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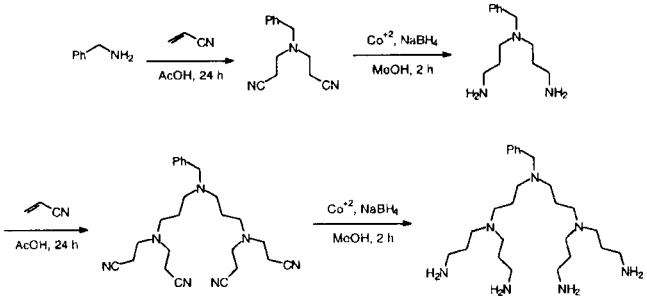
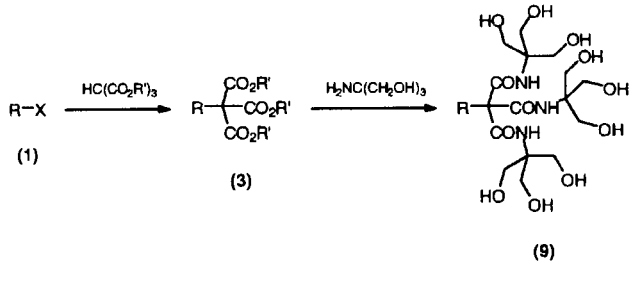
In 1978, Professor Vögtle [1] described the first "cascade synthesis" and thus the first example of a dendritic molecule. The application of their simple iterative **1** → **2** iterative *N*-branching iterative process, depicted in Scheme 1, to polymer chemistry has lead numerous researchers [2] to create diverse novel cascade or dendritic macromolecules. Figure 1 shows the development of a multifaceted tree, which starts to incorporate different scientific disciplines and areas of thought so necessary to design new macromolecules possessing unique nanoscopic properties. This presentation will, I hope, expand our initial simple synthetic **1** → **3** branching procedure (Scheme 2) into the field of heterocyclic chemistry affording an approach to tailor-made inner "void" regions within these macromolecules; thus affording new routes to molecular inclusion or recognition as well as access to water-soluble catalysts and drug and molecular delivery systems.



Scheme 1



Scheme 2

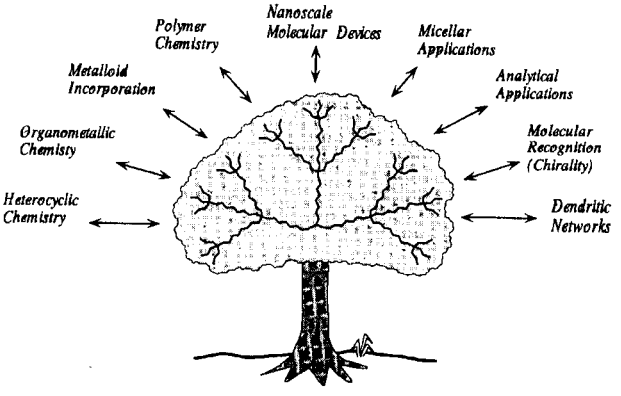
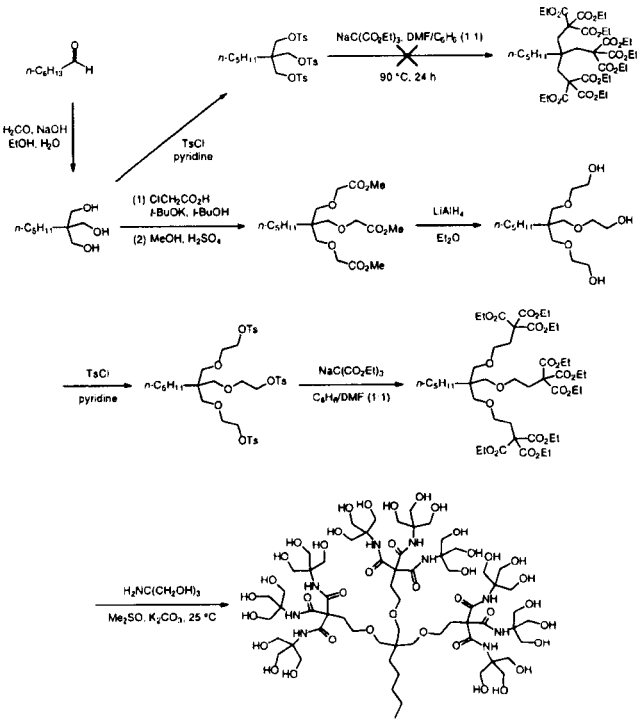


Figure 1

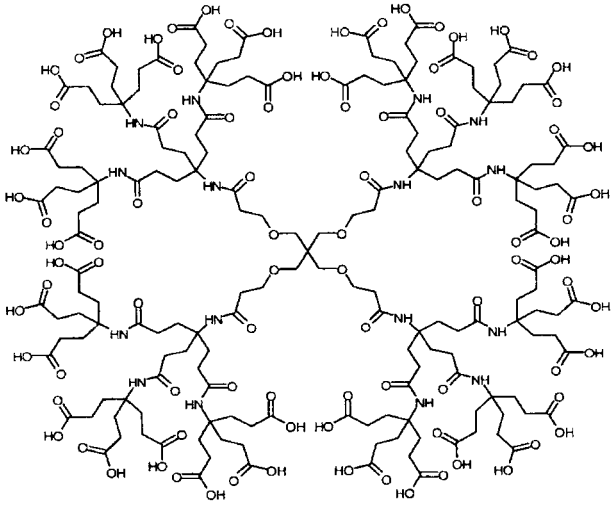
In 1983, we began our adventures into cascade construction based on an article published by Professor Tomlinson, [3] who described and depicted the architecture design of trees in the rain forests of South America. In that article, it was the "Leeuwenberg" model of a tree that changed our synthetic directions in chemistry, since the simple application of a **1** → **3** branching pattern (reminiscent of say chloroform or methanol) had the potential to remove the "molecular ceiling" in organic chemistry, as will be demonstrated. At that point in history, most man-made organic compounds possessed a molecular weight less than three thousand a.m.u. and thus application of this **1** → **3** progression afforded a repetitive synthesis which would generate molecular structures with no weight ceilings in the 10^7 a.m.u. range. Although our initial synthesis, published in early 1985, was not strictly an iterative process, it did create a route to macromolecules possessing well defined structures and grew by a **1** → **3** → **9** → **27** progression; Scheme 3 shows that original synthesis [4]. We called these original polyols "arborols", in that "arbor" meant tree and the surface was a polyol; this was also the advent of one type of "unimolecular micelle," since these structures have the potential of acting as a *single* molecule capable of molecular encapsulation. Several years later this was proven [5] to be the fact for other related *C*-based dendritic macromolecule series.

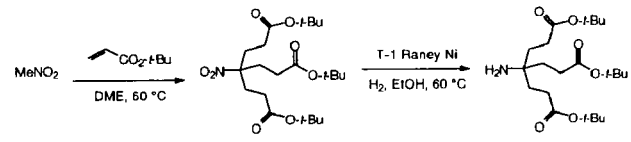
Since these arborols utilized a quaternary carbon as the branching point and subsequent nucleophilic substitution, necessary for continued growth, would be at a neopentyl center, it was necessary to prepare a new family of monomeric building blocks or molecular bricks to permit



Scheme 3

easy construction thus circumventing the hindrance associated with the neopentyl substitution pattern. Scheme 4 shows the easy preparation of what we now call "Behera's amine"; this amine {di-*tert*-butyl 4-amino-4-[2-(*tert*-butoxycarbonyl)ethyl]-1,7-heptanedioate} can be synthesized [6] in nearly quantitative yields in two steps from nitromethane and *tert*-butyl acrylate, followed by catalytic reduction. Other novel monomeric bricks were also generated and reported [7] to permit the facile polyfunctionalization of the macromolecular surface.





Scheme 4

To demonstrate the ease of macromolecular construction, based on a simple core, prepared from pentaerythritol and acrylonitrile, followed by hydrolysis, [8] the family of polyamido acids was prepared by simple peptide coupling of the tetraacid core with "Behera's amine" affording the 1st generation cascade. Simple and nearly quantitative hydrolysis of the *tert*-butyl groups with aqueous formic acid gave the dodecaacid, which can be reacted with twelve equivalents of "Behera's amine" to afford the 2nd tier ester. This simple iterative procedure affords the polyamido family shown in Figure 2. This related series has been totally proven [9] by traditional spectral and analytical techniques.

The introduction of other terminal groups was accomplished [7] by utilization of different specifically designed monomeric bricks; the "smart" behavior of the different terminated macromolecules was demonstrated [9]. Related acid, alcohol, and amine terminated dendrimer series were prepared and it was shown by *p*H studies that the amine terminated series exhibited *p*H-size behavior opposite to that for the acid terminated family and the polyol series showed no change in the hydrodynamic radius as a function of *p*H. The dendritic acid terminated series has been shown to be a micelle replacement for the separation of alkyl parabanes *via* electrokinetic capillarychromatography employing aqueous mobile phase conditions [10] (Figure 3); separations utilizing these dendrimers afforded excellent efficiency and resolution.

Generation (G)	Number of Terminal Groups (Z)	Formula Weight	{Cascade} (mM)	D (cm^2s^{-1}) / Hydrodynamic Radius (Å)		
				Acidic pH	Neutral pH	Basic pH
1	12	1,341	1.00	2.41×10^{-6} 8.24	1.62×10^{-6} 12.3	1.68×10^{-6} 11.8
2	36	4,092	1.00	1.74×10^{-6} 11.4	1.15×10^{-6} 17.3	1.26×10^{-6} 15.8
3	108	12,345	1.00	1.15×10^{-6} 17.3	8.32×10^{-7} 23.9	9.09×10^{-7} 21.9
4	324	37,102	0.97	8.79×10^{-7} 22.6	6.01×10^{-7} 33.1	6.87×10^{-7} 28.9
5	972	111,373	0.34	7.83×10^{-7} 25.4	5.35×10^{-7} 37.1	6.17×10^{-7} 32.3

Figure 2

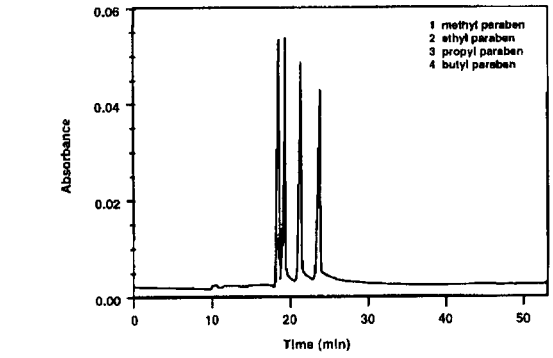
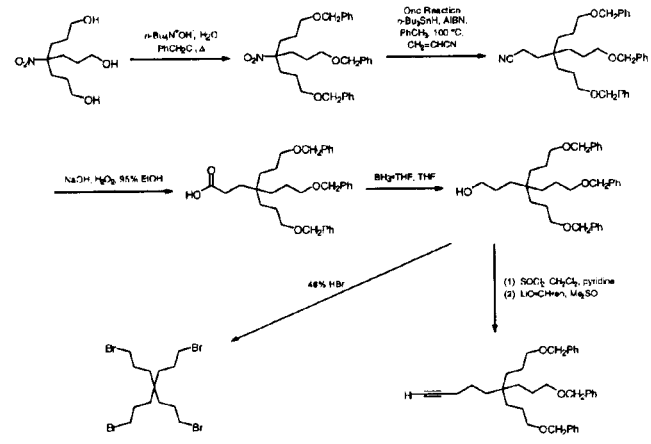
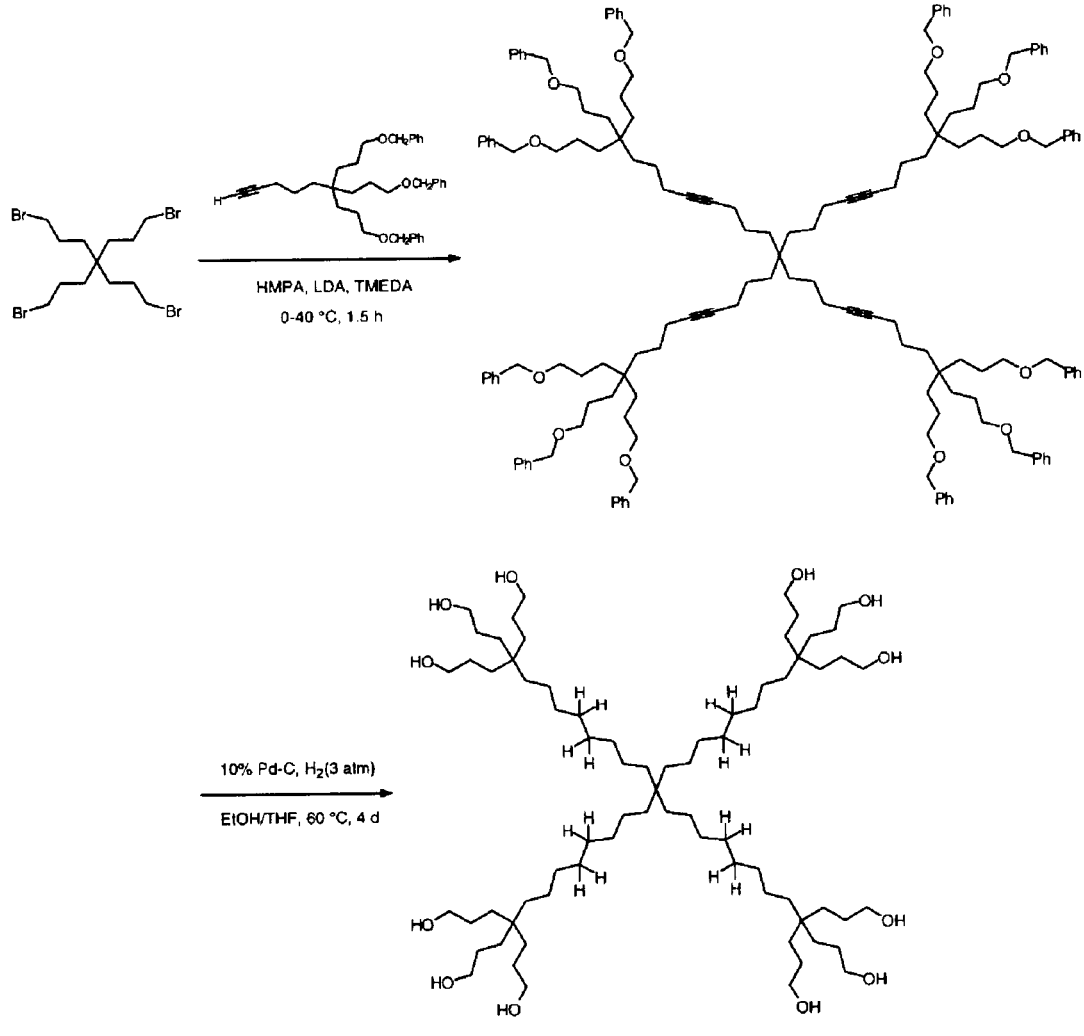


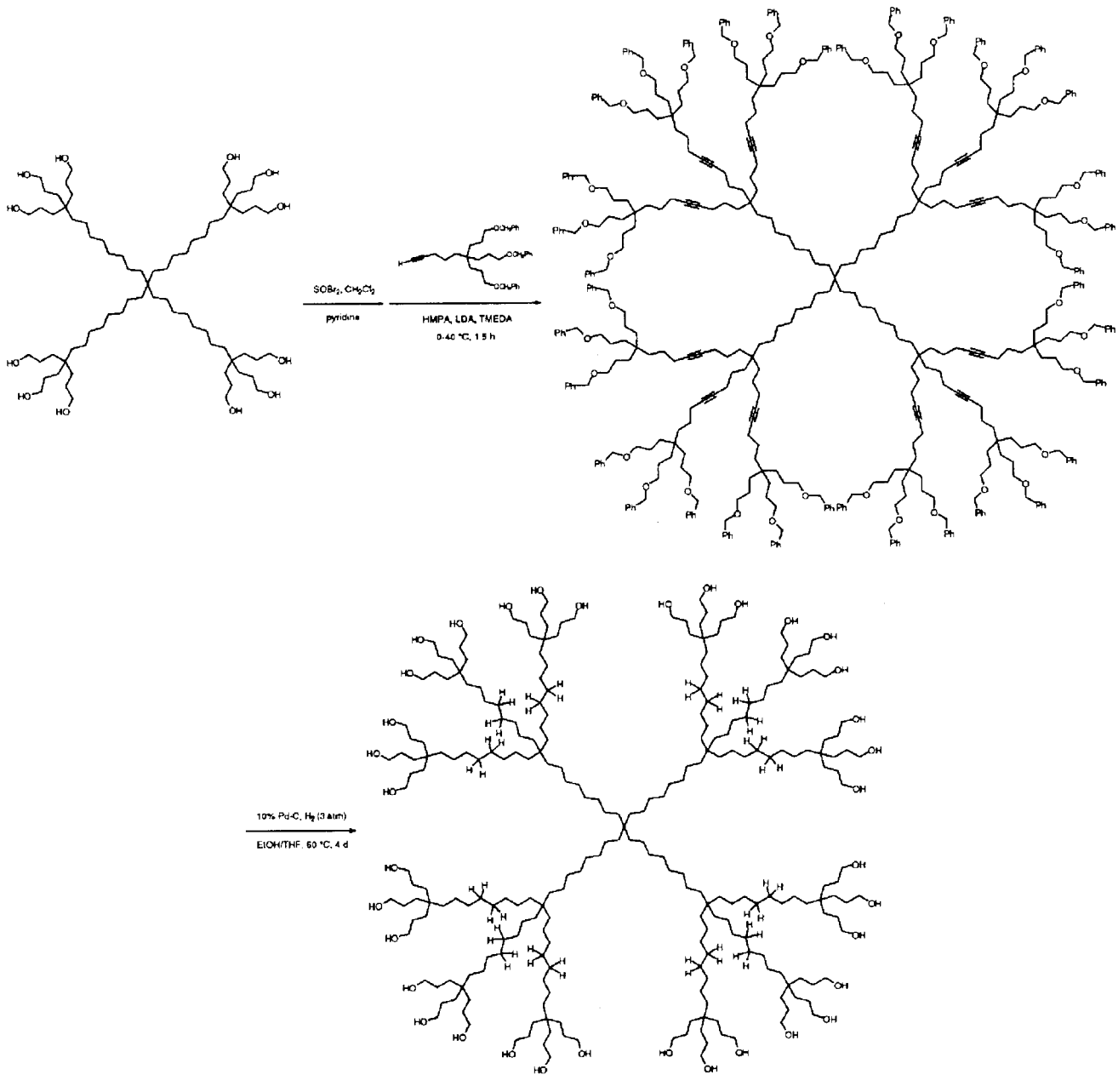
Figure 3



Scheme 5



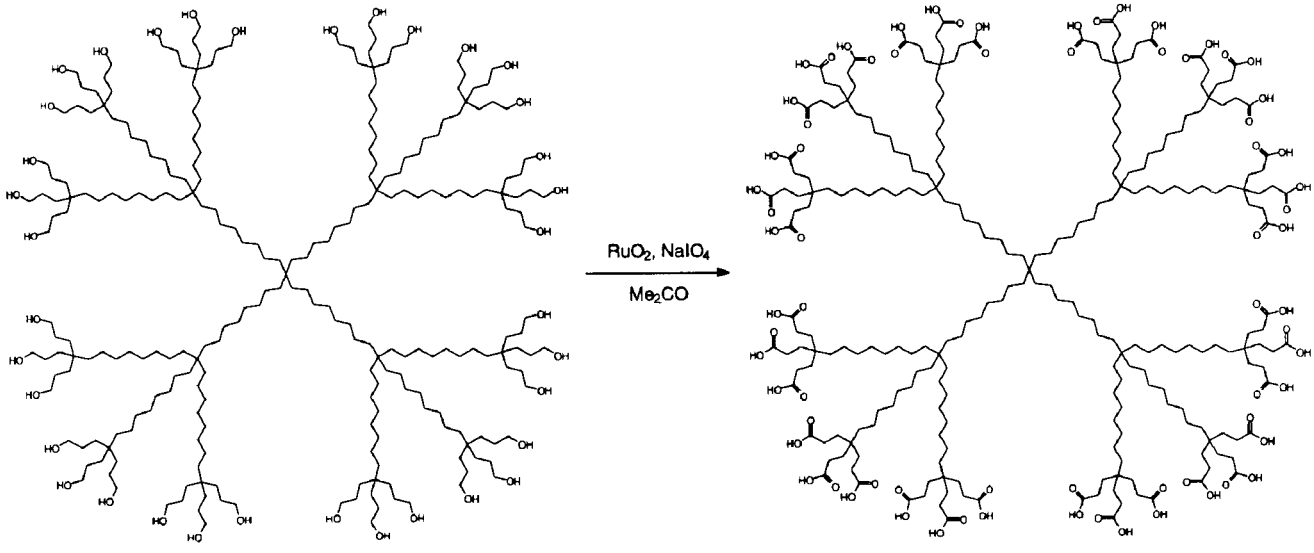
Scheme 6



Scheme 7

In order to create the ultimate "unimolecular micelle", it was deemed necessary to prepare an all carbon symmetrical, four-directional, macromolecule [11] (Figure 4). Schemes 5-8 show the general procedures to create the *N*-Cascade:methane[4]:(nonylidyne)^{m}; propanoic acid series [12] {denoted as the *N*-Micellanoic Acid™ series} (Figure 5). Application of traditional methods to demonstrate micelle characteristics were applied [5] to this Micellane™ series; thus, UV studies of guest molecules, such as phenol blue, pinacyanol chloride, naphthalene and chlortetracycline, and the fluorescence lifetime decay experiments of diphenylhexatriene confirmed the micellar behavior of the NMe_4^+ salt of the 36-Micellanoic Acid™. Electron microscopy was used to determine the monodispersity, size, and absence of intermolecular aggregation.

The proof of molecular inclusion was demonstrated but can one incorporate specific metal atom loci or clusters within the macromolecular framework at predetermined sites? Since polyacetylenes were intermediates in the preparation of the all carbon cascade series, they were chosen to demonstrate the attachment process. Treatment of the tetra- and dodeca-yne polybenzyl ether terminated



Scheme 8

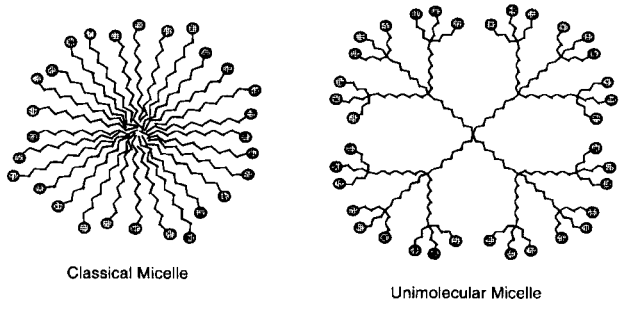


Figure 4

precursors with $Co_2(CO)_8$ showed the rapid and nearly quantitative synthesis of tetra- and dodeca-dicobalt clusters, [13] deemed as one type of Metallomicellane™ cascades (Scheme 9). Treatment of the same 2nd generation docaalkyne with activated decaborane ($B_{10}H_{14}$) gave essentially quantitative yield of the dodeca-*o*-carborane (Scheme 10) [14]. Catalytic reduction to remove the benzyl protecting groups afforded the desired polyol (considered the first example of a Metalloidomicellane™ cascade). The limited water solubility of this polyol can be circumvented by treatment with chlorosulfonic acid to give the corresponding polysulfate, whose alkali metal salt was completely water soluble.

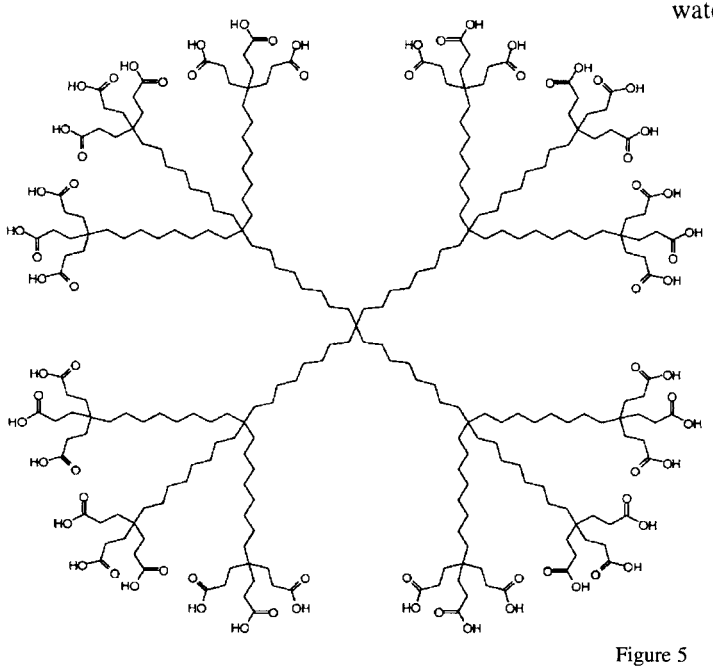
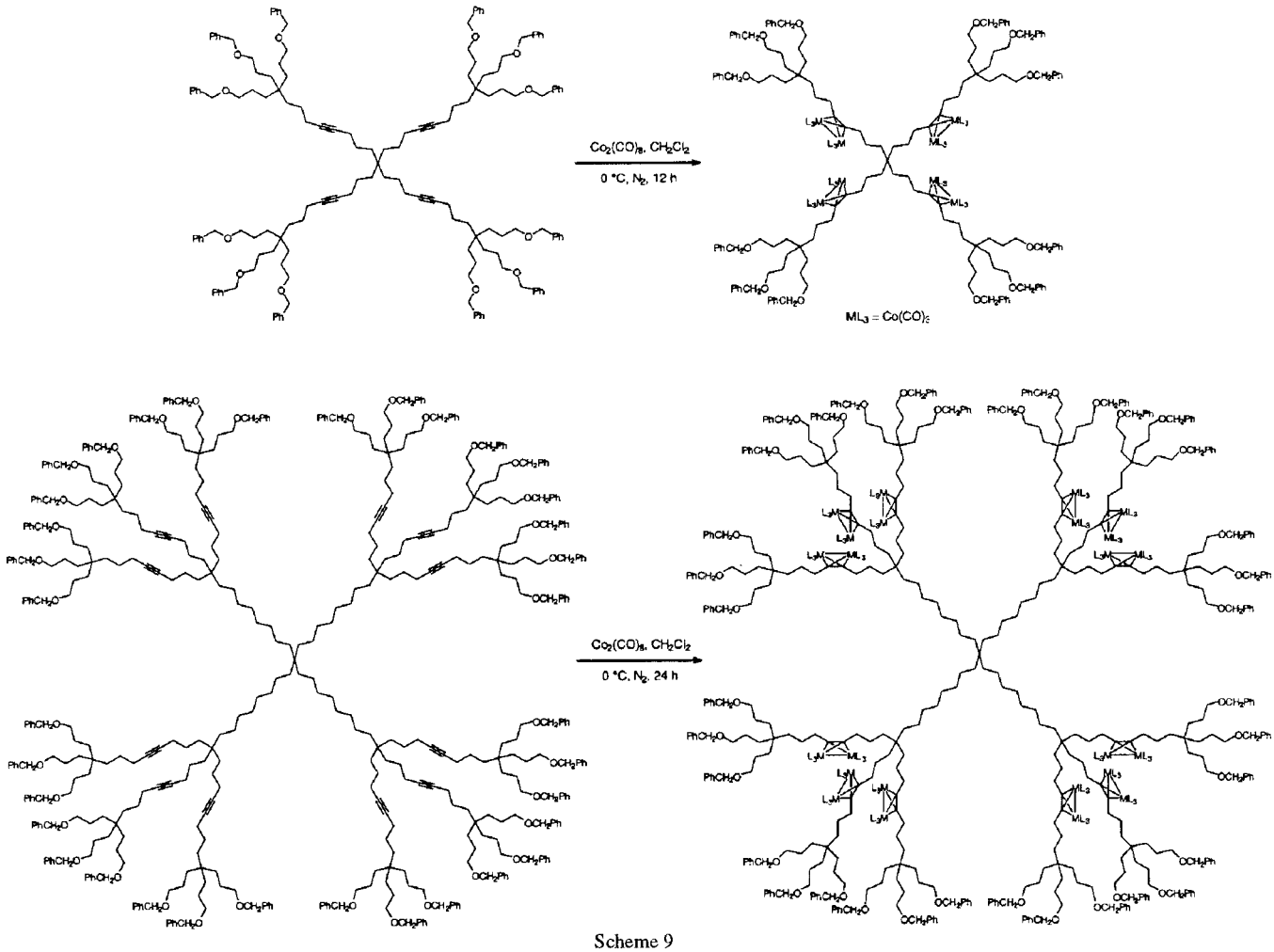


Figure 5

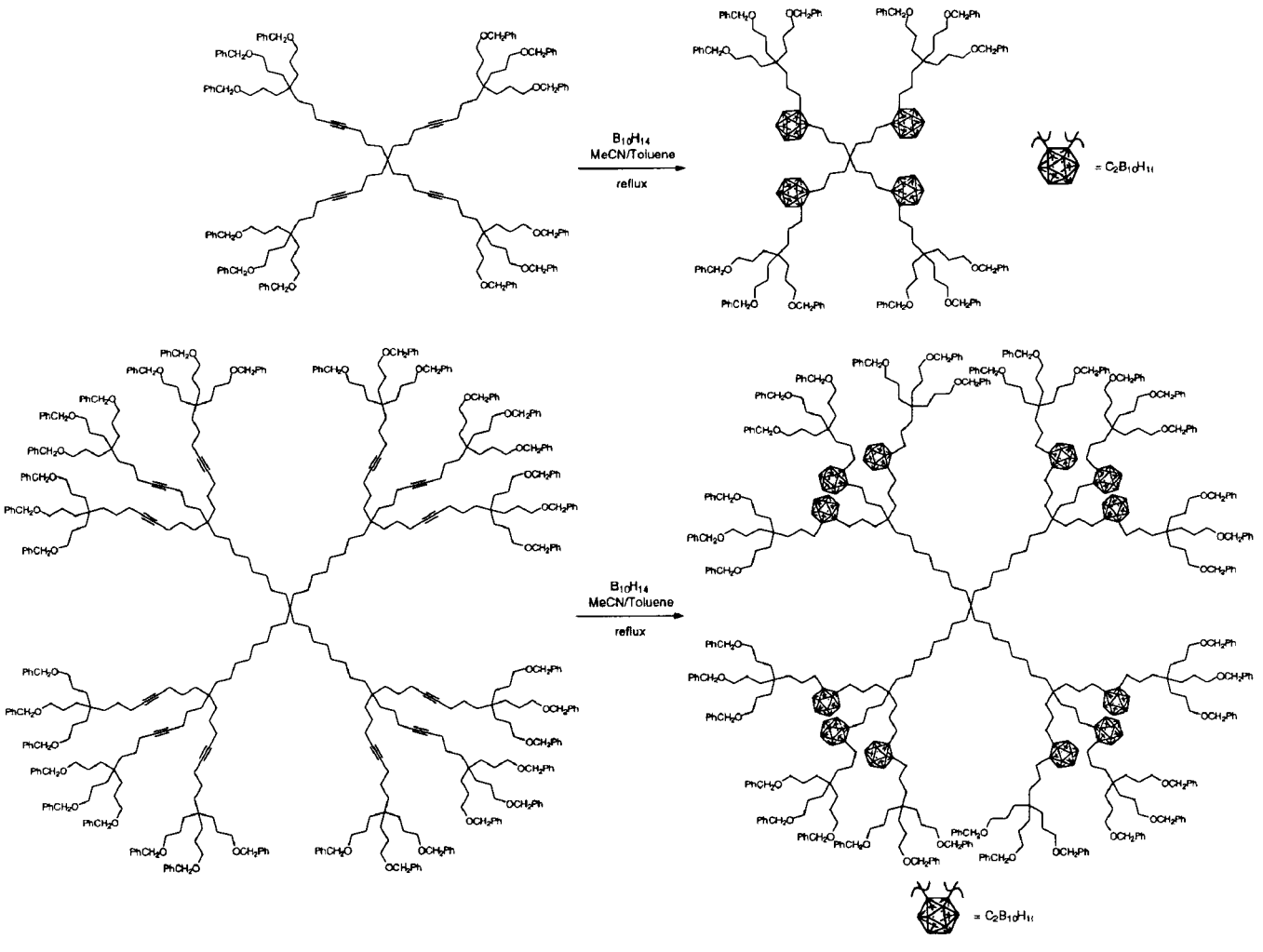
Generation (*G*)	Number of Terminal Moieties (*Z*)	Nominal Formula Weight
0	4	304
1	12	1,385
2	36	4,630
3	108	14,363
4	324	43,563
5	972	131,163



Scheme 9

So far in this presentation, there has yet been no mention of heterocycles, even though this is a Heterocyclic Congress! Thus, I hope to convince you that there are ample opportunities for heterocyclic chemists to have a field day in this macromolecular arena. Based on the availability of diverse monomeric divergent ligating bricks, novel Metallomicellane™ macromolecules can be prepared that utilize metal-centered chelating connectivity [15]. To demonstrate, the treatment of bis*homo*tris [16] with 4'-chloroterpyridine [17] gave an amine, (Scheme 11) which can be coupled by known methodology to the previously described tetraacid to give the dodeca-terpyridine cascade (Scheme 12). The necessary Ru^{+3} containing building block was prepared, (Scheme 13) from the precursor of the previously described all-carbon unimolecular micelle, and subsequently coupled to the dodecaterpy core with concomitant reduction to afford the dodecametallocascade. In this simple example, the metal centers are easily proven by classical electrochemical techniques (Figure 6); this will be an important aspect of the proof-of-construction as the molecular size increases since the normal spectral and analytical procedures fail to distinguish the inherent faults in construction.

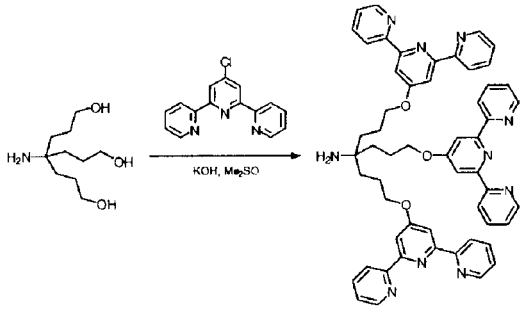
The application of this type of "connectology" can give rise to Ru-mediated assembly of novel well-defined cascade macroassemblies possessing a **1** → **3** carbon branching multiplicity. In the route to dendritic networks, the preparation of *bis*-dendrimers demonstrates the basic concept [18]. Scheme 14 shows the preparation of the two halves of the assembly: one with a short and one with a long bridge between the carbon core and the terpyridine linker moieties. The reductive coupling of the two halves *via* a ruthenium metal center was easily achieved (Schemes 15-17). In that both halves can be structurally characterized by traditional organic techniques and certain of the coupled structures exceed the current analytical thresholds for structural confirmation, the presence of the metal center is shown to be critical to the proof of structure. Thus, the use of electrochemical results become useful tools for the rapid assessment of the structure proof of these nanoscopic complexes.



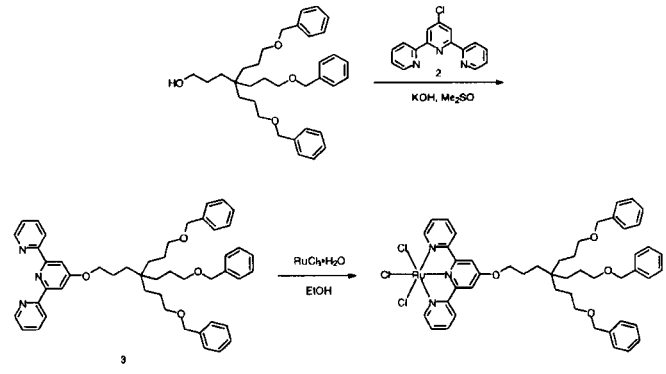
Scheme 10

These Ru-terpyridine redox-active connective centers (Figures 7 & 8) are readily probed by standard electrochemical techniques [18]. The cyclic voltammograms of the simplest members [1:1- and 2:2- tiers] in the series demonstrate that both the cationic and anionic scans yield electrochemical and chemically reversible processes; whereas, for the 2:3-tiered structure the redox couples remain electrochemically and chemically reversible *except for the first cathodic couple*. Thus for the first time electrochemical irreversibility is detected for the first cathodic couple and the second cathodic process remains electrochemically quasi-reversible and chemically reversible. Irreversible behavior first becomes apparent for the sterically congested 1:4 tiered complex; complete irreversible behavior is clearly demonstrated for the 2:4-tiered complex. The redox behavior of these Ru-connected dendrimers suggest an interesting entrance to redox-driven "unlocking" of a complex and a reversible formation - decomposition mechanism.

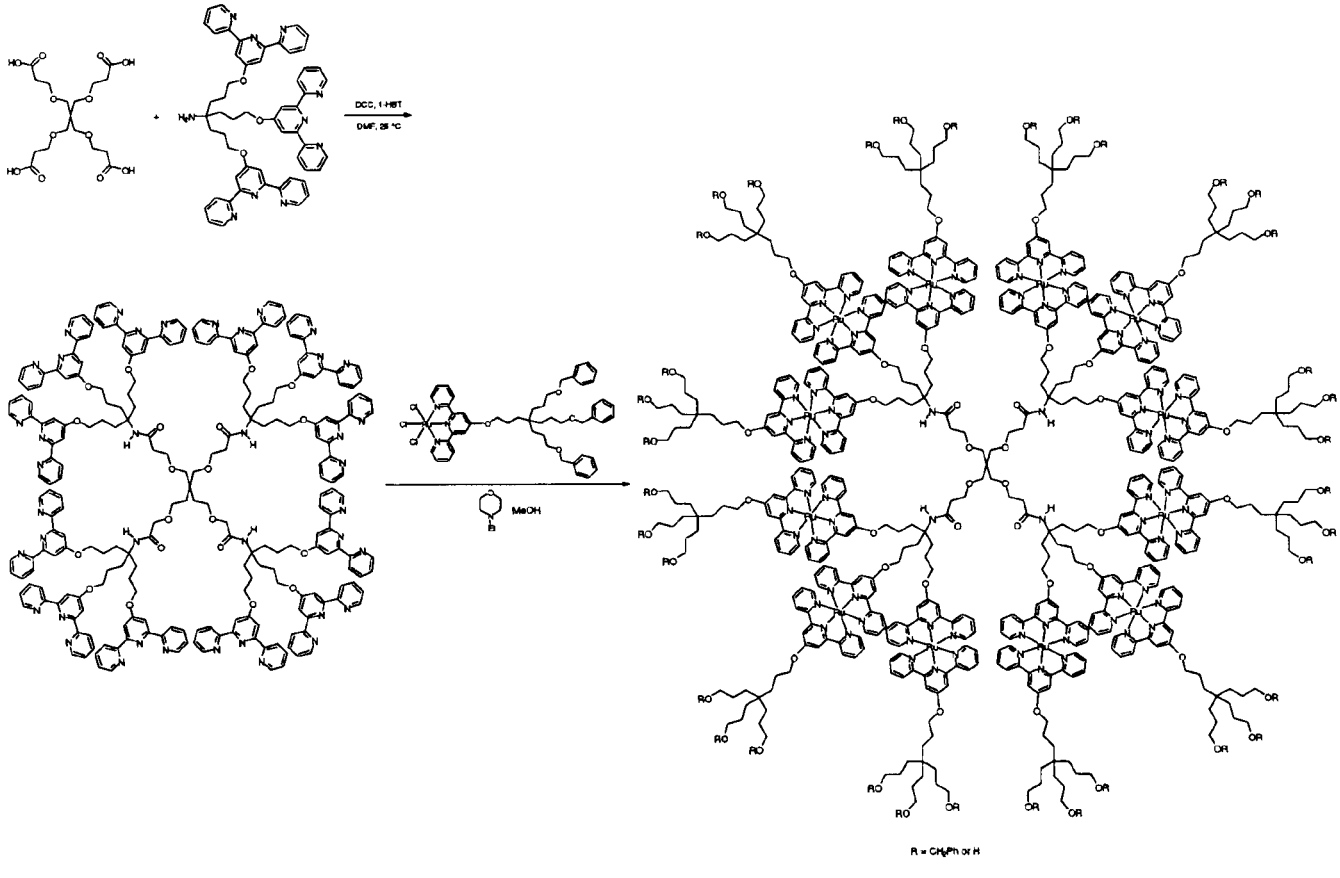
The introduction of diverse specific binding sites into the structural framework of the dendritic skeleton has also been undertaken [19]. Again the ready availability of simple monomeric building blocks, described above, will show the potential to the construction of dendritic arms with incorporated functionality to support chemical and complimentary attachments. To demonstrate this procedure, Scheme 18 shows the one-step route to a functionalized (*e.g.*, 5,5'-bipyridine) dendron (dendritic arm). The subsequent attachment of this arm to the same tetraacid core affords the 1st tiered utilitarian dendrimer. Subsequent construction of the subsequent generation follows the above described procedure with "Behera's amine". Treatment of the tetrafunctionalized dendrimers with simple metal salts afford the corresponding tetracomplexes. The metal centers are localized at the bipyridine loci; NMR studies confirms the location of the metal sites (Figure 9).



Scheme 11



Scheme 13



Scheme 12

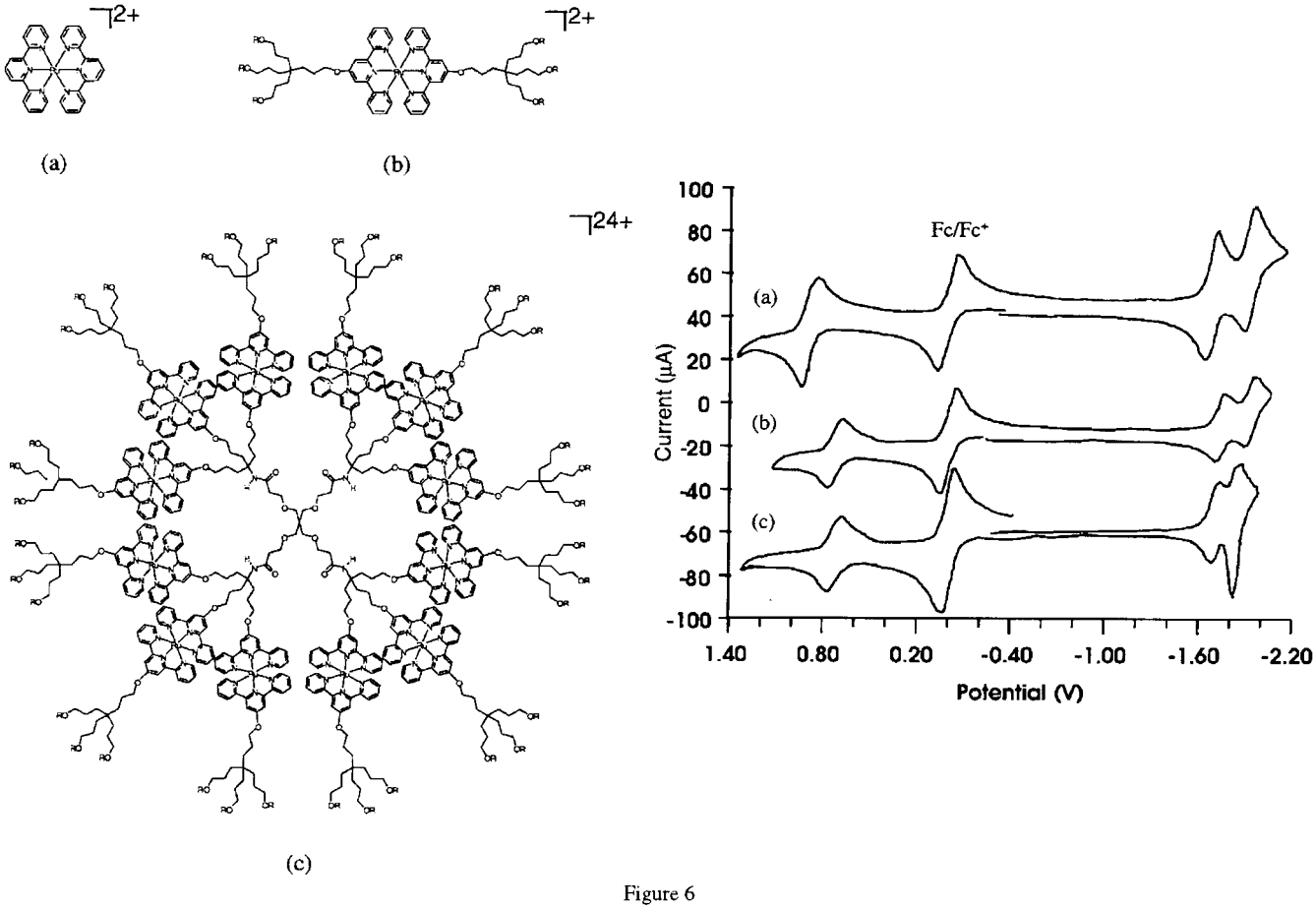
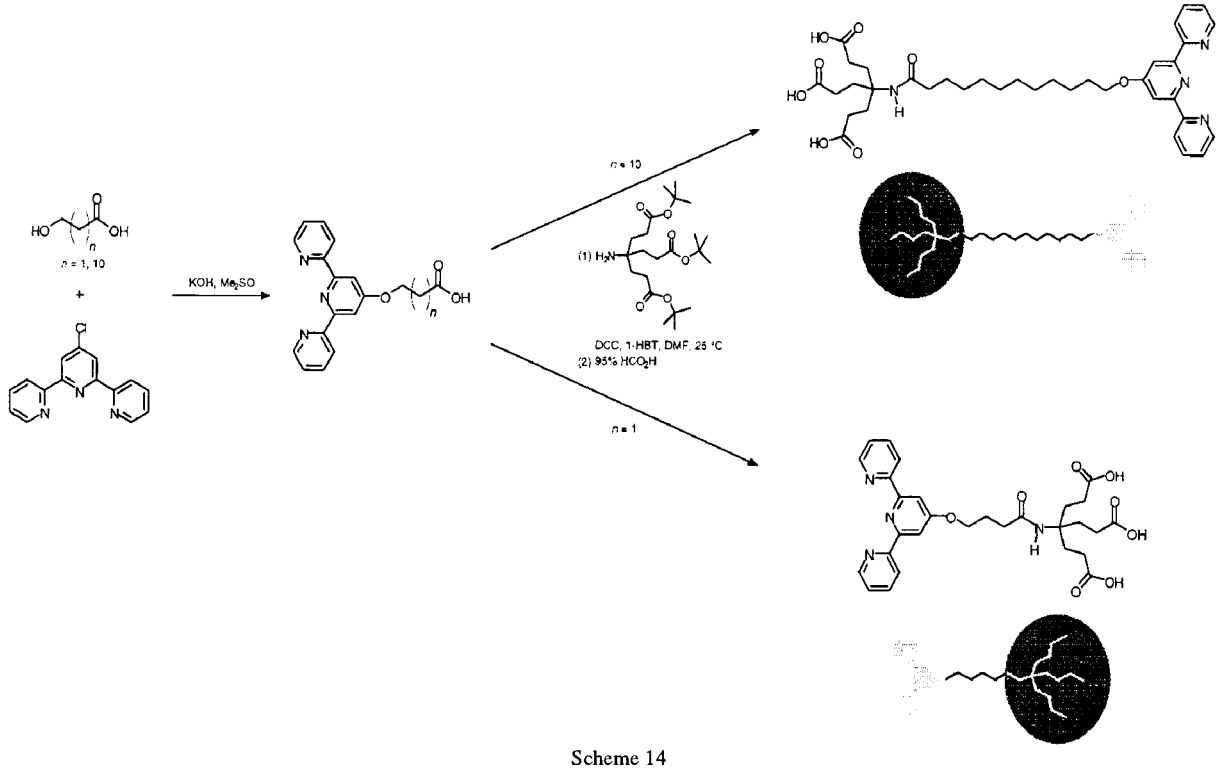
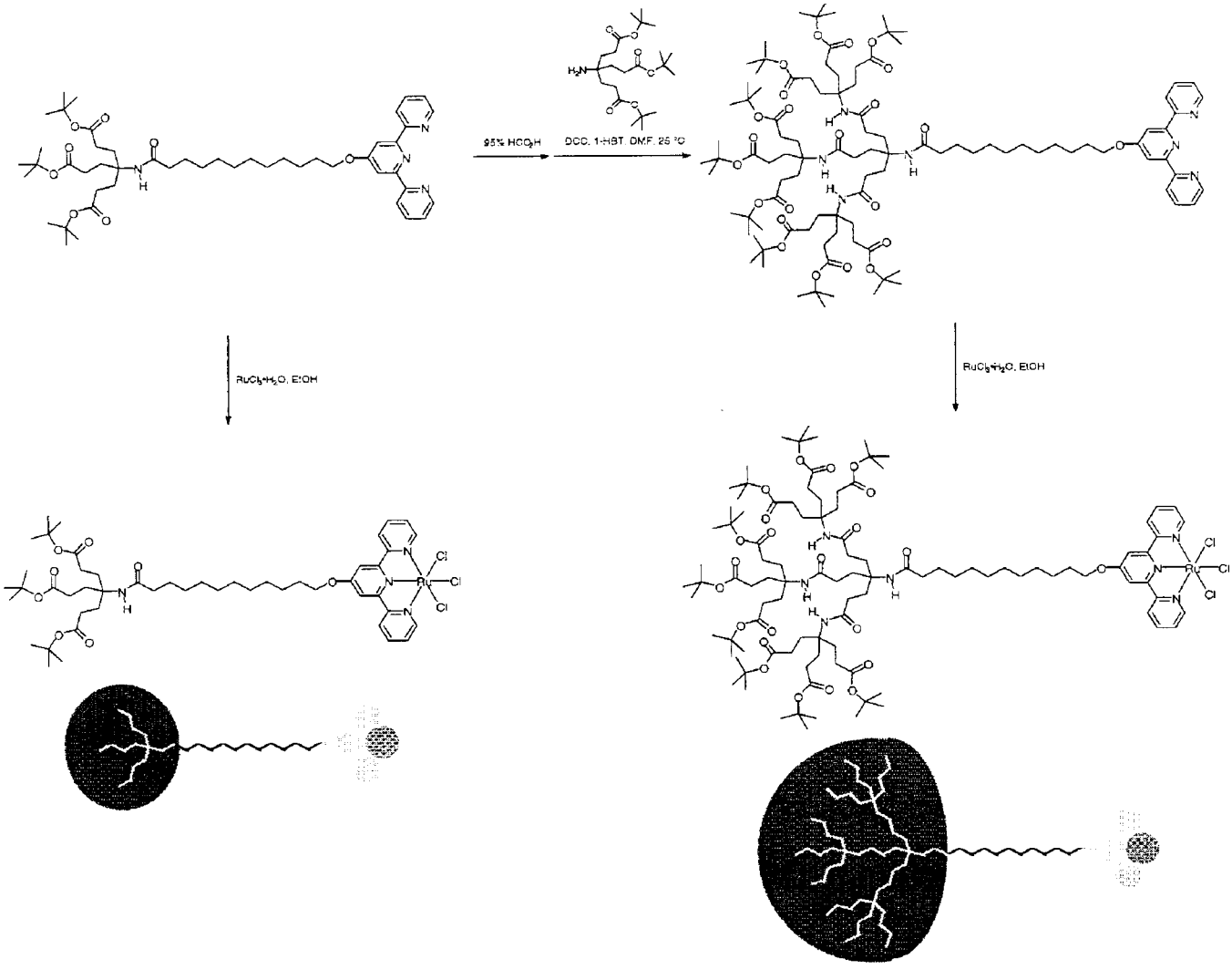


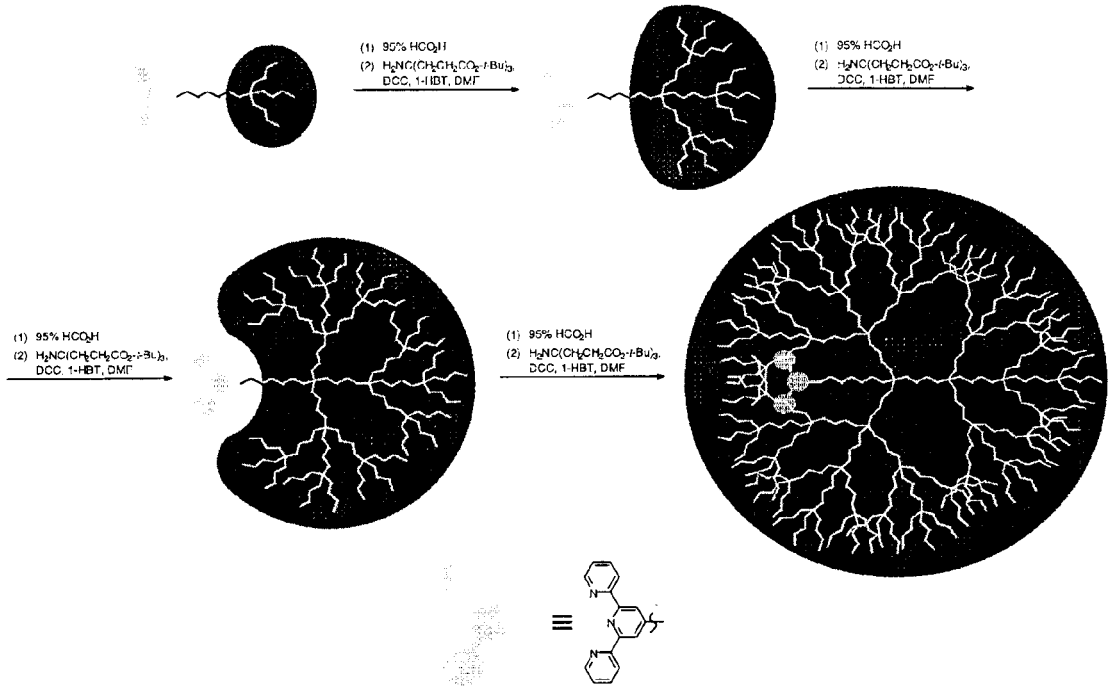
Figure 6



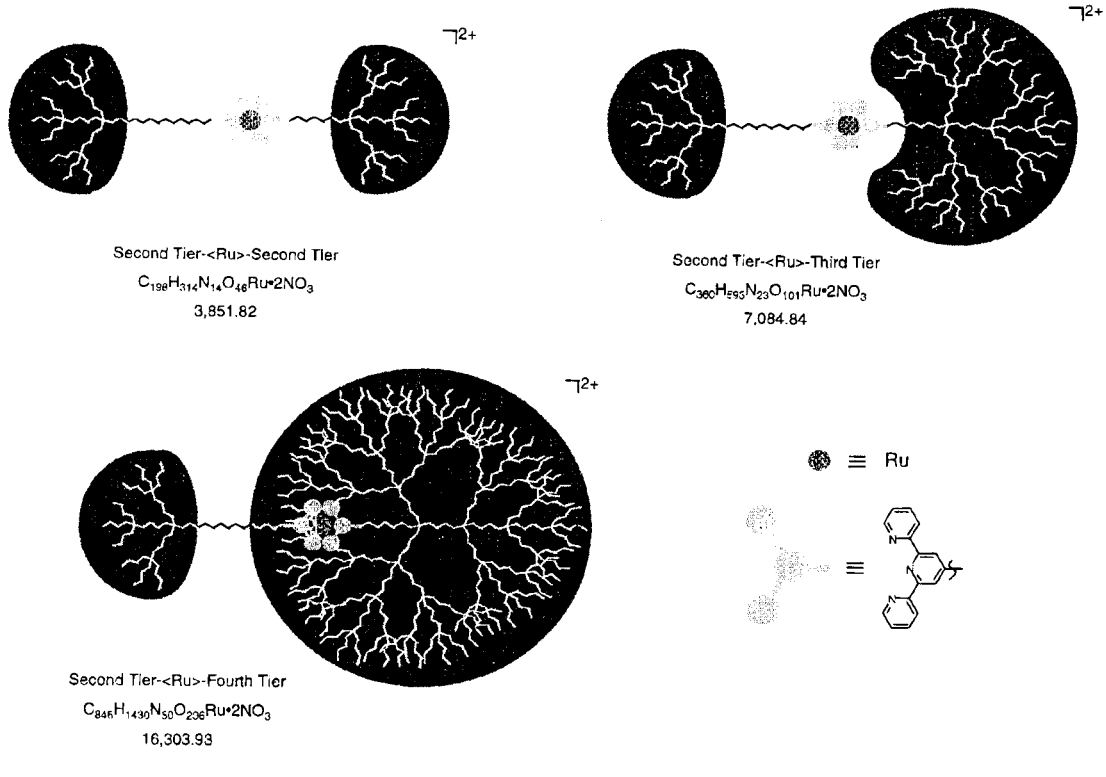
Scheme 14



Scheme 15



Scheme 16



Second Tier-<Ru>-Second Tier
$C_{198}H_{314}N_{14}O_{46}Ru{\cdot}2NO_3$
3,851.82

Second Tier-<Ru>-Third Tier
$C_{360}H_{595}N_{23}O_{101}Ru{\cdot}2NO_3$
7,084.84

Second Tier-<Ru>-Fourth Tier
$C_{846}H_{1430}N_{50}O_{206}Ru{\cdot}2NO_3$
16,303.93

Scheme 17

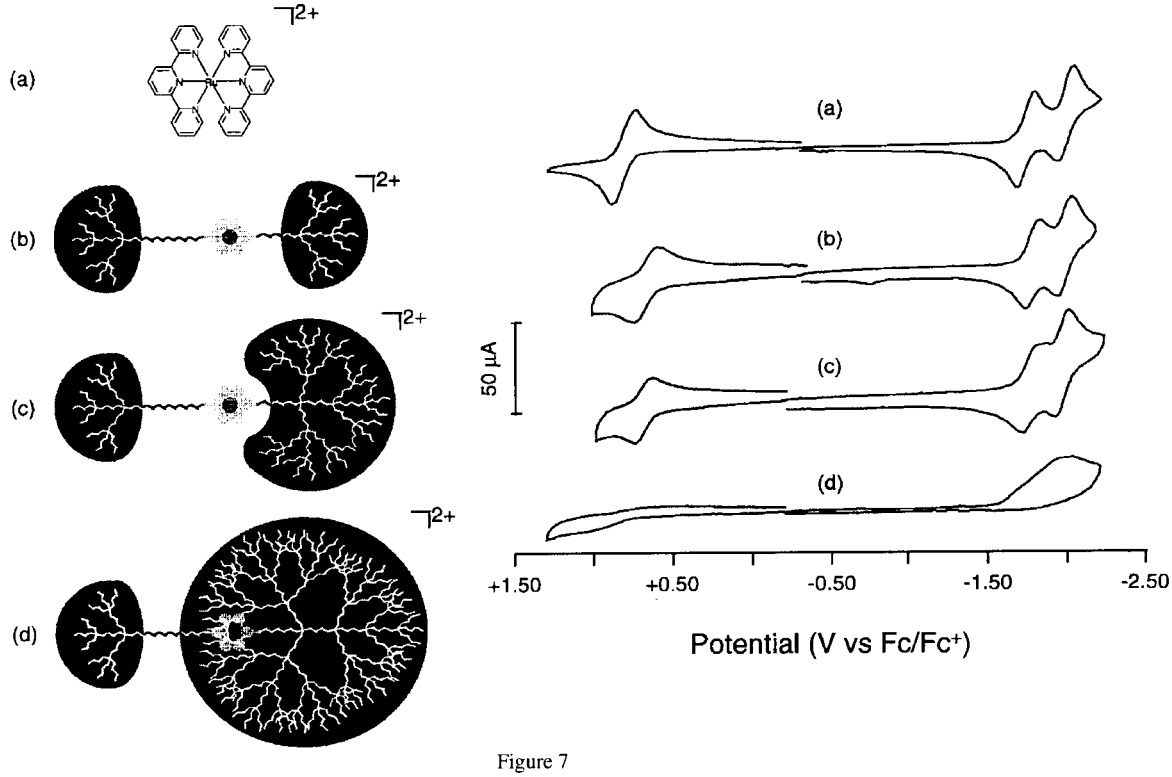


Figure 7

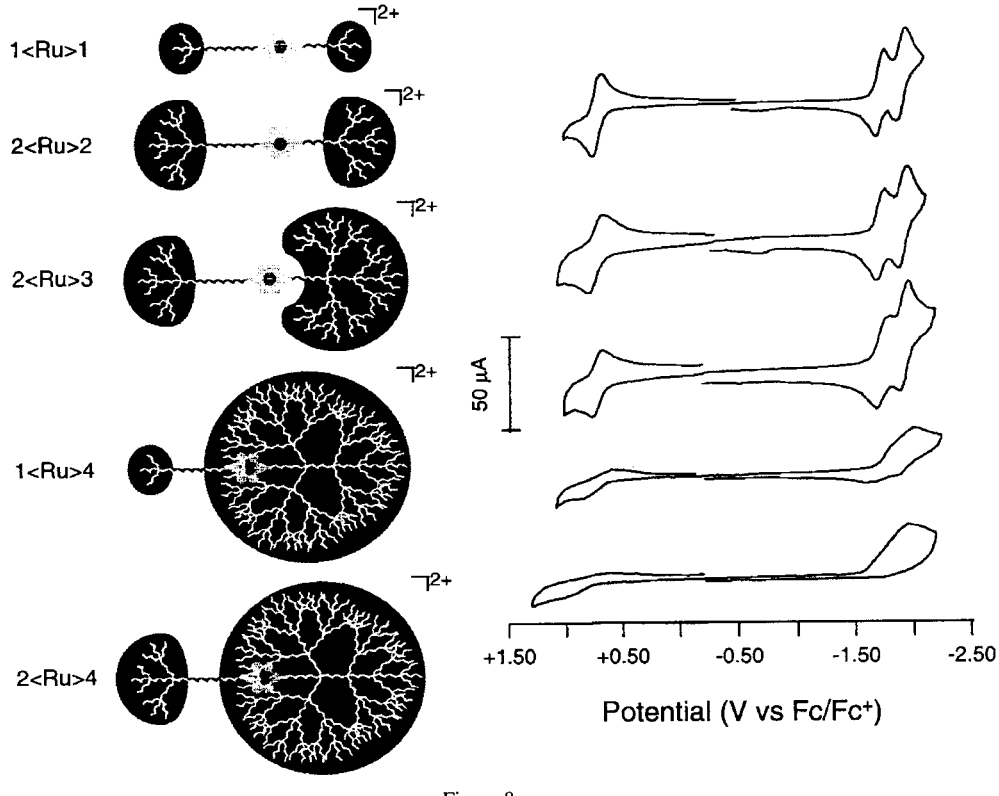
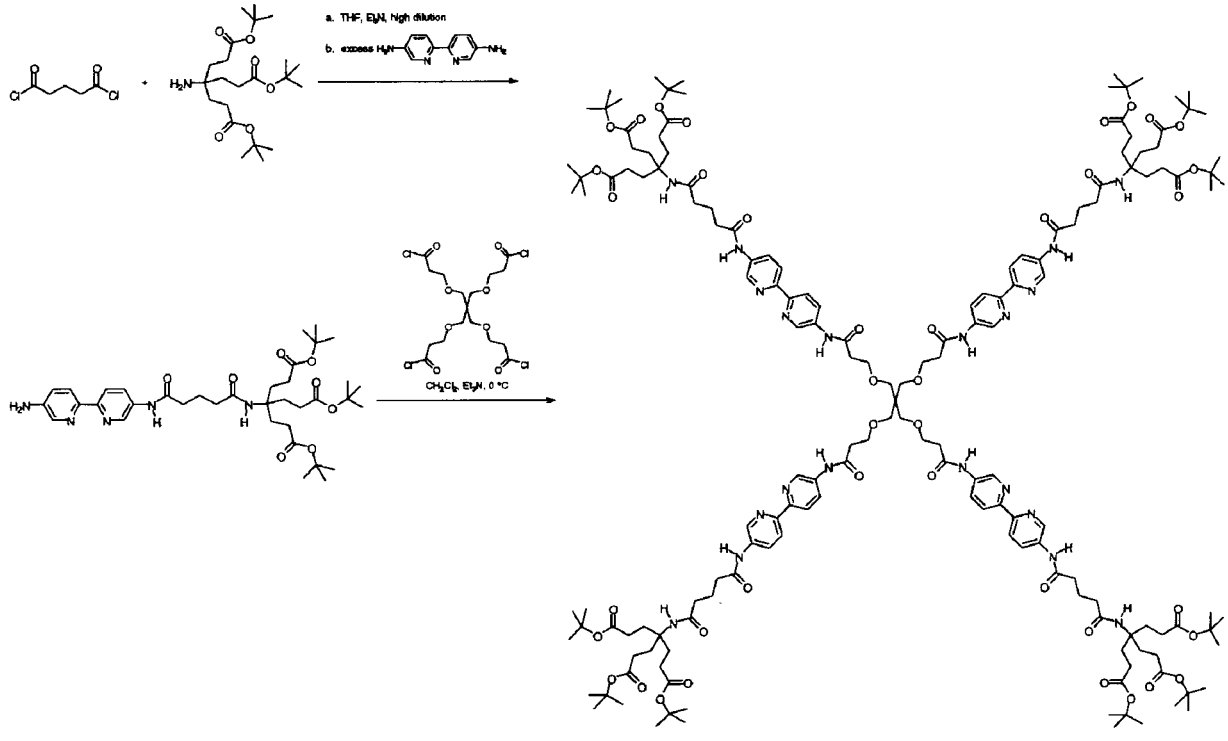


Figure 8



Scheme 18

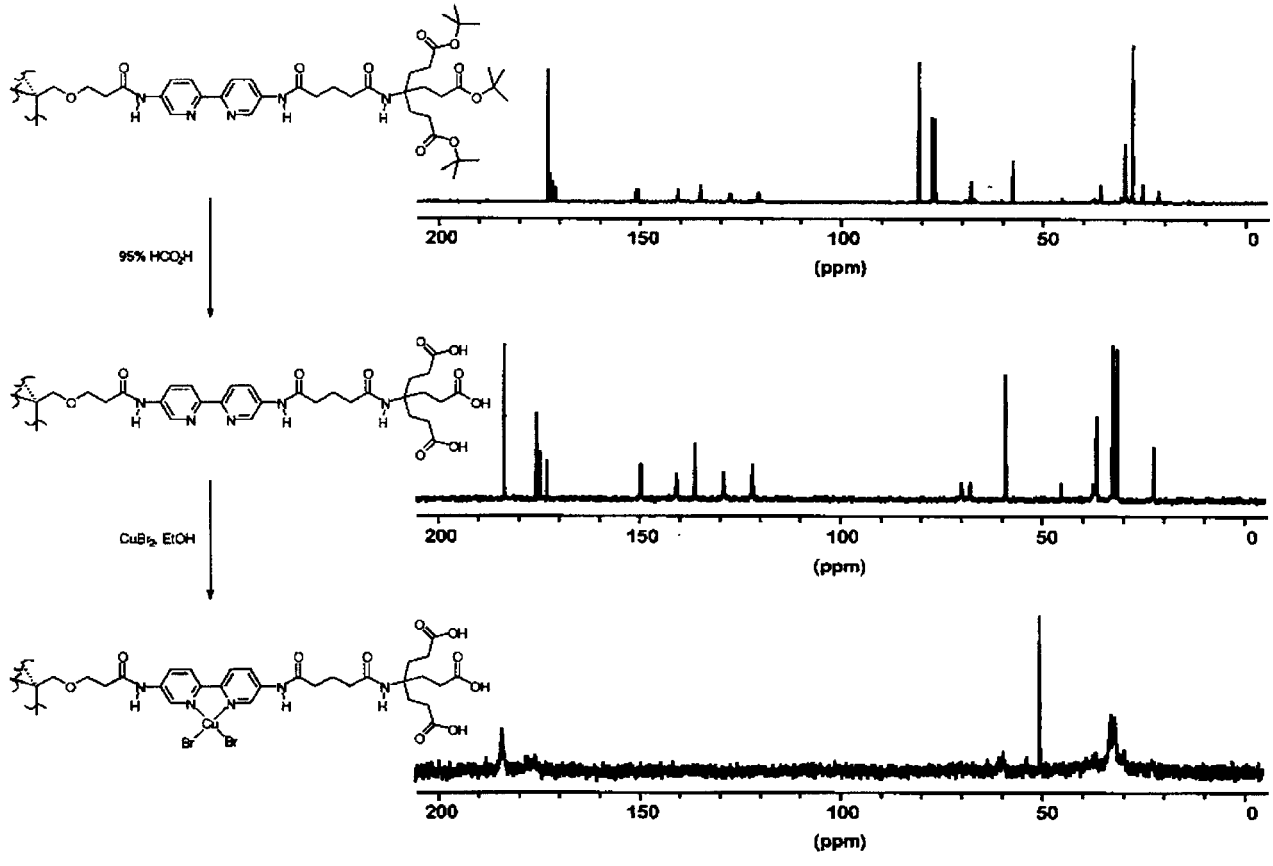


Figure 9

The similar introduction of 2,6-diaminopyridine in the dendritic arm (Schemes 19 & 20) gives entrance to the concept of molecular recognition and guest inclusion within the "void" regions within these cascade macromolecules [20]. Preliminary studies [21] have shown (NMR data) that AZT can be complexed selectively at the diaminopyridine subunit centers (Figures 10 & 11).

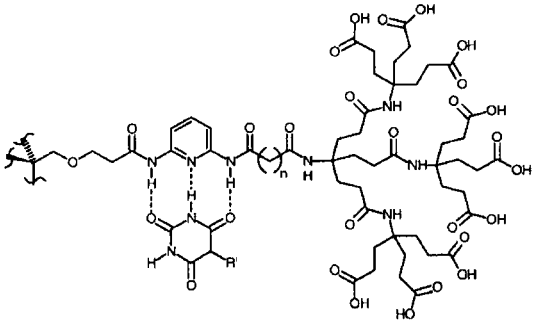


Figure 10

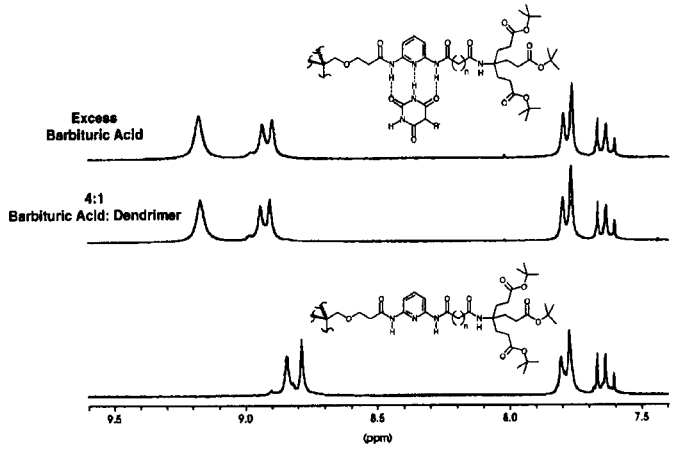
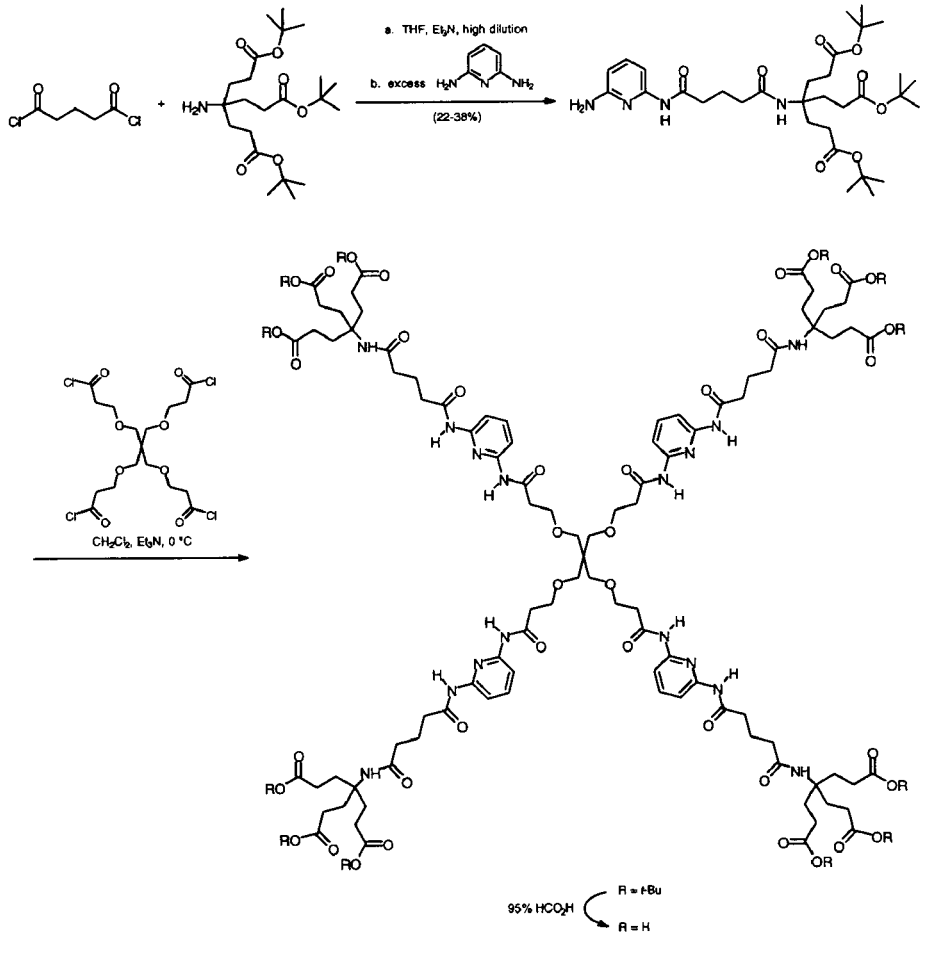
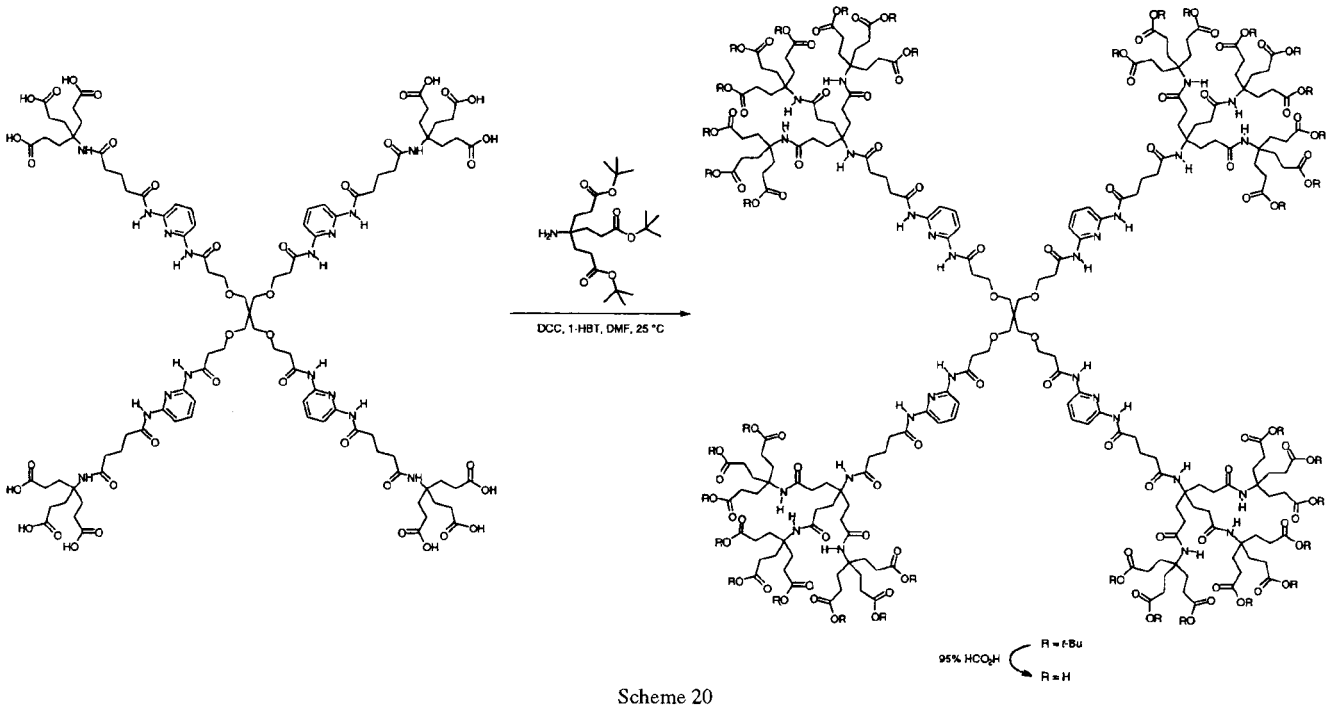


Figure 11



Scheme 19



Scheme 20

Application of heterocyclic chemistry to the "connectology" of dendritic components offers an exciting new frontier to the specific construction of macromolecular assemblies and networks. The simple basic concept is shown in Figure 12 where the linkages are either metal coordination sites or complementary heterocyclic binding loci. The "molecular ceiling", which has constrained the organic chemist for nearly two centuries, has now be broken and the combination of heterocyclic chemistry and dendritic construction opens a wide vista for future exploration.

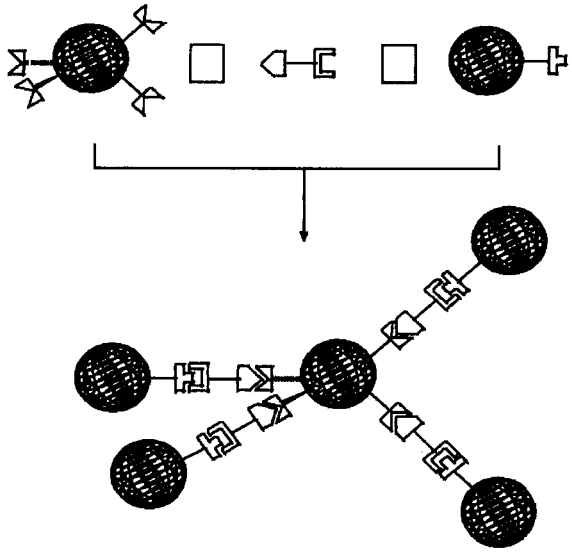


Figure 12

Acknowledgments.

This article covers research conducted over the past decade by a group of excellent coworkers, whose names, in part, appear in the references cited; their efforts and the following support made this presentation possible. This work was supported, in part, by the National Science Foundation (DMR-92-17331; 92-08925), the US Army Office of Research (DAAH04-93-0048), and the Petroleum Research Fund, administered by the American Chemical Society (PRF 26365-AC7,3) as well as Engelhard Industries for furnishing the precious metals.

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