Synthesis and Characterization of a Novel Dendritic Acrylic Monomer

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Introduction

Over the past decade, dendrimers and their controlled cascade architecture have attracted considerable attention. These three-dimensional molecules have three architectural regions: a core, an interior, and a highly functionalized surface, all of which are spatially defined by branch cells tethered to the core by chemical bonds.[1−3] These versatile molecules with controllable sizes are some of the most powerful synthetic building blocks available today for the construction of giant macromolecules and supramolecular systems with a complete architecture, precise shape, and functionality. New materials with potentially significant and scarcely explored properties may be obtainable using these compounds. [4−10]

These structural features have aroused the interest of synthetic organic chemists, and several valuable contributions to the synthesis and characterization have been reported over the past few years.[11−15] Current studies are mainly focused on their potential properties and applications in such diverse areas as organic chemistry, analytical chemistry, biology, medicine, materials science, pharmacology, agrochemistry, environmental chemistry, and chemical engineering.[16−18]

In view of the increasing interest in these new compounds, we report the synthesis and characterization of a new dendrimer (**1**) bearing acrylic functions and masked hydroxyl groups.

The core of the monomers was synthesized following the strategy proposed by Newkome et al.,[19] which is based on the pentaerythritol and acrylonitrile reaction. As depicted retrosynthetically in Scheme 1, two strategies were used for the synthesis of multiacrylic dendrimer **1**: disconnection *aa′* based on a divergent synthetic pathway, and disconnection *b*, which involves a convergent strategy. In this report we analyze these approaches, both of which had challenging features.

This new kind of dendritic monomer with reactive acrylic double bonds on its surface would be of particular interest if it could be used to obtain new materials through simple and available polymerization processes.

We expect that deprotection of the hydroxyl groups after free radical polymerization of the monomer would lead to a macromolecular structure possessing numerous hydroxyl groups, which should give the resulting material a very pronounced hydrophilicity and reactivity with some further chemical modifications. We are currently attempting to transform these ideas into reality.

Results and Discussion

(I) Monomer Synthesis. Two pathways for the synthesis of the desired dendritic monomer were studied, as shown in Scheme 2.

Our first choice for the synthesis of product **11** was made through stages A, B, C, and D. Various experimental conditions were tested to maximize the yields of the different steps. Thus, pentaerythritol **2** and acrylonitrile **3** in dioxane/water gave tetranitrile **4** in 85% yield by the Michael reaction. Tetramethyl ester **5** was then obtained in 50% yield by methanolysis of **4** in an acidic medium. The hydroxyl-functionalized monomer **7** was obtained from nucleophilic substitution amidation between **5** and **6** in DMSO, base-catalyzed with K_2CO_3.

Once **7** was obtained, we sought to protect 1,3-diol pairs by reaction with benzaldehyde, acetone, or 2,2-dimethoxypropane (DMP) **9** in different solvents and acid-catalyzed with HCl or *p*-toluenesulfonic acid (*p*-TSA). Despite the various conditions used to protect the diol moiety in **7** by condensation with a carbonyl function, complete acetalization was not achieved.

The relatively low reactivity of the hydroxyl groups of **7** could be explained by a clear-cut tendency to develop aggregation which leads to gelation through hydrogen-bonding interactions. We confirmed that self-assembly of dendrimers with hydroxyl groups on the surface leads to gelation depending on the balance of external hydrophilic and internal hydrophobic groups.[20,21] Similar results were obtained when the reaction with acryloyl chloride was attempted to form random acrylic end groups. The yields were much lower than expected (>15%).

To overcome the problem encountered in the first approach, a convergent synthetic pathway (E + F + G)

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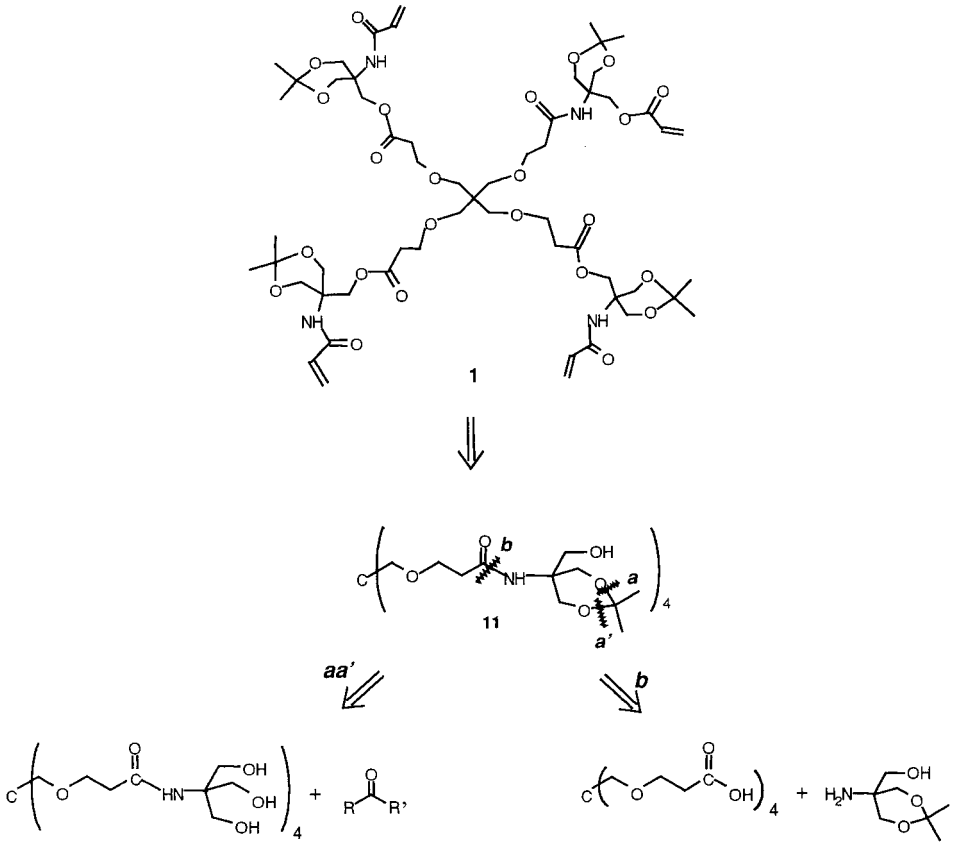
Scheme 1. Retrosynthesis of Multiacrylic Dendrimer 1



was examined. Once tetramethyl ester **5** was obtained as described above, hydrolysis gave the tetraacid **8** in 75% yield.

Compound **10** was obtained as a white solid by protection of 1,3-diols of Tris by acetal formation, acid-catalyzed with *p*-TSA. The best conditions for the trans-acetalization of 1,3 hydroxyl groups of **6** with 2,2-dimethoxypropane **9** were an equivalent ratio of 1:3 (Tris:DMP) in acetone for 3 h at 25 °C, which gave a yield of 60%. In these types of reactions, short reaction times avoided the formation of a Schiff base.

Products **8** and **10** were linked through a convergent synthesis where different variables were studied in an attempt to obtain product **11** in optimal yields.

A convergent synthesis was carried out with tetraacid **8**, activated with 1,3-dicyclohexylcarbodiimide (DCC) or 1,1′-carbonyldiimidazole (CDI) prior to use, and protected amine **10**. When using DCC in THF or CDI in methanol, incomplete conversion was obtained, with an average of 50% of branches reacting. When activation was carried out with CDI in acetonitrile (ACN) or THF, a mixture of amide and ester products in **11**, albeit in different proportions, was obtained in optimized yields of 60 to 70%.

The presence of both products in **11** is reasonable, since the acid groups activated with CDI yielded a very reactive intermediate which, with the ambident nucleophile **10**, was turned into both ester and amide products. However, a hydroxyl attack to yield an ester was the main pathway, and there were important changes in the [amide]/[ester] ratio when the reactions were made in THF.

Other reaction conditions, with regard to time, temperature and dilution, were studied in THF, and the results are shown in Table 1.

Table 1. Variables Effects in Amidation G in THF

	time (h)	temp (°C)	[dendrimer] (M)	% amide[a]	A_{1745}/A_{1660} (ester/amide)[b]
time effect	3	25	0.125	26	2.48
	overnight[c]			38	1.62
	18			56	0.97
	36			55	0.78
temp effect	3	0	0.125	17	5.64
		25		26	2.48
		65		43	1.77
dilution effect	3	25	0.125	26	2.48
			0.050	19	4.48
			0.025		6.15

[a] Quantified by ^{1}H NMR. [b] Absorbance (cm^{-1}), ester and amide I bands ratio by FT-IR. [c] In solution after workup.

An increase in reaction time, temperature, and concentration of the initial reagents led to a rise in the amide percentage. These variations may be explained by the reaction mechanism presented in Scheme 3, in which attack of a hydroxyl group is favored because it is less hindered, followed by an intramolecular rearrangement by attack of the amine at the ester carbonyl to yield the amide. Although many studies have been devoted to the mechanism of the aminolysis of esters, the mechanistic details are not yet entirely clear. The mechanism appears to be essentially $B_{AC}2$, probably assisted by another amine, which could be corroborated by the dilution effect.[22] Aside from temperature and solvent, K_{eq} is a function of the basicity of the amine and steric factors.[23]

The amide percentage was quantified by ^{1}H NMR using the peaks of methylene protons near the ester (2.58

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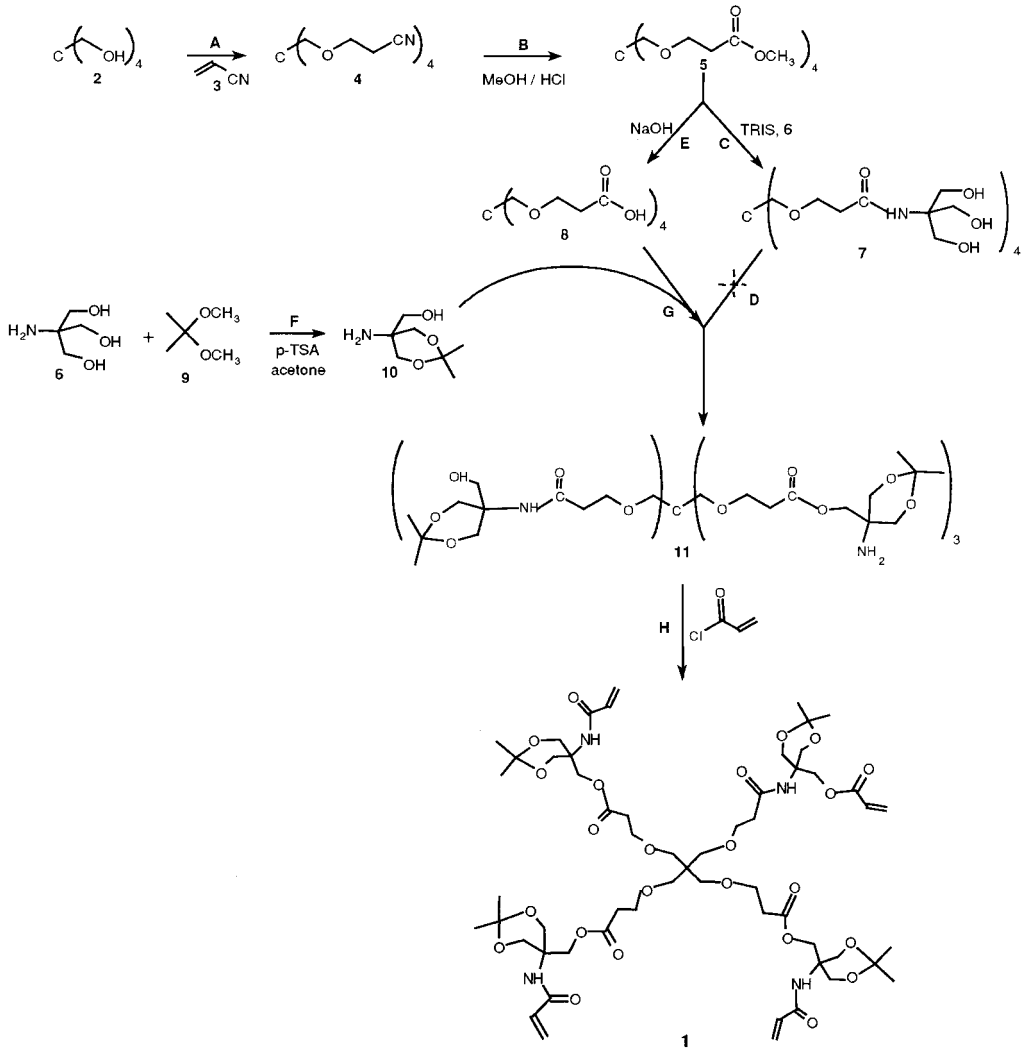
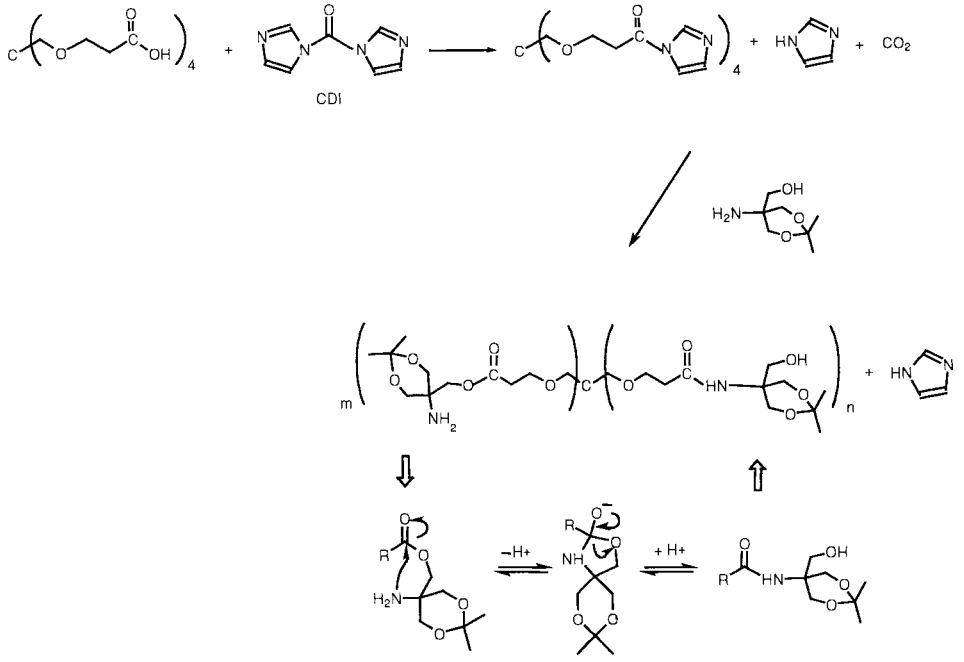
Scheme 2. Synthetic Pathway Leading to the Dendritic Monomer 1



Scheme 3. Mechanism Proposed for Aminolysis of Esters



ppm) and the amide (2.47 ppm), and by FT-IR using the ester and amide I band ratio.

Once the dendrimer with ester/amide groups at known ratios was obtained at low temperature in a short period

of time (for a minimum of amide groups), the reaction of its free amine and hydroxyl groups with acryloyl chloride gave the multiacrylic dendrimer **1** in 80% yield of the total product, with an average of 3.5 acrylic groups per molecule, as estimated by ^{1}H NMR.

Studies on the reactivity of **1** as a monomer in radical polymerization and to characterize the ensuing polymers are in progress.

Conclusion

Two pathways for the synthesis of the desired dendritic acrylic monomer **1** were studied: a divergent method and a convergent method. The latter approach gave monomer **1** in better yield and consisted of the synthesis of **8** (A + B + E), which through a reaction with **10** gave **11** (G). Finally, **1** was easily and rapidly obtained in very good yield from **11** and acryloyl chloride. This novel dendritic monomer could be an interesting building block to obtain partly cross-linked products.

Experimental Section

Reagents. Pentaerythritol was obtained from Riedel de Häen, acrylonitrile from Carlo Erba, tris(hydroxymethyl)aminomethane (TRIS) from Anedra, 2,2-dimethoxypropane (DMP) from Sigma, silica gel 60 from Merck, anhydrous K_2CO_3 and NaOH from Cicarelli, and benzaldehyde, *p*-toluenesulfonic acid (*p*-TSA), 1,3-dicyclohexylcarbodiimide (DCC), 1,1′-carbonyldiimidazole (CDI), acryloyl chloride, triethylamine, 2,2′-azobisisobutyronitrile (AIBN), ethylene glycol dimethacrylate (EGDMA), $CDCl_3$, and D_2O from Aldrich. All chemicals were used without modification. Solvents were obtained from Sintorgan purified by distillation, and, when necessary, dehydrated by 4 Å molecular sieves.

Monomer Synthesis.

A. Tetranitrile 4 (Cyanoethylation). Polyol **2** (33.50 g, 0.25 mol) was reacted with acrylonitrile **3** (194 mL, 2.95 mol) in basic medium in 1.06 L of a dioxane/water mixture to favor substrate dilution. The reaction mixture was stirred for 24 h at room temperature. When the reaction was complete, the solvent was evaporated under vacuum, and the residue was dissolved in chloroform and washed with water. The crude product was purified by liquid chromatography on silica gel and eluted with methylene chloride/acetone (90/10 v/v). Yield was 85%.

B. Tetramethyl Ester 5 (Esterification). Tetranitrile **4** (34.50 g, 0.072 mol) was dissolved in 400 mL of dry methanol acidified with HCl(g), and the reaction mixture was refluxed for 3 h. After the solvent was removed under vacuum, the crude product was purified by liquid chromatography on silica gel, and eluted with methylene chloride/acetone (90/10 v/v). Yield was 50%.

C. Dendrimer 7 (Aminolysis of Tetramethyl Ester 5). Tetramethyl ester **5** was converted into the corresponding dendritic structure **7** with 12 hydroxyl end groups by reaction with tris(hydroxymethyl)aminomethane (Tris) **6** in DMSO catalyzed by K_2CO_3. Purification was carried out by precipitation in acetone. Yield: 60%.

D. Diol Protection of Polyhydroxylate Dendrimer 7. Polyhydroxylate dendrimer **7** was dissolved and mixed with a protective group as described in Table 1. After the reaction time shown, the solvent was evaporated, and the residue was analyzed by ^{1}H NMR. Small or no signals at 7.34, 7.51, and 8.11 ppm for protection with benzaldehyde, and at 1.41 and 1.44 ppm for protection with acetone or DMP, demonstrated that complete acetalization was not achieved.

E. Tetraacid 8 (Hydrolysis of Tetramethyl Ester 5). Tetraester **5** (21 g, 0.050mol) was mixed with 210 mL of an aqueous 3 M NaOH solution for 24 h at room temperature. When the reaction was complete, the product was acidified and extracted with ethyl ether. Yield: 75%.

F. Hydroxyamine 10 (Diol Protection of Tris 6). The best yields were obtained when Tris (12.7 g, 0.11 mol) was mixed with DMP (41 mL, 0.33 mol) in 300 mL of dry acetone, with a 0.5% excess of *p*-TSA, for 3 h at room temperature. When the reaction was complete, the solvent was removed under vacuum, and the product was dissolved in water. The pH of the aqueous solution was raised to 9, and extraction was performed with Cl_2CH_2. The product migrated into the organic phase whereas the unreacted Tris **6** and the salt of *p*-TSA remained in the aqueous phase. Yield: 60%.

G. Dendrimer 11 (Esterification−Amidation of Tetraacid 8 with Amine 10). General Procedure. Tetraacid **8** was dissolved, and an activator (DCC or CDI) was added. After 45 min at room temperature, amine **10** was added, and the reaction was allowed to proceed for the time shown. When the reaction was complete, the solvent was evaporated under vacuum, and the residue was purified by column chromatography if necessary. When using CDI in THF or ACN, the crude product was dissolved in chloroform and washed with water, and the organic phase was dried with $CaCl_2$, filtered, and dried.

H. Multiacrylic Dendrimer 1 (Double Bond Attachment). To a solution of product **11** with 17% amide and 83% ester (1.03 g, 1.04 mmol) and triethylamine (1.73 mL, 12.5 mmol) in 10 mL of THF was added acryloyl chloride (0.68 mL, 8.31 mmol) dissolved in 5 mL of THF dropwise at 0 °C. After the solution was allowed to warm to room temperature, it was stirred for 3 h. The solvent was then evaporated under vacuum, and the residue was dissolved in chloroform and washed with water to remove the ammonium salts. Yield: 80%.

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Supporting Information Available: Characterization data for compounds **1**, **4**, **5**, **7**, **8**, **10**, and **11.** This material is available free of charge via the Internet at http://pubs.acs.org.

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