *Stochastic Genius*²⁰ simulation code. Figure 1 illustrates the specific topology we studied. Note that one bead at each junction

of tecto and central dendrimers was shared. We varied the generation of dendritic growth G for both the central and the tecto-units, as well as the number of attached peripheral dendrimers T . One thousand statistically independent samples were saved and analyzed from each simulation trajectory. The molecules were initially generated via a kinetic growth algorithm beginning from the central bead of the coarse-grained model. Specifically, each new bead in the molecule was placed in a random trial location one bond length away from its topological predecessor (working from the central bead of the central dendrimer outward). If the bead did not overlap any other in the molecule, the trial location was accepted. If an overlap occurred, a new position was tried. Up to 5000 new positions were tested for each bead. If an acceptable position could not be located after 5000 trials, the molecule was begun again from the first bead. Several thousand independent attempts to grow a new molecule were allowed for each. Upon the successful growth of a molecule, Brownian dynamics began. This growth algorithm is analogous to the divergent synthetic scheme, significant to the discussion below.

When considering these molecules one immediately encounters a fundamental question that bears directly upon the limitations to their synthesis; what is the maximum number T_{Max} of tecto-units that can be placed around the central dendrimer? Equivalently, how many spheres of a given radius R_T can be placed around a sphere of radius R_C ? This puzzle impacts not only the physics of tecto-dendrimers, but also a host of other subjects including tumor irradiation. Remarkably, this seemingly straightforward question remains open. Mansfield²¹ and coworkers addressed this subtle question within the context of tecto-dendrimers and found that an analytical form yielded itself in the limit where the central unit is much larger than the tecto-units. Specifically,

they found that $T_{Max} = \frac{2\pi}{\sqrt{3}} \left(\frac{R_C}{R_T} + 1 \right)^2$ with R_C the radius of the central dendrimer and R_T the radius of an individual tecto-unit. Uppuluri and coworkers found experimentally that this limit over estimates the actual number of tecto-units that can be synthetically attached via a convergent addition. Those authors discuss possible reasons for this disagreement. Here we take a more heuristic approach and arrive at an expression that covers a broader range of the size ratio than accessible to Mansfield's expression. First, we note that real synthetic dendrimers are not featureless spheres and possess a limited number T_0 of available reactive sites on which to add the tecto-units. As pointed out by Mansfield, we also know that Newton demonstrated that the maximum number of same-sized spheres that can pack around an identical sphere is 12. Thus, we direct our attention to the ratio T_{Max}/T_0 rather than simply T_{Max} and expect that in the limit that all dendrimers are of the same size, this ratio becomes $12/T_0$. Now, we expect that in the limit that the central dendrimer is larger than the tecto-units, this ratio is greater than $12/T_0$ and falls off rapidly as the ratio approaches unity. In the region where the tecto-units are larger than the central dendrimer, this ratio must be smaller than $12/T_0$ (indeed, it must ultimately reach $2/T_0$ in the utmost of this limit, but we neglect that extreme here). This suggests a simple logarithmic correction to Newton's result such that $\frac{T_{Max} - 12}{T_0} = \epsilon \ln[R_C/R_T]$. The coefficient ϵ captures the rate at which the T_{Max} sites are filled and varies with the size of the central unit.

Figure 2 illustrates the validity of our estimation of T_{Max} . The graph presents all of the values of T_{Max} that exceeded T_0 . Note that T_{Max} always exceeded T_0 for $G_C = 2$ and 3, as well as the pair $G_C = 4$ and $G_T = 2$. For the instances where our data set overlaps the

synthetic results of Uppuluri and company, our estimates for T_{Max} greatly exceed their experimental counterparts. Several possible reasons for exist, including those enumerated by Uppuluri in the context of Mansfield's result. However, we posit that the primary source of this discrepancy lies in the differences in how the molecules were grown in the simulation versus the synthetic scheme. The latter relied upon a convergent growth method, attaching fully formed tecto-units to a preexisting central dendritic core. As more tecto-units are added to the central dendrimer, this scheme undoubtedly results in slower addition kinetics as physical access to the reactive sites becomes hindered. Conversely, our simulations employed a divergent growth scheme analogous to that used in the synthesis of many dendrimers. The advantage of this approach is that at each stage of growth, space must be found for only one molecular segment, not an entire dendrimer. Thus, the kinetic limitations are mitigated and one should be able to reach the limiting values of T_{Max} in a reasonable time. We predict that this will be born out in future synthetic studies.

We examined the mass distribution within the tecto-dendrimers to facilitate future efforts to exploit them in guest-host applications. To do this, we partitioned space around the central core of the tecto-dendrimer into a set of concentric shells. The density as a function of distance r from this central core was estimated as the average number of molecular segments found in each shell multiplied by the bead volume V_b divided by the volume of each shell. Figure 3A contains the density profile for the central dendrimer segments, $\rho_C(r)$, with $G_C = 6$ and various numbers of attached tecto-units with $G_T = 5$. As found in nearly every computational study of dendritic molecules to-date, a radially decaying profile describes $\rho_C(r)$. We also note that, independent of the number or

generation of growth of the tecto-units added, the central dendrimer's density profile remains unaltered and the tecto-units do not appear to penetrate the central dendrimer. Indeed, examining the density profile of the entire molecule, $\rho(r)$, reveals a slight minimum in the total density profile at the junction of the central and tecto-units. This is illustrated in Figure 3B for a set of molecules with varying number of $G_T = 5$ tecto-units and $G_C = 6$. Note that the minimum becomes more pronounced as the number of tecto-units T increases. Though not shown, we also found that the terminal groups were distributed throughout the molecule in much the same manner as $\rho(r)$.

Thus informed about the mass distribution, we relate the squared radius of gyration $\langle R_g^2 \rangle$ of a tectodendrimer to the number of tecto-units T , the mass of the central unit N_c , and the mass of a single tecto-unit N_T by a simple argument. One may calculate $\langle R_g^2 \rangle$ by using the mass distribution ρ as $\langle R_g^2 \rangle = \frac{\int d\vec{R} (\vec{R} - \vec{R}_{com})^2 \rho(\vec{R})}{\int d\vec{R} \rho(\vec{R})}$.

Here, $\vec{R}_{com}$ is the center of mass of the molecule, which we assume is always located at the center of the central unit. Further assuming spherical symmetry reduces the 3-D

integral to $\langle R_g^2 \rangle = \frac{\int_0^\infty dr r^4 \rho(r)}{\int_0^\infty dr r^2 \rho(r)}$. Now, as discussed above, the tecto-units do not

appreciably penetrate the central unit. This allows us to further decompose the integrals into two regions by noting that $\rho(r) = \rho_c(r)$ for r less than the maximum extent of the central dendrimer, R_C . Similarly, we approximate $\rho(r) = T\rho_T(r)$ for r greater than R_C but less than the maximum extent of the entire molecule R_M . Thus, we find that we must evaluate four integrals:

$$\langle R_g^2 \rangle = \frac{\int_0^{R_C} dr r^4 \rho_C(r) + \int_{R_C}^{R_M} dr r^4 T \rho_T(r)}{\int_0^{R_C} dr r^2 \rho_C(r) + \int_{R_C}^{R_M} dr r^2 T \rho_T(r)} = \frac{V_b \langle R_g^2 \rangle_C N_C + \int_{R_C}^{R_M} dr r^4 T \rho_T(r)}{V_b N_C + V_b T N_T}. \quad \text{The first}$$

integral in the numerator is the un-normalized squared radius of gyration of the central dendrimer, $\langle R_g^2 \rangle_C$. The sum of the two integrals in the denominator is proportional to the total mass of the molecule. The bead volume V_b terms are needed to maintain consistency with our definition of ρ above.

The remaining integral is non-trivial to evaluate. However, we make progress by appealing to well-known scaling arguments. Most polymeric systems obey a simple relationship between their mass N and their size, $\langle R_g^2 \rangle = \alpha N^{2\nu}$. The proportionality constant α carries units of length squared. The scaling exponent ν captures both the connectivity of the polymer and its interactions. Our dendrimer model and many synthetic dendrimers display a value of ν of approximately $1/3$ at generations greater than 2, indicative of globular behavior. Thus, $R_M = \alpha^{1/2} [2N_T^{1/3} + N_C^{1/3}] / \gamma$, the sum of the absolute radius of the central unit and the diameter of a tecto-unit. The ratio γ of the radius of gyration to the absolute radius depends upon the mass distribution within a molecule. Next, we approximate $T \rho_T(r) \approx \frac{TN_T V_b}{4/3 \pi (R_T^3 - R_C^3)}$, note that for our dendrimer models $\gamma \approx 0.4$, and the integral becomes trivial to evaluate. We arrive at

$$\langle R_g^2 \rangle = \frac{\alpha [N_C^{5/3} + KT\beta]}{N_C + TN_T}. \text{ The constant } K = \frac{3}{20\pi\gamma^2} \approx 0.3 \text{ and}$$

$$\beta = N_T \frac{[2N_T^{1/3} + N_C^{1/3}]^5 - N_C^{5/3}}{[2N_T^{1/3} + N_C^{1/3}]^3 - N_C}, \text{ again taking advantage of the globular scaling.}$$

Figure 4 presents a plot of the simulation results for all model molecules spanning $G_C = 2 - 6$, $G_T = 2 - 5$, and $T = 3 - T_{\text{Max}}$. The results are presented with the root-mean square radius of gyration normalized by the numerator of our prediction, capturing the connectivity, varying as a function of the inverse mass. As expected, all of the data fall on essentially a single line (note that the plot is linear-linear) except for those points representing low values of T . This systematic deviation at low T values derives from the breakdown of our central assumption above; namely, that the center of the central dendrimer lies coincident with the center of mass.

Note that our prediction for $\langle R_g^2 \rangle$ indicates that the size of the molecule initially rises rapidly with increasing number of tecto-units T , but then reaches an asymptotic limit. Conversely, the total mass of the molecule continues to rise linearly with increasing T . This suggests that a curious trend should be observed when the intrinsic viscosity $[\eta]$ is plotted as a function of T . Typical linear polymers display a power-law increase in $[\eta]$ with increasing molecular weight. However, dendrimers (as opposed to tecto-dendrimers) exhibit a peak in $[\eta]$ as a function of their generation of growth G^{22} . Lescanec and Muthukumar²³ argued that this occurs because $[\eta]$ varies directly with the cubed radius of the molecule and inversely with its total mass. While the mass grows exponentially with G , the radius obeys an effective scaling rule that

changes when low generations of growth are considered. Similarly, we predict that $[\eta]$ for the tecto-dendrimers will also exhibit a maximum when plotted as a function of T. Again, $[\eta]$ will vary directly with the cubed radius of the molecule and inversely with the mass (this scaling law is easily obtained and underlies the familiar Mark-Houwink expression relating intrinsic viscosity to molecular weight). The radius will reach an asymptotic value as T is increased, but the mass will continue to grow (albeit linearly) with T. To test this, we employed the estimate $[\eta] \propto \frac{R_H^3}{M}$ where M is the total mass of the molecule and R_H approximates the hydrodynamic radius as the average of the inverse distance between each molecular segment. Figure 5 contains the simulation predictions for $[\eta]$ as a function of T for $G_C = 6$ and various values of G_T . The predicted peak occurs and becomes more pronounced with increasing values of G_T . To our knowledge, this prediction has not yet been challenged experimentally.

Many of the proposed applications of tecto-dendrimers require that they interact with biological membranes. Experimental studies by Mecke²⁴ and coworkers demonstrate that dendrimers create holes in lipid bilayers while tectodendrimers do not. Specifically, they considered PAMAM and a $G_C = 7$, $G_T = 5$, $T = 10$ -12 PAMAM-based tecto-dendrimer. They postulate that the lipids form a stable bilayer vesicle around the approximately spherical dendrimers, but cannot do so to surround the less spherical tecto-dendrimers. This leads to poor association between the tecto-dendrimers and the lipids. If this postulate is correct, sphericity may play a major role in determining the bioavailability of tecto-dendrimers. We find that the apparent sphericity of our model tecto-dendrimers depends upon the relative sizes of the central dendrimer and the tecto-units, but more strongly upon the number of tecto-units attached. Figure 6 illustrates a

few typical conformations for $G_C = 6$, $G_T = 5$ tecto-dendrimers with $T = 1, 5$, and 24 . As one would suspect, the apparent sphericity increases with increasing values of T . At lower values of T , in the range studied by Mecke, the molecules are rather asymmetric, supporting Mecke's conjecture. However, at higher values of T , they appear essentially spherical. This suggests that a given tecto-dendrimer's ability to pass a cell membrane may be controlled by the number of tecto-units attached.

In summary, our analytical and computational studies of tecto-dendrimers yield several predictions that should impact both their synthesis and application. Though variegated, we find that their dimensions and the limits to their synthesis succumb to relatively simple theoretical predictions embodied in the equations above. Our computational estimates for the maximum number of tecto-units that can be attached exceed that realized in convergent synthetic schemes, suggesting that a divergent scheme (doubtlessly more difficult to devise) may result in a greater number of linked tecto-units. They present a minimum in their density profile near the junction of the central- and tecto-units, a property that may play a role in future guest-host applications. We predict that the intrinsic viscosities of the materials will display an unusual peak with increasing numbers of tecto-units attached, a trait analogous to that observed in dendrimers. Finally, we note that the sphericity of the tecto-dendrimers depends upon the number of tecto-units attached. In light of the experimental work by Mecke and company, this suggests that their bioavailability may be tuned by varying the number of tecto-units present. We hope that these predictions stimulate and facilitate further investigations of these fascinating materials.

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Figure 1. The image on the left illustrates a typical snapshot from the simulations. The tecto-units are shown in red while the central units are in blue. The right contains a sketch of the topology studied. Here, $G_C = 5$, $G_T = 3$, and $T = 10$.

Figure 2. Simulation results for the maximum number of tecto-units attached T_{Max} plotted in accordance with our predicted dependence on the ratio of the central and tecto-unit radii, R_C and R_T , respectively. Data for $G_C = 4, 5$, and 6 shown. Only those points where T_{Max} was less than the total possible attachment sites T_0 are included.

Figure 3. A) The radial density profile of the central dendrimer unit. B) The radial density profile of the entire tecto-dendrimer. Data for $G_C = 6$ and $G_T = 5$ shown in both.

Figure 4. Simulation results for the square radius of gyration R_g^2 plotted in accordance with our predicted dependence on the mass of the central dendrimer N_C , the mass of the tecto-units N_T , and the number of tecto-units attached T . K is a constant discussed in the text and β is a coefficient depending upon the masses of the units (see text).

Figure 5. Estimated trends for the intrinsic viscosity $[\eta]$ from the simulations. Data from $G_C = 6$ shown.

Figure 6. Typical snapshots from the simulations. Data for $G_C = 6$ and $G_T = 5$ shown. From the top left, $T = 1, 5$, and 25 .

Fig. 7

Fig 2

Fig 3 A

Fig 3b

Fig 4

Fig. 5

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