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Effect of Guest Molecule Flexibility in Access to Dendritic Interiors

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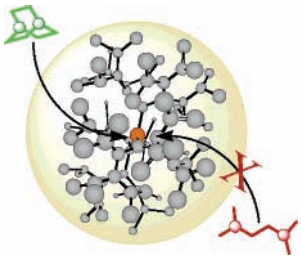
ABSTRACT



Dendrimers are attractive scaffolds for catalysis, since catalytic sites can be isolated and the catalysts are recoverable and reusable. Herein, we show that conformationally constrained molecules have better access to dendritic cores compared to the more flexible counterparts. The results reported here should have implications in utilizing dendrimers as scaffolds for artificial selectivity in catalysis.

Encapsulation of catalytically active functionalities using dendrimers has attracted much attention in recent years.[1] While the properties of an encapsulated electroactive species could be elucidated from studying electron-transfer kinetics and thermodynamics,[2] catalytic activity is dependent on the bimolecular collision efficiency between the encapsulated species and the substrate. One could reasonably expect that at higher generations, when the species at the cores of dendrimers is encapsulated, the dendritic backbones could act as gatekeepers for substrate access to the catalytic centers. In fact, this is one of the ways that enzymes maintain high substrate specificity in nature. While there have been reports on selectivity in access to dendritic interiors,[3] a systematic investigation on structural factors in substrates that govern their access to dendritic cores has been lacking. Conventional wisdom about dendrimers would suggest that the access would mainly depend on the size of the guest molecules. However, here we report that conformational flexibility of the guest molecules plays a significant role in accessibility to the cores of dendrimers.

We used distance-dependent excited-state quenching through photoinduced electron transfer as the probe for this study.[4] For this purpose, we synthesized benzyl ether dendrons **1**−**4** and dendrimers **5**−**8** up to the fourth generation with anthracene as the fluorescent unit at the focal point and core, respectively (Figure 1).[5] Benzyl ether dendrons were as-

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(1) (a) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (b) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828. (c) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181. (d) Brunner, H. *J. Organomet. Chem.* **1995**, *500*, 39. (e) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710. (f) Enomoto, M.; Aida, T. *J. Am. Chem. Soc.* **2002**, *124*, 6099.

(2) (a) Dandliker, P. J.; Diederich, F.; Gisselbrecht, J. P.; Louati, A.; Gross, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2725. (b) Cardona, C. M.; Mendoza, S.; Kaifer, A. E. *Chem. Soc. Rev.* **2000**, *29*, 37. (c) Gorman, C. B.; Smith, J. C. *Acc. Chem. Res.* **2001**, *34*, 60. (d) Gorman, C. B. *C. R. Chimie* **2003**, *6*, 911. (e) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74. (f) Stone, D. L.; Smith, D. K.; McGrail, P. T. *J. Am. Chem. Soc.* **2002**, *124*, 856 and references therein.

(3) For examples, see: (a) Diederich, F.; Felber, B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *59*, 4778. (b) Niu, Y.; Yeung, L. K.; Crooks, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 6840. (c) Bhyrappa, P.; Young, J. K.; Moore, J. S.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5708. (d) Kimura, M.; Shiba, T.; Yamazaki, M.; Hanabusa, K.; Shirai, H.; Kobayashi, N. *J. Am. Chem. Soc.* **2001**, *123*, 5636. (e) Mak, C. C.; Chow, H. F. *Macromolecules* **1997**, *30*, 1228.

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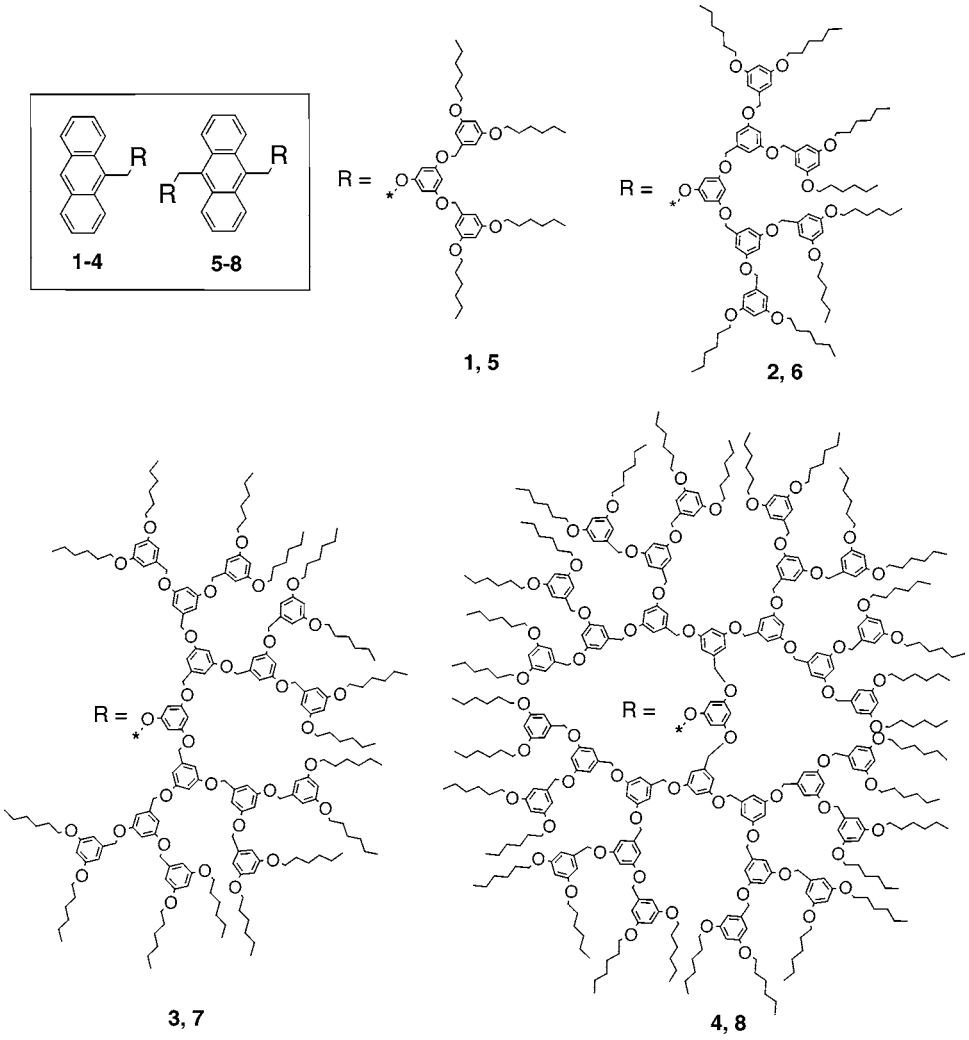
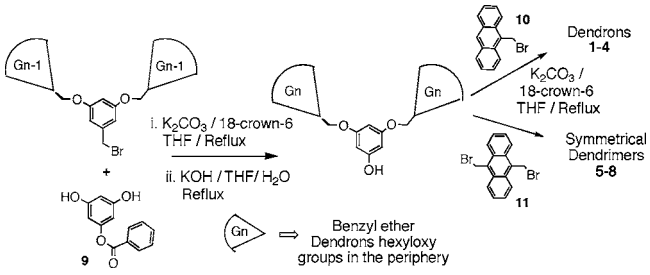


Figure 1. Structures of anthracene-cored dendrons and dendrimers.

sembled using methods previously reported in the literature.[6] The reactive functionality at the focal point of the benzyl ether dendrons involves a bromomethyl moiety. We attempted the synthesis of 9,10-dihydroxyanthracene to incorporate it as the core. However, the poor stability of this chromophore hampered the isolation of the compounds in their pure form. Therefore, we converted the functional group at the focal point of the dendrons from a bromomethyl moiety to a phenolic moiety by treatment with a monoprotected phloroglucinol **9**, as shown in Scheme 1. Deprotection of the benzoyl moiety followed by treatment with 9-bromomethylanthracene (**10**) or 9,10-bis(bromomethyl)anthracene (**11**) afforded the dendrons **1**−**4** or dendrimers **5**−**8**, respectively.

Scheme 1. Synthesis of the Anthracene-Cored Dendrimers



(4) For Stern−Volmer quenching with dendrimers, see: (a) Devadoss, C.; Bharathi, P.; Moore, J. S. *Macromolecules* **1998**, *31*, 8091. (b) Kleinman, M. H.; Flory, J. H.; Tomalia, D. A.; Turro, N. J. *J. Phys. Chem. B* **2000**, *104*, 11472. (c) Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J.; Maskus, M.; Abruña, H. D. *Chem. Mater.* **1998**, *10*, 30. (d) Pandey, S. Redden, R. A.; Fletcher, K. A.; Sasaki, D. Y.; Kaifer, A. E.; Baker, G. A. *Chem. Commun.* **2004**, 1318. (e) Vögtle, F.; Plevoets, M.; Nieger, M.; Azzellini, G. C.; Credi, A.; de Cola, L.; de Marchis, V.; Venturi, M.; Balzani, V. *J. Am. Chem. Soc.* **1999**, *121*, 6290. (f) Kuneida, R.; Fujitsuka, M.; Ito, O.; Ito, M.; Murata, Y.; Komatsu, K. *J. Phys. Chem. B* **2002**, *106*, 7193. (g) Plevoets, M.; Vögtle, F.; de Cola, L.; Balzani, V. *New J. Chem.* **1999**, *23*, 63. (h) Rio, Y.; Accorsi, G.; Nierengarten, H.; Bourgogne, C.; Strub, J.-M.; Dorsselaer, A. V.; Armaroli, N.; Nierengarten, J.-F. *Tetrahedron* **2003**, *59*, 3833. (i) Murata, Y.; Ito, M.; Komatsu, K. *J. Mater. Chem.* **2002**, *12*, 2009. (j) Matos, M. S.; Hofkens, J.; Verheijen, W.; De Schryver, F. C.; Hecht, S.; Pollak, K. W.; Fréchet, B.; Dehaen, W. *Macromolecules* **2000**, *33*, 2967.

(5) See Supporting Information for details.

(6) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

Dendritic effects on access to differently sized substrates were then assessed by measuring the Stern−Volmer efficiency of various molecules to quench the excited state of anthracene chromophore. Trialkylamines of different sizes and shapes were used as molecules that could quench the fluorescence of anthracene through a photoinduced electron-transfer process. The excited-state quenchers used in this study are triethylamine (Et_3N), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethyltris(2-aminoethyl) amine (TREN-Me_6), diazabicyclooctane (DABCO), and *N*,*N*-dimethylaminoadmanatane (ADM-NMe_2).

Addition of the alkylamine quenchers to compounds **1**−**8** resulted in a decrease in emission intensity. Fluorescence intensity decreases upon addition of increasing amounts of an alkylamine quencher, as exemplified in Figure 2. Redox

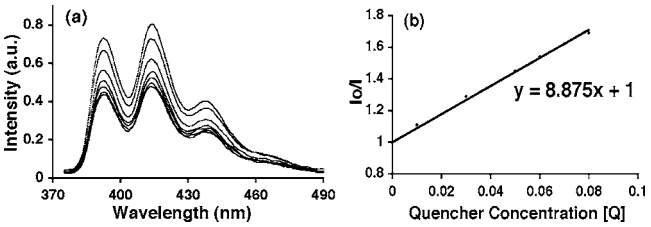


Figure 2. (a) Fluorescence spectra of **3** with various concentrations of the quencher TREN−Me_6 in THF/acetonitrile (1:1). (b) Stern−Volmer plot of the fluorescence spectra shown in panel a.

potentials, excited-state energies, and substituents suggest that this quenching is due to an intermolecular photoinduced electron-transfer process and that alternate energy transfer and heavy-atom-based processes are not viable. To ensure that the observed quenching is a dynamic process, Stern−Volmer constants were obtained from steady-state and time-resolved spectroscopy experiments. We carried out these experiments side-by-side for compound **8** with TMEDA as the quencher. In both combinations, the Stern−Volmer constants obtained from the time-resolved and steady-state experiments agreed to within 15%, confirming that the observed fluorescence quenching is a dynamic process (example shown in Figure 3).

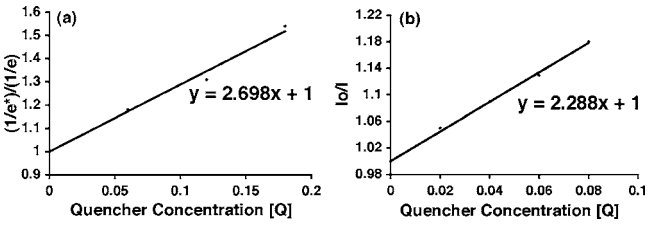


Figure 3. Stern−Volmer plots from (a) time-resolved and (b) steady-state spectroscopic measurements for compound **8** with quencher TMEDA.

The fluorescence intensity in the absence (I_0) and presence (I) of a quencher can be related to its concentration ([Q]) using the Stern−Volmer equation: $I_0/I = 1 + K_{SV}$ [Q]. A plot of I/I_0 vs [Q] affords K_{SV}, which is related to the bimolecular quenching rate constant k_q ($K_{SV} = k_q\tau_0$, where τ_0 is the fluorescence lifetime of dendrimer in the absence of quencher). The values of k_q for various dendrimer−quencher combinations are shown in Table 1.[7] Note that the

Table 1. Bimolecular Quenching Constants of **1**−**8** with Various Alkylamines

	Et_3N (122 Å^3)[a] $k_q \times 10^9$ M^{-1} s^{-1}	TMEDA (133 Å^3)[a] $k_q \times 10^9$ M^{-1} s^{-1}	TREN−Me_6 (263 Å^3)[a] $k_q \times 10^9$ M^{-1} s^{-1}	DABCO (111 Å^3)[a] $k_q \times 10^9$ M^{-1} s^{-1}	ADM−NMe_2 (193 Å^3)[a] $k_q \times 10^9$ M^{-1} s^{-1}
1	4.3	4.8	6.5	15.6	9.1
2	5.0	5.0	6.1	15.2	6.7
3	4.8	5.0	6.7	11.7	6.5
4	4.4	4.4	6.2	14.1	7.8
5	3.5	7.4	8.0	21.9	5.2
6	3.2	3.0	4.5	11.6	6.0
7	2.9	2.3	5.3	10.8	5.8
8	2.0	1.7	2.2	11.3	4.9

[a] Volume was calculated after geometry optimization using MM2.

magnitudes of k_q values themselves are quite different from one quencher to another. This is of little concern to the dendritic effect, since this magnitude is related to the inherent redox potential of the trialkylamine.[8] This is clearly seen from the k_q value difference for compound **1** with different amine quenchers. The dendritic effect, on the other hand, involves relative magnitudes upon increasing generation of the dendrimer host.

Monodendrons **1**−**4** exhibited essentially no difference in quenching efficiency with increase in generation. This observation is in sharp contrast to the results observed with the symmetrical dendrimers **5**−**8**, where significant differences in quenching efficiency were observed with generation. This observation seems to be consistent with previous reports, where the unsymmetrical monodendrons retain an open structure.[2f,9] Also note that most of the quenchers had a decrease in k_q between the first- and second-generation dendrimers **5** and **6**, respectively. At early generations, however, it is too early to label such a decrease as a real dendritic effect.[10] Therefore, we attributed this to simple steric differences.

Interesting differences were observed when the quenching studies were carried out with the symmetrical didendrons **5**−**8**. For example, when triethylamine was used as the fluorescence quencher, the k_q value for the dendrimer **8** was 2.0 compared to the value of 2.9 for dendrimer **7**. This change

(7) Experimental error in these measurements is about 5%.

(8) For example, the redox potential of Et_3N is 0.96 mV, relative to SCE, whereas that of DABCO is 0.57 mV. See: Kavarnos, G.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401.

(9) Cardona, C. M.; Kaifer, A. E. *J. Am. Chem. Soc.* **1998**, *120*, 4023.

(10) Dendrimers are thought to undergo a change from an extended structure to a globular structure between the third and fourth generations. For example, see: Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375.

in value represents a quenching efficiency decrease of about 31%, which is attributed to the dendritic effect. When TMEDA was used, the change was about 26%. Therefore, the quenching efficiency change upon going from the third-generation dendrimer **7** to the fourth-generation dendrimer **8** is similar within experimental error for both Et_3N and TMEDA. When TREN−Me_6 was the quencher, the difference in quenching efficiency between **7** and **8** was about 59%. This trend is attributed to the bigger size of TREN−Me_6 compared to both Et_3N and TMEDA. Since Et_3N and TMEDA are similar in volume, the quenching efficiencies are about the same.

The most surprising results were obtained when DABCO was used as the quencher. There was essentially no difference in quenching efficiency between dendrimers **6**−**8** with DABCO as the quencher.[11] This is intriguing, because DABCO is different by only four hydrogen atoms from TMEDA. One could look at DABCO as the conformationally constrained version of TMEDA.[12] Since it is constrained, the volume occupied by DABCO is also smaller than TMEDA. Therefore, the lack of difference in k_q between **7** and **8** with DABCO could be attributed to the smaller size of DABCO. We could not, however, rule out whether conformational restriction does play a role. To analyze the possibilities, we looked for a trialkylamine that is bigger in size but conformationally more restricted than TMEDA. *N*,*N*-Dimethylaminoadamantane (ADM−NMe_2) is one of the few molecules that is synthetically easily accessible and satisfies the above requirements. ADM−NMe_2 occupies a volume of 192.9 $Å^3$, compared to the volume of 133.1 $Å^3$ for TMEDA.

The difference in quenching efficiency for dendrimers **7** and **8** with ADM−NMe_2 is only 15%, compared to the difference of 26% observed with TMEDA. This result, combined with the differences between TMEDA and DABCO, clearly suggests that conformational freedom of guest molecules plays a more crucial role in accessing the interiors of the dendrimers (Figure 4).

In summary, we have studied the access of various molecules to the cores of dendrimers using fluorescence quenching as a probe. We observed that conformationally restricted molecules could access the dendritic core much better than flexible ones. This could be due to the difference in conformational entropy of the amines while passing through the channels formed by the dendrimer backbone.[13] From an applications standpoint, the results could have implications in catalysis. The demonstration that conformational freedom of molecules would make a difference in accessibility to dendritic cores suggests that substrate selectivity could be achieved, where a catalytic center is incorporated at the core of a dendrimer and the backbone acts as a selective gatekeeper. Efforts are underway in our laboratories to further understand the fundamental reasons for the observed differences in accessibility.

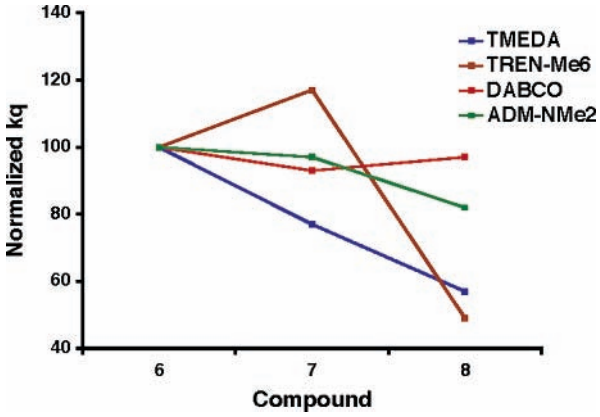


Figure 4. Comparison of quenching efficiency of amines in dendrimers **6**−**8**.

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Supporting Information Available: Synthetic and other experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Since this was a rather surprising result for us, we repeated the TMEDA and DABCO experiments with dendrimers **7** and **8** several times. The values obtained were within the 5% experimental error.

(12) We ran MM2-based energy minimizations on DABCO and TMEDA. We got several low-energy conformations for TMEDA in which the N1−N2 through-space distance ranged from 2.8 to 3.8 Å. However, with DABCO, this distance was always 2.6 Å in as many iterations. See also: Wong, N. B.; Cheung, Y. S.; Wu, D. Y.; Ren, Y.; Tian, A.; Li W. K. *J. Phys. Chem. A* **2000**, *104*, 6077.

(13) For an analogy with DNA passing through protein channels, see: Kong, C. Y.; Muthukumar, M. *Electrophoresis* **2002**, *23*, 2697.