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Dendrimeric Catalysts for the Activation of Hydrogen Peroxide. Increasing Activity per Catalytic Phenylseleno Group in Successive Generations

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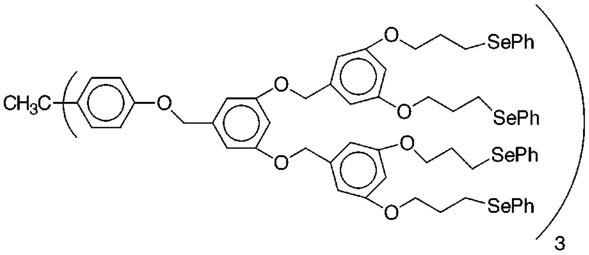
ABSTRACT



Dendrimeric polyphenylselenides are prepared in high yield using propyloxy spacers to connect the phenyseleno groups to the dendrimeric core. The selenides catalyze the oxidation of bromide with hydrogen peroxide to give positive bromine species that can be captured by cyclohexene in two-phase systems. The increase in the rate of catalysis exceeds statistical contributions for the first few generations with 3, 6, and 12 phenylseleno groups.

We report our initial studies toward the development of highly efficient catalysts for peroxide activation that are based on dendrimeric molecules terminating in phenylseleno groups. Although the dendrimeric catalysts have minimal water solubility with values of log $P > 4$, they are efficient catalysts in two-phase systems and show large increases in catalytic activity per phenylseleno group with each successive generation of dendrimer.

Recent developments in the synthesis of dendrimeric molecules[1] suggest that materials with improved catalytic activity can be designed through statistical rather than chemical means. Traditionally, the molar activity of catalysts has been optimized through structure−activity relationships derived from substituent changes. In dendrimeric molecules, catalytic functionality can be placed at the terminus of the individual arms of the molecule and the reactivity of the molecule on a molar basis then becomes a function of the total number of individual reactive groups as well as the reactivity of the individual groups. Dendrimers also impose order within the molecules since reactive groups will be the same distance from the central core. In certain catalytic systems, a dendrimer effect is observed in which the catalytic activity of individual groups increases with dendrimer generation.[1,2]

Diorganotellurides are catalysts for oxidations with hydrogen peroxide.[3,4] Peroxide oxidation gives the corresponding dihydroxytellurane, which then acts as an oxidant

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(1) For reviews of dendrimeric molecules: (a) Tomalia, D. A.; Durst, H. D. *Top. Curr. Chem.* **1993**, *165*, 193. (b) van der Made, A. W.; van Leeuwen, P. W. N. M.; de Wilde, J. C.; Brands, R. A. C. *Adv. Mater.* **1993**, *5*, 466. (c) Service, R. F. *Science* **1995**, *267*, 458−459. (d) Dagani, R. *Chem. Eng. News* **1996**, *74*, 20. (e) Newkome, G. R.; Moorefield, C.; Vögtle, F. *Dendritic Macromolecules: Concepts, Syntheses, Perspectives*; VCH: Weinheim, Germany, 1996. (f) Gorman, C. *Adv. Mater.* **1998**, *10*, 295. (g) Chow, H.-F.; Mong, T. K.-K.; Nongrum, M. F.; Wan, C.-W. *Tetrahedron* **1998**, *54*, 8543−8660.

(2) For one example, see: Lee, J.-J.; Ford, W. T.; Moore, J. A.; Li, Y. *Macromolecules* **1994**, *27*, 4632−4634.

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(kinetically superior to hydrogen peroxide) for a variety of substrates, including halide salts, thiols, selenols, and dye precursors. The corresponding diorganotelluride is regenerated in the process to continue the catalytic cycle. Diorganoselenides undergo the same chemistry, but they are poorer catalysts for peroxide activation due to slower rates of oxidation of the selenides and due to slower rates of reaction of the corresponding dihydroxyselenanes with the substrates. The tellurides and selenides mimic enzymes that activate hydrogen peroxide such as horseradish peroxidase (HRP)[5] and vanadium bromoperoxidase (VBPO).[6] In two-phase systems, the most efficient catalysts have shown some aqueous solubility as the telluride or selenide with *n*-octanol/water partition coefficients (log *P*) of ≤ 2.[3,4]

Synthesis. The oxidizing environment experienced by peroxide catalysts limits the selection of core molecules and stable linkages that can be employed in the synthesis of dendrimeric arrays. The use of 1,1,1-tris(4-hydroxyphenyl)ethane (**1**; Figure 1) as a core molecule to which dendritic wedges can be attached has been elegantly developed by Fréchet.[7] Compound **1** should be relatively unreactive toward either hydrogen peroxide or the hypohalous acids produced under the conditions described herein. Attachment of arms containing a single selenide functionality directly to the hydroxy groups of **1** would generate molecules with three catalytic groups.

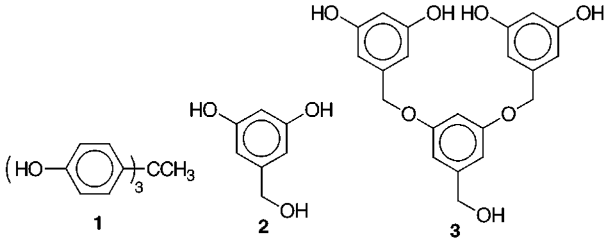
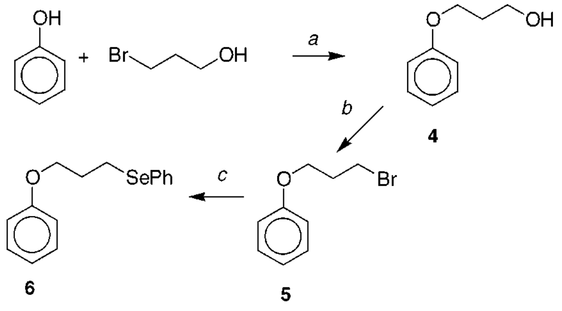


Figure 1. Building blocks for dendritic catalysts.

3,5-Dihydroxybenzyl alcohol (**2**) can be used to construct dendritic wedges[8] that are also stable to hyrogen peroxide (Figure 1). Attachment of arms containing a single selenide functionality directly to **2** would provide the first-generation dendritic wedge. Higher generations can be derived by the linking of compound **2** to itself in an iterative process to produce dendritic wedges such as **3** that can then be joined to the central core.[8]

Arylselenide groups were successfully linked to phenolic hydroxy groups through propyloxy spacers as shown in Scheme 1. Importantly, both the introduction of the 3-bromo-1-propyloxy spacer and the nucleophilic phenylselenide-substitution reaction proceed in high yield ($\geq 90\%$). These reactions should be suitable for the many iterations necessary to produce either dendritic wedges or complete dendrimers. In addition to demonstrating the feasibility of the chemistry, the 3-phenoxypropyl phenylselenide **6**[9] represents a control monoselenide, to which the catalytic activity of the dendrimeric molecules described below can be compared.

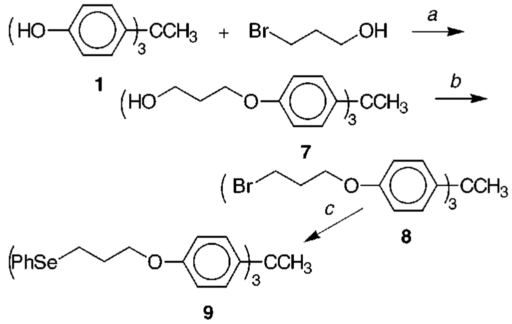
Scheme 1[a]



[a] Key: (a) 18-crown-6, K_2CO_3, acetone, 90%; (b) CBr_4, PPh_3, THF, 93%; (c) NaSePh from $(PhSe)_2$/$NaBH_4$ in EtOH/THF, 92%.

Attachment of three 3-bromopropanol molecules to the core molecule **1** gave triol **7** in 90% isolated yield, as shown in Scheme 2. The triol was converted to the tribromide **8** in 93% isolated yield, and the tribromide **8** was then converted to triselenide **9** in 93% isolated yield. The average yield of each of the individual iterations of these reactions was greater than 96%. Full characterization of all new compounds is provided in the Supporting Information.

Scheme 2[a]



[a] Key: (a) 18-crown-6, K_2CO_3, acetone, 90%; (b) CBr_4/PPh_3, THF, 93%; (c) NaSePh from $(PhSe)_2$/$NaBH_4$ in EtOH/THF, 93%.

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(3) (a) Detty, M. R.; Gibson, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 4086−4088. (b) Detty, M. R.; Gibson, S. L. *Organometallics* **1992**, *11*, 2147−2155.

(4) Detty, M. R.; Zhou, F.; Friedman, A. E. *J. Am. Chem. Soc.* **1996**, *118*, 313−318.

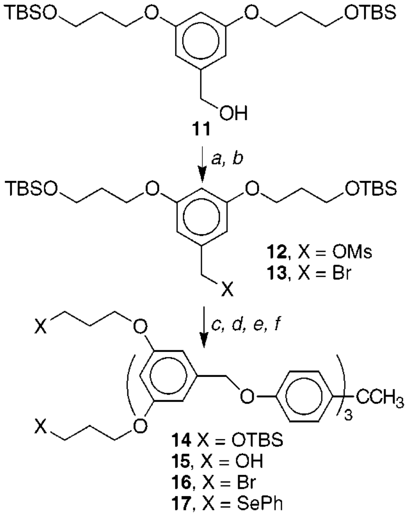
(5) (a) Thorpe, G. H. G.; Kricka, L. J.; Mosely, S. B.; Whitehead, T. P. *Clin. Chem.* **1985**, *31*, 1335−1341. (b) Ishikawa, E. *Clin. Biochem.* **1987**, *20*, 375−385. (c) Ikemoto, M.; Ishida, A.; Tsunekawa, S.; Ozawa, K.; Kasai, Y.; Totani, M. *Clin. Chem.* **1993**, *39*, 794−799. (d) Larue, C.; Calzolari, C.; Bertinchant, J.-P.; Leclercq, F.; Grolleau, R.; Pau, B. *Clin. Chem.* **1993**, *39*, 972−979.

(6) (a) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937−1944. (b) Butler, A. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1992; pp 425−445. (c) Butler, A.; Carrano, C. J. *Coord. Chem. Rev.* **1991**, *109*, 61−105. (d) Wever, R.; Kreenn, M. B. E. In *Vanadium in Biological Systems*; Chasteen, N. D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1990; pp 81−97.

(7) (a) Hawker, C.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010−1013. (b) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

3-Bromo-1-propanol was converted to its *tert*-butyldimethylsilyl ether **10**, and 2 equiv of **10** was attached to benzyl alcohol **2** with potassium carbonate and catalytic 18-crown-6 to give **11** in 73% overall yield from 3-bromo-1-propanol. Benzyl alcohol **11** was converted to the corresponding benzyl bromide in two steps (Scheme 3). The mesylate **12** was first prepared (90%) and was then treated with lithium bromide to give benzyl bromide **13** in 98% isolated yield. Three equivalents of dendritic wedge **13** was attached to core molecule **1** to give dendrimer **14** with six arms terminating in *tert*-butyldimethylsilyl ethers in 91% isolated yield. The silyl protecting groups were removed to give alcohol **15** in 91% yield, and **15** was converted to bromide **16** in 81% overall yield via the mesylate as an intermediate. The addition of NaSePh to bromide **16** gave dendrimer **17,** bearing six phenylseleno groups in 85% isolated yield. It should be noted that direct displacement of the mesylate with NaSePh gave **17** in less than 30% isolated yield.

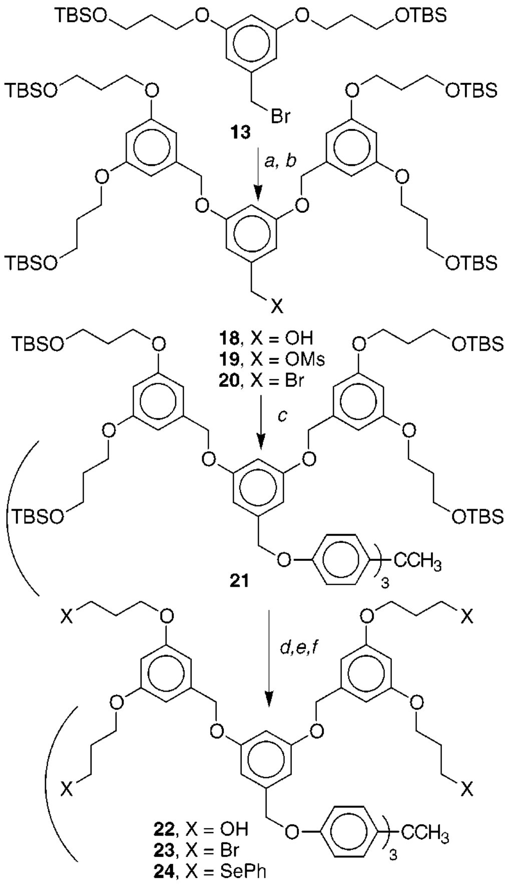
Scheme 3[a]



[a] Key: (a) MsCl, Et_3N, CH_2Cl_2, 90% of **12**; (b) LiBr, THF, 93% of **13**; (c) **1**, 18-crown-6, K_2CO_3, acetone, 91% of **14**; (d) Bu_4HF, THF/DMF, 91% of **15**; (e) (i) MsCl, Et_3N, THF/CH_2Cl_2, (ii) LiBr, 81% of **16**; (f) NaSePh from $(PhSe)_2$/$NaBH_4$ in 0.2 M NaOEt in EtOH/THF, 85% of **17**.

Two equivalents of bromide **13** was attached to the phenolic hydroxyls of 3,5-dihydroxybenzyl alcohol (**2**), as shown in Scheme 4, to give alcohol **18** in 91% isolated yield. The alcohol **18** was converted to the corresponding bromide in two steps via initial formation of the mesylate **19**, which was then treated with LiBr in THF to give the dendritic wedge **20** in 81% overall yield. Compound **20** was attached to the core molecule **1** to give dendrimer **21** in 70% yield. The silyl protecting groups were removed to give alcohol **22** in 91% yield, and **22** was converted to bromide **23** in two steps via the mesylate in 74% overall yield. The addition of NaSePh to bromide **23** gave dendrimer **24** bearing 12 phenylseleno groups in 66% isolated yield.

Scheme 4[a]



[a] Key: (a) **2**, 18-crown-6, K_2CO_3, acetone, 24 h, 91% of **18**; (b) (i) MsCl, Et_3N, THF/CH_2Cl_2 to give **19**, (ii) LiBr, THF, 74% of **23**; (d) Bu_4NF, THF/DMF, 91% of **22**; (e) (i) MsCl, Et_3N, THF/CH_2Cl_2, (ii) LiBr, THF, 74% of **23**; (f) NaSePh from $(PhSe)_2$/$NaBH_4$ in 0.2 M NaOEt in EtOH/THF, 66% of **24**.

Catalysis. Selenide **6** and dendrimers **9**, **17**, and **24** are sparingly soluble in water (log $P > 4$), which necessitated the use of two-phase systems for evaluation of their catalytic activity. The oxidation of bromide with hydrogen peroxide was followed by the initial rate of formation of *trans*-1,2-dibromocyclohexane (**25**) and *trans*-2-bromocyclohexanol (**26**) in a two-phase system of 0.5 M cyclohexene in CH_2Cl_2 for the organic phase and an aqueous phase of H_2O_2 (3.0 M) and NaBr (2.0 M) in pH 6 phosphate buffer at 296.0 ± 0.1 K.[10] The bromination of cyclohexene was rapid and

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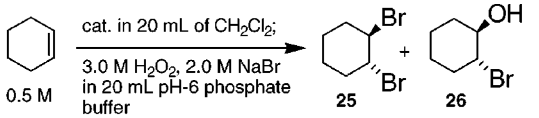
(8) (a) Groenendaal, L.; Fréchet, J. M. J. *J. Org. Chem.* **1998**, *63*, 5675−5679. (b) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1059−1067. (c) Leon, J. W.; Kawa, M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 8847−8859.

(9) All new compounds gave satisfactory elemental analyses and/or parent ions by mass spectroscopy. ^1H and ^{13}C NMR spectra were consistent with ≥97% purity. Spectral and analytical data for the new compounds of this study can be found in the Supporting Information.

(10) In typical experiments, 0.05 mmol of **6**, **9**, or **17** or 0.008 mmol of **24** was added to a two-phase system of 20 mL of a stock solution of 0.5 M cyclohexene in CH_2Cl_2 (8.20 g (0.100 mol) in 200 mL of CH_2Cl_2 with diphenyl ether (170 mg, 1.00 mmol, 5×10^{-3} M) as an internal standard) for the organic phase and an aqueous phase of H_2O_2 (12.5 mL of a 30% solution) and NaBr (6.63 g, 0.065 mol) in 20 mL of pH 6 phosphate buffer

served as a good indicator of the generation of “Br^+” species. It should be noted that **25** and **26** were the only products of reaction. The control experiments were then compared to catalyzed reactions at 296.0 ± 0.1 K in which 2.5 mM **6**, **9**, or **17** or 0.4 mM **24** was present (Table 1). The **25**/**26** ratios in the catalyzed runs were similar to those in the uncatalyzed runs, although somewhat more 2-bromocyclohexanol (**26**) was formed in the presence of catalyst (Table 1).

Table 1. Rates of Catalysis for the Oxidation of Bromide by Hydrogen Peroxide in the Presence of Phenylseleno-Containing Molecules As Determined by the Rate of Bromination of Cyclohexene



cat.	no. of PhSe groups	mM	initial rate, μM s^{-1} [a]	v_{init}, μmole (**25+26**)/s/ mole catalyst[b]	v_{init}(rel)	v_{init}(rel)/ PhSe	ratio **25/26**[c]
none	0	--	5.85 ± 0.05	--	--	--	45:55
6	1	2.5	6.45 ± 0.05	0.24	1	1	42:58
9	3	2.5	16.5 ± 0.2	2.36	9.8	3.2	37:63
17	6	2.5	82.5 ± 0.4	30.6	130	21	44:56
24	12	0.40	66.75 ± 0.05	152	630	53	38:62

[a] Average of duplicate runs. [b] Corrected for uncatalyzed reaction.
[c] Average of duplicate runs which agreed within ± 0,3%.

The rates of catalysis for selenide **6** and dendrimers **9**, **17**, and **24** increased as the number of phenylseleno groups increased in each molecule, but the increase far exceeded the statistical changes in the number of phenylseleno groups. As shown in Table 1, the monoselenide **6** displayed little catalytic activity with a conversion rate of 0.24 mol of **25** + **26**/(s (mol of **6**)) when corrected for the background reaction. The dendrimer **9** with three phenylseleno groups was 1 order of magnitude more efficient than **6**, while dendrimer **17** with six phenylseleno groups was more than 2 orders of magnitude more efficient than **6**. Dendrimer **24** with 12 phenylseleno groups continues the trend and is more than 600-fold more efficient as a catalyst than **6**. The catalytic activity of **24** is more than 50 times the reactivity expected from strictly statistical arguments based on the reactivity of **6**. The deviation from statistical rate increases is expressed in Table 1 as the relative initial rate (ν_{init}) per phenylseleno group.

The catalysts **17** and **24** displayed high turnover numbers for the generation of **25** and **26** in preparative runs.[11] For catalyst **17**, a turnover number of ≥1030 mol of **25** + **26**/mol of **17** was observed while catalyst **24** gave a turnover number of ≥5200 mol of **25** + **26**/mol of **24**. The catalysts were recovered from the organic phase of the reaction and were reused without apparent loss of activity.

We speculate that the “dendrimer effect” observed in the catalysis may be due to the micelle-like nature of the oxidized catalyst where polar dihydroxyselenanes are layered equidistant from the core. Higher generation dendrimers may be necessary to confirm this effect, since early generation dendrimers are still capable of folding back on the core.[12] However, the redox reaction with bromide proceeds rapidly in the dendrimeric environment.[4] These studies lay the foundation for the design and synthesis of other dendrimeric systems with improved properties that may be generally useful to the synthetic chemist. We are currently preparing water-soluble dendrimeric catalysts for halogenation reactions that are free of organic solvent, and we are preparing dendrimeric catalysts with chiral organochalcogen groups to explore chiral halogenations.

Acknowledgment. We thank the Augmentation Awards for Science and Engineering Research Training (AASERT) Program, Office of Naval Research, for partial financial support of this work.

Supporting Information Available: Full characterization data for compounds **6**−**9**, **11**, **13**−**18**, and **20**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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at 296.6 ± 0.1 K. Compounds **25** and **26** were identified by GC−mass spectroscopy with comparison to authentic samples for retention time. Relative response factors of 5.0 × 10^{-3} M solutions of **25** or **26** were determined and compared to the response of the 5.0 × 10^{-3} M diphenyl ether internal standard. The organic phase was sampled periodically by gas chromatography, and initial rates are reported on the basis of the first 25% of reaction.

(11) In preparative runs, catalyst **24** (0.008 mmol) was added to a two-phase mixture of 0.050 mol of cyclohexene in 50 mL of CH_2Cl_2 and an aqueous phase of H_2O_2 (12.5 mL of a 50% solution) and NaBr (10.2 g, 0.100 mol) in pH 6 phosphate buffer (50 mL) at 293 K. When the rate of appearance of products began to plateau, a second 12.5 mL aliquot of H_2O_2 was added (approximately 1 h). After 3 h, the cyclohexene was consumed and 4.05 g (16.7 mmol) of **25** and 4.51 g (25.2 mmol) of **26** were isolated, which corresponds to 41.9 mmol (84% yield) of brominated product from 0.008 mmol of **24** (a turnover number of >5200). Under identical conditions, catalyst **17** (0.010 mmol) gave 10.3 mmol of brominated products after 3 h for a turnover number of >1030. In the latter reaction, starting cyclohexene had not yet been consumed. The catalysts were recovered from the organic phase following a bisulfite wash and chromatography on silica. No loss of catalytic activity was observed upon further use.

(12) Naidoo, K. J.; Hughes, S. J.; Moss, J. R. *Macromoloecules* **1999**, *32*, 331−341.