

# Effect of Terminal Group Sterics and Dendron Packing on Chirality Transfer from the Central Core of a Dendrimer

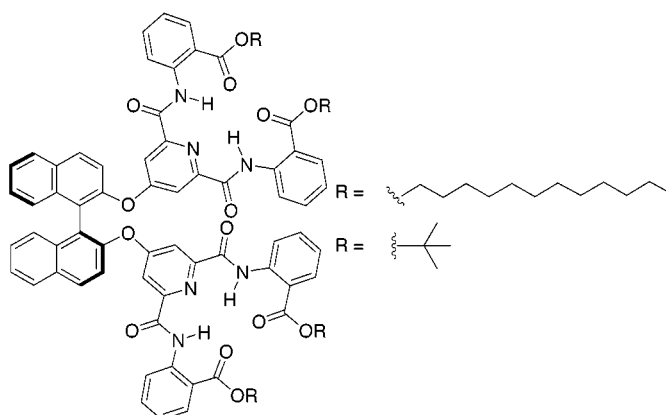
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## ABSTRACT



The conformational properties of intramolecularly hydrogen-bonded dendrimers constructed from (*S*)-1,1'-bi-2-naphthol as a chiral central core are described. Circular dichroism studies revealed that chirality transfer to the periphery occurs only when sterically demanding terminal esters are employed and when packing interactions are present.

The potentially globular morphology of dendrimers suggests that these structurally well-defined, three-dimensional macromolecules may be excellent synthetic mimics of proteins.<sup>1</sup> Therefore, there has been tremendous interest in characterizing and controlling the conformational equilibria of dendrimer systems.<sup>2</sup> An understanding of the structural factors that control the conformational behavior of dendrimers would facilitate the design of functional systems that capitalize on their supramolecular organization for function in potential applications. However, recent evidence indicates that the structures of most dendrimers are quite flexible wherein terminal groups “backfold” toward the interior of the structure.<sup>3</sup> Consistent with this highly dynamic conforma-

tional equilibria, the majority of chiral dendrimers that have been reported exhibit optical rotations or circular dichroisms that vary linearly with the number of repeating chiral chromophores, suggesting a lack of stable secondary structural order.<sup>4</sup> However, some peptide-based dendrimers have been reported to exhibit SEC behavior that suggested the presence of folded conformations.<sup>5</sup>

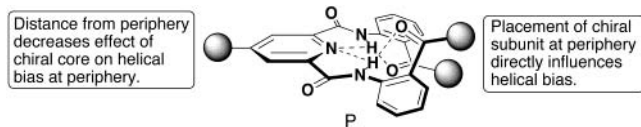
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(4) For some reviews of chiral dendrimers, see: (a) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125. (b) Peerlings, H. W. I.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1563. (c) Thomas, C. W.; Tor, Y. *Chirality* **1998**, *10*, 53.

The ability to transmit smaller amounts of chiral information over increasingly greater length scales will be critical in developing highly responsive macromolecular materials that function through their supramolecular conformations. We have recently reported that chiral, helical secondary structure can be induced in dendrimers rigidified through intramolecular hydrogen-bonding interactions.<sup>6</sup> Chiral, non-racemic subunits incorporated at the periphery bias the helical secondary structure toward an M-type chirality as a result of intramolecular packing interactions that produce cooperativity in the conformational equilibria of the peripheral subunits.<sup>7</sup> However, controlling the helical bias at the periphery of a dendrimer using a chiral subunit placed at the central core requires transmission of chiral information over a longer distance to more achiral groups than placement at the periphery requires (Figure 1). Therefore, biasing the



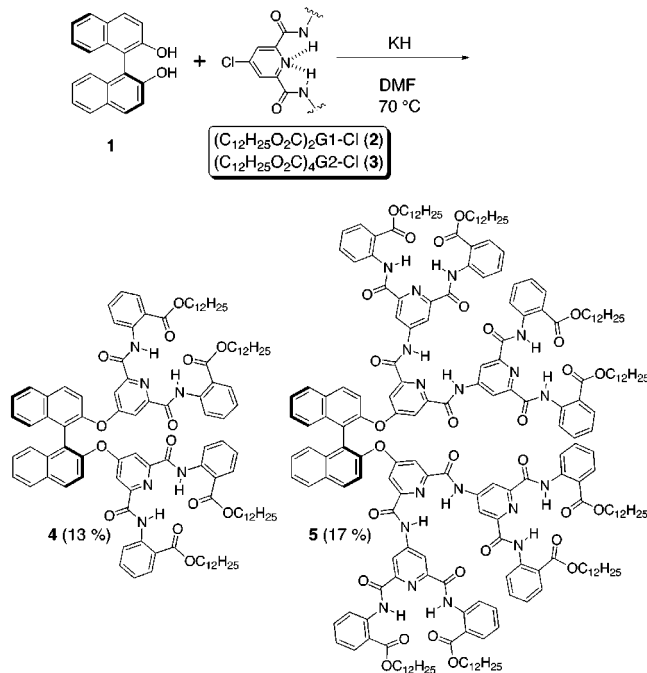
**Figure 1.** Placement of chiral, nonracemic subunit at central core or termini to bias dendron conformation.

conformation of a dendrimer with a single, chiral central core is significantly more difficult than with several chiral peripheral groups. Accordingly, dendrimers constructed from chiral, nonracemic central cores have not exhibited chirally biased conformational equilibria in the branch segments or at the periphery.<sup>8</sup> In this communication, we show that both intramolecular packing interactions and increased steric demands of the termini are required to bias the helical conformation of a dendrimer elaborated from (*S*)-1,1'-bi-2-naphthol as a central core.

Dendrimer construction proceeded by base-mediated O-arylation of dendrons having a chloro function at the focal point. Accordingly, the first generation dendrimer (**4**) was prepared by treating (*S*)-1,1'-bi-2-naphthol (**1**) with 2 equiv

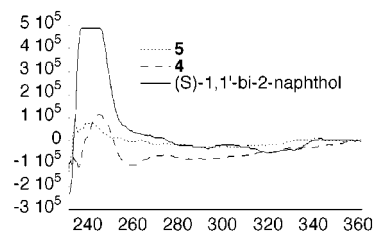
of ( $C_{12}H_{25}O_2C$ )<sub>2</sub>[G1]-Cl (**2**)<sup>6c</sup> in the presence of KH in DMF at 70 °C (Scheme 1).<sup>9</sup> Second generation dendrimer (**5**) was

**Scheme 1.** Synthesis of Dendrimers with (*S*)-1,1'-bi-2-naphthol Central Core and Dodecyl Ester Termini



prepared in a similar fashion using ( $C_{12}H_{25}O_2C$ )<sub>4</sub>[G2]-Cl (**3**). Although the overall conversion to bis-arylated dendrimer was relatively low, displacement of the chloride was carried out at  $\leq 80$  °C to avoid racemization of (*S*)-1,1'-bi-2-naphthol (**1**).<sup>10</sup>

Circular dichroic spectra (molar ellipticity) for (*S*)-1,1'-bi-2-naphthol (**1**) and the first (**4**) and second (**5**) generation dendrimers are shown in Figure 2. The peak at approximately



**Figure 2.** CD spectra of (**1**) and first (**4**) and second (**5**) generation dendrimers with dodecyl termini.

240 nm is the long wavelength portion of an exciton couplet centered at 220 nm (<sup>1</sup>B transition) due to excitonic coupling of a transition polarized along the long axis of each binaphthyl ring consistent with the *S* axial-type stereochemistry of the 1,1'-binaphthyl central core.<sup>11</sup> The intensity of this couplet has been shown to decrease as the dihedral angle between these electric transition moments expands.<sup>8j,11</sup>

(5) (a) Kim, Y.; Zeng, F.; Zimmerman, S. C. *Chem. Eur. J.* **1999**, *5*, 2133. (b) Brouwer, A. J.; Mulders, S. J. E.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2001**, *10*, 1903.

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(7) For examples of cooperativity in helical polymers, see: (a) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, *268*, 1860. (b) Langeveld-Voss, B. M. W.; Waterval, R. J. M.; Janssen, R. A. J.; Meijer, E. W. *Macromolecules* **1999**, *32*, 227. (c) Palmans, A. R. A.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2648.

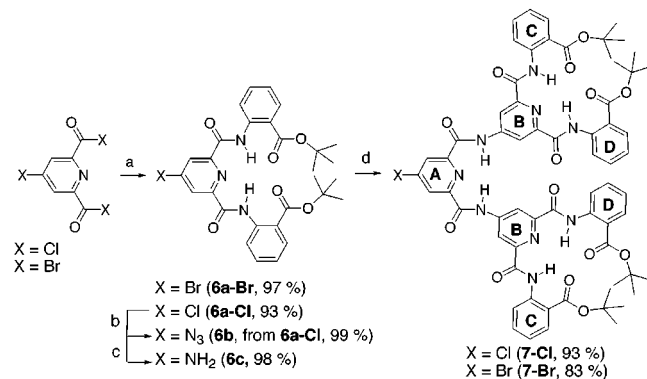
(8) (a) Seebach, D.; Lapierre, J. M.; Skobridis, K.; Greiveldinger, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 440. (b) Seebach, D.; Lapierre, J. M.; Greiveldinger, G.; Skobridis, K. *Helv. Chim. Acta* **1994**, *77*, 1673. (c) Chaumette, J.-L.; Laufersweiler, M. J.; Parquette, J. R. *J. Org. Chem.* **1998**, *63*, 9399. (d) Rohde, J. M.; Parquette, J. R. *Tetrahedron Lett.* **1998**, *39*, 9161. (e) Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **1998**, *573*, 3. (f) Chen, Y.-M.; Chen, C.-F.; Xi, F. *Chirality* **1998**, *10*, 661. (g) Dubber, M.; Lindhorst, T. K. *Chem. Commun.* **1998**, 1265. (h) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528. (i) Lellek, V.; Stibor, I. *J. Mater. Chem.* **2000**, *10*, 1061. (j) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, *61*. (k) Gong, L.-Z.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 2358.

Consequently, the decrease in intensity of the couplet going from **1** to **5** is due to an increasing steric effect imparted by the dendrons on the binaphthyl core that increases this dihedral angle. The terminal anthranilate chromophores exhibit a  $\pi \rightarrow \pi^*$  transition in the UV spectrum at 316 nm that is polarized along the axis containing C3 and C6 of the anthranilate ring (see TDDFT electronic structure calculations, Supporting Information).<sup>12</sup> The lack of any Cotton effects (CE) in the region of 316 nm indicates that the binaphthyl core was not creating a chirally biased helical conformation at the periphery in **4** or **5**.

We reasoned that increasing the steric demands of the terminal esters would induce a more rigidly helical conformation relating the terminal anthranilate groups. This structural modification should enhance the helical conformation in a manner that would more effectively express the chirality of the central core. An X-ray structure of second generation dendron,  $(\text{CH}_3\text{O}_2\text{C})_4[\text{G2}]\text{-Cl}$ , displaying methyl anthranilate groups at the periphery supported this hypothesis.<sup>6c</sup> In the solid state, this dendron displayed a “flattened” nonhelical orientation of adjacent methyl anthranilate terminal groups that was, in part, due to the insufficient steric requirements of the methyl ester groups.

Therefore, to increase the degree of helicity, *tert*-butyl esters were incorporated at the periphery following a synthetic sequence analogous to that reported for the dodecyl ester terminated dendrons (Scheme 2).<sup>6c</sup> To increase the focal

#### Scheme 2. Synthesis of *tert*-butyl Ester Terminated Dendrons<sup>a</sup>



<sup>a</sup> Key: (a) *tert*-butyl anthranilate, pyr- $\text{CH}_2\text{Cl}_2$ , DMAP; (b)  $\text{NaN}_3$ , DMF, 50 °C; (c)  $\text{H}_2/\text{Pd}-\text{C}$  EtOAc/MeOH; (d) 4-halopyridine-2,6-dicarbonyl halide ( $\text{X} = \text{Cl}, \text{Br}$ ), pyr- $\text{CH}_2\text{Cl}_2$ .

point electrophilicity, dendron monobromides were prepared in addition to the corresponding chlorides by employing 4-bromopyridine-2,6-dicarbonyl bromide<sup>13</sup> in each generational growth step.

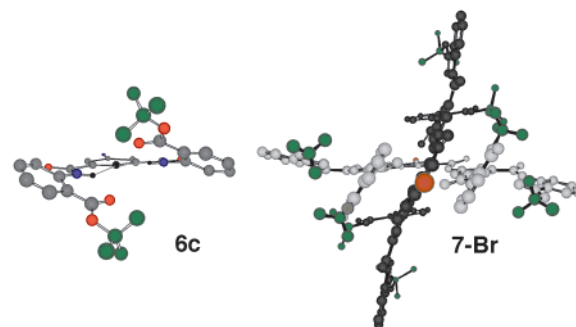
X-ray crystal structures of first (**6c**) and second (**7-Br**) generation dendrons provided preliminary confirmation that

(9) Exposure of (*S*)-1,1'-bi-2-naphthol (**1**) to these reaction conditions did not cause significant racemization.

(10) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.

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the *tert*-butyl esters induced a more rigidly helical conformation in the dendrons (Figure 3). A clear, orthorhombic crystal



**Figure 3.** X-ray structures of  $(t\text{-C}_4\text{H}_9\text{O}_2\text{C})_2[\text{G1}]\text{-NH}_2$  (**6c**) and  $(t\text{-C}_4\text{H}_9\text{O}_2\text{C})_4[\text{G2}]\text{-Br}$  (**7-Br**). Each dendron of the interdigitated dimer in the asymmetric unit for **7-Br** is designated by dark and light shading.

with a *Pnn2* space group was obtained for first generation dendron **6c** by crystallization from  $\text{CH}_2\text{Cl}_2$ .<sup>14</sup> In contrast to the flattened conformation of  $(\text{CH}_3\text{O}_2\text{C})_4[\text{G2}]\text{-Cl}$  in the solid state,<sup>6c</sup> **6c** displayed a helical conformation relating the two *tert*-butyl anthranilate terminal groups.

Second generation dendron **7-Br** similarly crystallized from  $\text{CH}_2\text{Cl}_2$ , affording a clear, monoclinic crystal with a *C2/c* space group.<sup>15</sup> Similar to  $(\text{CH}_3\text{O}_2\text{C})_4[\text{G2}]\text{-Cl}$ , X-ray diffraction showed that the asymmetric unit was a dimer composed of two virtually identical, interdigitated monodendrons with four associated molecules of  $\text{CH}_2\text{Cl}_2$ . The dimeric structure is stabilized by face-to-face  $\pi$  stacking interactions that sandwich the focal A ring of one dendron between the adjacent terminal D rings of the other dendron. The stacked arrangements display closest edge-to-edge distances that vary from 3.33 to 3.68 Å. Whereas the analogous dendron with methyl ester termini could assume a conformation that permitted all seven rings to pair in stacked arrangements, the *tert*-butyl esters create a more helical arrangement of the anthranilate rings that sterically precludes distortion of the T-shaped conformation to permit further stacking interactions.

Dendrimer synthesis proceeded by O-arylation of (*S*)-1,1'-bi-2-naphthol (**1**) with **6a-Cl** in the presence of  $\text{Cs}_2\text{CO}_3$  at 80 °C; however, only **mono-8** was obtained in 63% yield as a result of the low reactivity of the focal chloride (Scheme 3). In contrast, employing the more reactive **6a-Br** under the same conditions afforded **bis-8** in 56% yield. Unfortun-

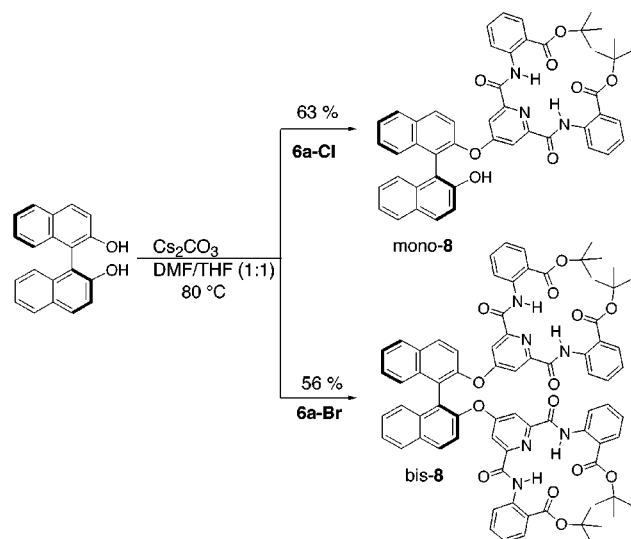
(12) The direction of the electric transition moment was calculated for methyl 2-acetamidobenzoate using TDDFT theory and the B3LYP functional (see Supporting Information).

(13) Prepared in 66% yield by treating chelidamic acid with  $\text{PBr}_5$  and purified by distillation (see Supporting Information).

(14) General crystallographic information:  $T = 203$  K; *Pnn2*,  $a = 22.4784$  Å (5),  $b = 11.5942$  Å (2),  $c = 12.1470$  Å (3);  $\beta = 90.135^\circ$  (1);  $V = 10714.3$  (3) Å<sup>3</sup>;  $Z = 8$ ; 18847 unique data;  $R_w = 0.063$ ; GOF = 1.060.

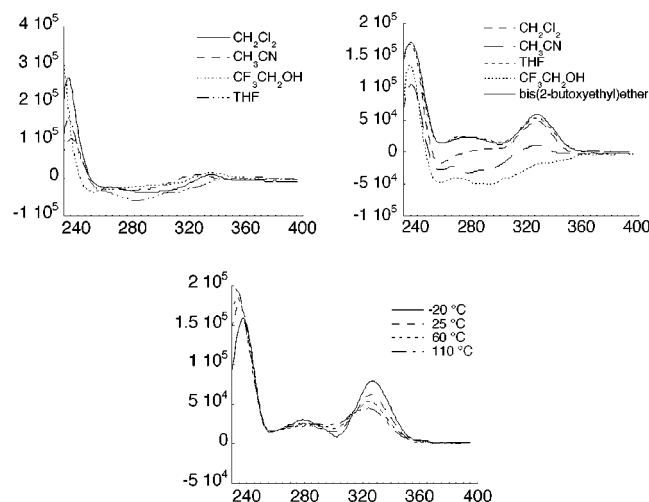
(15) General crystallographic information:  $T = 150$  K; *C2/c*,  $a = 20.3270$  Å (1),  $b = 30.0453$  Å (2),  $c = 25.0005$  Å (2);  $\beta = 94.3803$  (3);  $V = 15224$  (2) Å<sup>3</sup>;  $Z = 8$ ; 13431 unique data;  $R_w = 0.0775$ ; GOF = 1.033.

**Scheme 3.** Synthesis of *tert*-Butyl Ester Terminated Dendrimers



nately, we have been unable to prepare the second generation dendrimer using **7-Cl** or **7-Br**, presumably for steric reasons.<sup>16</sup>

Circular dichroism studies were carried out to determine whether this modification of the terminal groups would sufficiently rigidify the helical conformation to permit the chiral core to bias the helical equilibrium (Figure 4). The



**Figure 4.** CD spectra **mono-8** (top-left) and **bis-8** (top-right) as a function of solvent at 25 °C and temperature dependence of **bis-8** in bis(2-butoxyethyl)ether (bottom).

lack of any significant Cotton effects in the region of 316 nm of **mono-8** indicated that the peripheral helicity was unbiased by the core. The CD spectra were also not affected by changes in solvent or temperature. However, the spectra of **bis-8** displayed an intense CE at 327 nm in several different solvents at 25 °C. This CE corresponds to the long

wavelength portion of a positive excitonic couplet centered at 316 nm arising from a  $\pi \rightarrow \pi^*$  transition at 316 nm polarized along the anthranilate axis containing C3 and C6. The longer wavelength branch of the couplet is more intense than the shorter wavelength branch as a result of mixing of the couplet transition with other transitions, suggesting a highly congested environment.<sup>17</sup> On the basis of the direction of the electric transition moment associated with this transition and the positive chirality of the couplet, the absolute sense of helical chirality between each pair of anthranilate chromophores can be assigned as P-type helicity (see Supporting Information) (Figure 1). The intensity of the couplet was relatively insensitive to solvent choice with the exception of trifluoroethanol and acetonitrile, in which the couplet intensity was significantly reduced.<sup>18</sup> The helical bias was present up to 110 °C in bis(2-butoxyethyl)ether, indicating that this conformational preference was quite thermally stable.

It is noteworthy that although the **mono-8** failed to express the chirality of the central core at the periphery of the molecule, **bis-8** expressed a stable P-type helical preference identical to that of (S)-1,1'-bi-2-naphthol, which can also be considered as a P-type helix.<sup>19</sup> In dendrons constructed with chiral terminal groups, we have previously observed that the helical bias became more stable with increasing dendrimer generation.<sup>6</sup> This observation could be explained by the presence of intraterminal group packing interactions that induce correlated conformational equilibria of the peripheral subunits, causing small energetic differences between conformational states to be magnified.<sup>7</sup> The difference in conformational behavior of **mono-8** and **bis-8** is consistent with this interpretation, since intradendron packing-type interactions would be present in **bis-8** but not in **mono-8**.

Consequently, we can conclude that the increased steric requirements of the terminal groups in conjunction with dendron packing interactions are crucial for effective transfer of core chirality to the helical conformation of the dendrimer. Current efforts are directed at biasing the secondary structure of larger dendrimers using chiral central cores with a long-term goal of controlling conformational equilibria on increasingly greater length scales.

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**Supporting Information Available:** Experimental procedures and analytical data for **2–8**, output for the TDDFT-B3LYP calculations, ORTEP diagrams in stereo of **6c** and **7-Br**, and tables of X-ray structural data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) The source of the lower apparent reactivity of the *tert*-butyl ester dendrons relative to the dodecyl analogues is unknown.

(17) For a discussion, see: Gottarelli, G.; Mason, S. F.; Torre, G. *J. Chem. Soc. B* **1970**, 1349.

(18) Although the denaturing effect of these solvents cannot be fully rationalized, a solvent-induced disruption of the hydrogen-bonding interactions present in the dendrons is likely to be responsible.

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