Synthesis and Catalytic Activity of Unimolecular Dendritic Reverse Micelles with "Internal" Functional Groups

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The unique 3-dimensional structure of dendritic macromolecules, coupled with the ability to prepare a diverse range of functionalized materials, has sparked continued interest in this rapidly evolving field.[1] When compared to traditional linear polymers, one of the most interesting features of dendrimers is their similarity to natural catalytic systems such as enzymes. Like enzymes, the structure and functionality of dendrimers can be precisely controlled, resulting in regions of well-defined hydrophilic and hydrophobic character. This creates specific nanoscale environments[2] within dendrimers in which chemistry can be performed, guest molecules encapsulated,[3,4] or catalytic sites created.[5−9] In this communication we present novel unimolecular reverse micellar dendrimers[10] that combine a unique polar interior with activating functional groups at predetermined locations and a nonpolar corona that resembles the reaction solvent. These dendrimers are specifically designed to catalyze reactions in which a nascent positive charge is developed in the transition state.

Construction of the dendrimers by a convergent growth approach[11] involved the tetradecyl-substituted benzyl bromide, **1,** as the terminal unit and the methyl ester functionalized diphenol, **2,** as the repeat unit.[12] Growth of the dendritic structure was carried out using a two-step procedure, coupling of **1** with **2** under Williamson etherification conditions, followed by activation of the THP-protected hydroxymethyl group at the focal point by bromination with CBr₄/PPh₃. The activation procedure, which involves both a deprotection and a bromination reaction, can be carried out in a single step, thereby facilitating dendrimer synthesis. Dendron construction was carried out up to the fourth generation and the respective second, third, and fourth generation dendrons were then coupled to a trifunctional core to obtain the desired dendrimers, ([G-4]₃-[C], **3**, and [G-3]₃-[C], **5**). The 4th generation dendrimer, **3**, has an external layer containing 48 tetradecyl units surrounding an inner core of benzyl ether repeat units functionalized with a layered concentric arrangement of 21 ester functional groups (Scheme 1).

The presence of these internal functional groups permits the environment of the core to be readily modified. To increase the hydrophilic character of the dendritic interior, and provide hydrogen-bonding sites, the "inner" ester groups were reduced to the corresponding alcohols, (e.g. **4**, Scheme 1). Standard reaction conditions, excess LiAlH₄ in refluxing THF for 16 h, followed by purification by either flash chromatography or precipitation resulted in essentially 100% reduction with the reaction being easily monitored by ¹H NMR, FT-IR, and MALDI-TOF mass spectroscopy. In this way, reduced third and fourth generation dendrimers ([G-3]₃-[C]ᵣₑ𝒹, **6**, and [G-4]₃-[C]ᵣₑ𝒹, **4**) were prepared.[13] These dendrimers have a high "inner" density of aromatic rings and hydroxyl groups affording a unique nanoenvironment for reactions involving suitably polar transition states. Therefore, in analogy with enzymes, a positively charged transition state could be stabilized by noncovalent interactions such as hydrogen bonding, cation−π aromatic interactions, or simply the hydrophilic internal nanoenvironment of the dendrimer. To avoid product inhibition of the catalytic site, the reaction products should be nonpolar to allow its migration from the polar dendritic interior to the outside medium leading to high turnover numbers. Initially, S_N2 reactions and unimolecular elimination reactions (E1) were examined.

Tertiary alkyl halides were chosen as E1 substrates and an inorganic base was added to trap the acidic hydrogen halide byproduct.[14] Upon heating in cyclohexane at 70 °C for 24 h (Scheme 2), essentially complete conversions were obtained for both 2-iodo-2-methylpropane and 2-iodo-2-methylheptane, **7**, in the presence of 0.57 mol % of dendrimer, **4**. In contrast, little or no reaction could be observed for control experiments carried out under identical conditions but without **4**.[15] Increasing the substrate/dendrimer ratio had a minimal effect on product yields with ca. 90−99% conversion being observed after 43 h in the presence of less than 0.01 mol % of the dendrimer (Table 1). This correlates with a turnover number of approximately 17400, demonstrating that the dendrimer acts as a catalyst with each molecule involved in repeated reactions with uptake of substrate followed by release of product. Interestingly, the E1-elimination reaction of **7** leads to two possible products, an internal olefin, **8**,

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(12) The tetrahydropyranyl protecting group present in **2** was necessary to prevent oligomerization of **2** under the alkylation conditions.

(13) All dendritic structures were fully characterized using a variety of spectroscopic and chromatographic techniques. For example, [G-3]₃-[C]ᵣₑ𝒹, **6.** To a suspension of LiAlH₄ (0.1 g, 2.6 mmol) in 25 mL of anhydrous THF is slowly added a solution of [G-3]₃-[C], **5** (1.0 g, 0.123 mmol), in 25 mL of anhydrous THF. The mixture was refluxed overnight. The reaction was quenched by adding water dropwise until the solid turns white. The solid is then filtered and the filtrate evaporated to dryness. The residue is partitioned between water and dichloromethane. The aqueous phase is washed three times with dichloromethane, and the combined organic phase is dried (MgSO₄) and concentrated to dryness. The product is purified by precipitation from CH₂Cl₂/acetone. ¹H NMR: (CDCl₃) δ 0.85 (t, 72H, *J* = 7.1 Hz, CH₂C*H*₃), 1.20−1.50 (m, 528H, 24(C*H*₂)₁₁), 1.74 (m, 48H, C*H*₂CH₂O), 2.09 (s, 3H, CH₃), 3.91 (t, 48H, *J* = 6.3 Hz, CH₂C*H*₂O), 5.03 (m, 60H, ArC*H*₂O and CH₂OH), 6.38 (m, 12H, aromatic), 6.52 (m, 24H, aromatic), 6.63 (s, 18H, aromatic), 6.85 (d, 6H, *J* = 8.75 Hz, aromatic), 7.02 (d, 6H, 8.75 Hz, aromatic). ¹³C NMR: (CDCl₃) δ 14.12, 22.69, 26.07, 29.28, 29.37, 29.45, 29.70, 31.93, 54.82, 55.03, 68.07, 70.70, 100.82, 104.46, 105.61, 114.02, 117.70, 117.78, 129.68, 138.06, 138.71, 142.16, 156.16, 157.73, 157.81, 160.54. IR (neat): 3567, 2923, 2853, 1597, 1465, 1434, 1168 cm⁻¹. MS (MALDI) *m/z* 7856 [MNa⁺], calculated 7855.
(14) The alkyl halide (0.11 mmol), dendritic catalyst, sodium bicarbonate (1.5 equiv), and cyclohexane-*d*₁₂ (1 mL) were stirred at 70 °C in a sealed tube for 43 h. The conversion is measured by ¹H NMR using either the dendrimer or added benzene as internal standard.
(15) Control experiments were conducted under identical conditions (a) in the absence of dendrimer, (b) in the absence of dendrimer and in the presence of benzyl alcohol or methyl benzoate (equimolar in functional groups), and (c) in the absence of dendrimer and in the presence of a [G-1]-dendron (equimolar in functional groups).

Scheme 1

$$X = -CO_2Me; \; 3 \xrightarrow{\text{LiAlH}_4} X = -CH_2OH; \; 4$$
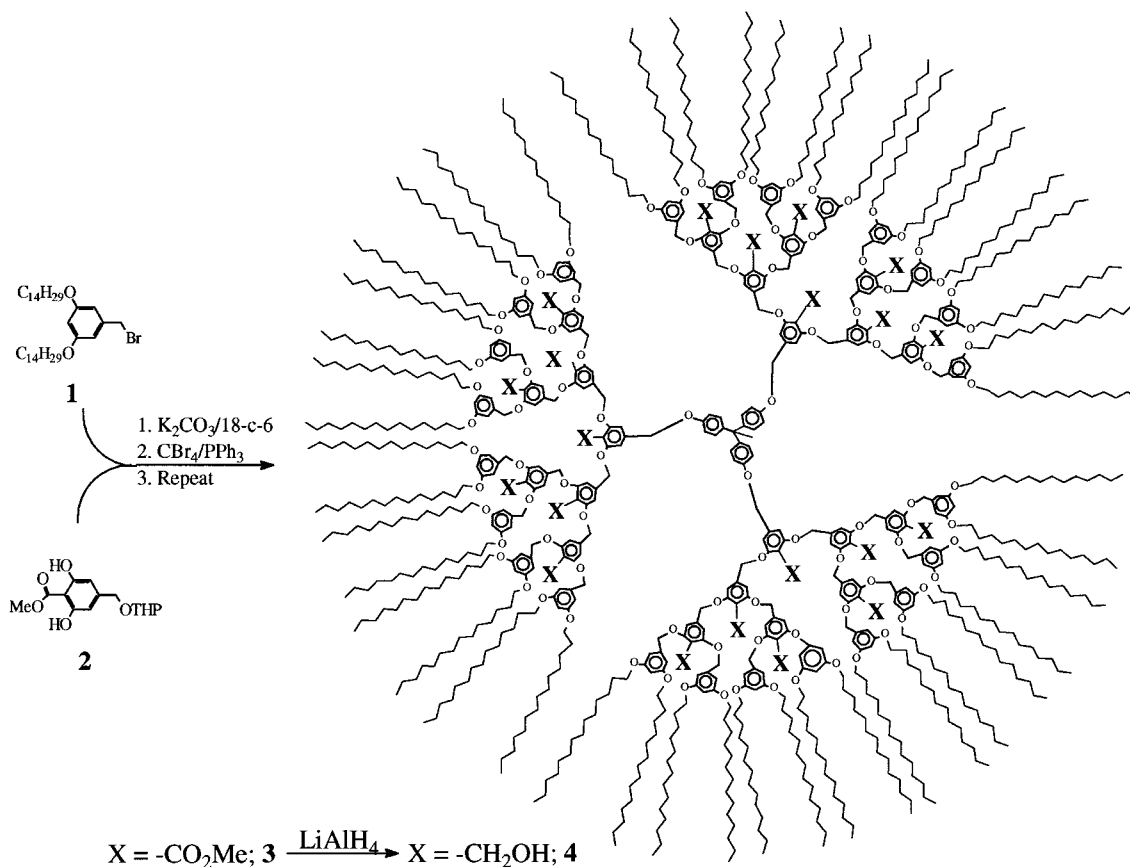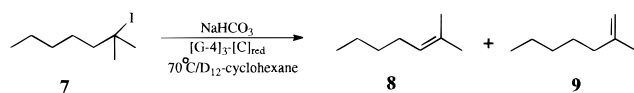
Scheme 2

Table 1. Effect of Changing the Dendrimer Structure and Concentration on the Yield and Turnover Number for the E1 Elimination Reaction of **7**

dendrimer	substrate/dendrimer	conversion, %	turnover no.
3	180 to 1	83	149
	90 to 1	84	76
4	176 to 1	99	174
	353 to 1	90	318
	1760 to 1	92	1619
	3530 to 1	94	3318
	17600 to 1	99	17400
5	90 to 1	68	61
6	87 to 1	73	63
	176 to 1	71	125
	870 to 1	67	580[a]

[a] Reaction performed for 68 h.

and a terminal olefin, **9**, and the product ratio, **8/9**, was found to be sensitive to the catalyst loading with values of 2 or greater being obtained in essentially each case.[16]

Variations in the structure and functionality of the dendrimer were found to have a marked effect on catalytic ability. Decreasing the size of the dendrimer from [G-4] to [G-3] resulted in a 15–20% reduction in both rate of reaction and turnover number. Changing the nature of the internal functional group also had an effect on the reaction with a 10–15% decrease observed upon replacing hydroxymethyl groups by ester groups. More importantly, the ester functionalized derivatives proved to be unstable under the reaction conditions with minor amounts of cleavage of the dendrimer backbone being detected to give lower molecular weight dendritic fragments. In contrast, the reduced hydroxymethyl derivatives were stable and demonstrated the same level of activity after repeated cycling, suggesting their potential use in flow-through reactor systems.

To further investigate the catalytic ability of these dendritic reverse micelles, the S_N2 alkylation of pyridine with CH_3I was studied. Equimolar amounts of pyridine and CH_3I were stirred at room temperature in cyclohexane with varying amounts (0.01–1.0 mol %) of dendrimers **3** or **4**. Catalytic activity was observed for all the dendrimers studied while no conversion was found for a variety of control experiments.[15] The highest catalytic ability was again observed for the 4th generation dendrimer, **4**. However in these examples, attempts to perform the reactions at low dendrimer concentrations resulted in incomplete conversions, most likely due to product inhibition since the polar alkylated pyridinium salts have a high affinity for the dendritic core.

This study demonstrates that dendrimers with appropriate inner and outer functionalities can perform as nanoscale unimolecular catalytic "systems". The high polarity of their inner core, contrasting with the low polarity of their outer corona and of the solvent, provides an ideal nanoenvironment for reactions that involve a polar transition state. Further investigations concerning the chemical properties and catalytic selectivity of these and related macromolecules are currently underway.

(16) The different values for the product ratio, **8/9**, were found not to be due to isomerization but were sensitive to the catalyst loading with higher substrate-to-dendrimer ratio leading to an increase in the ratio of **8:9**. Structure of the dendrimer, as well as the nature of the internal functionality, was also found to have an effect. The reason for this is not completely understood and is currently under investigation.