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Metal-Directed Self-Assembly of Ethylenediamine-Based Dendrons

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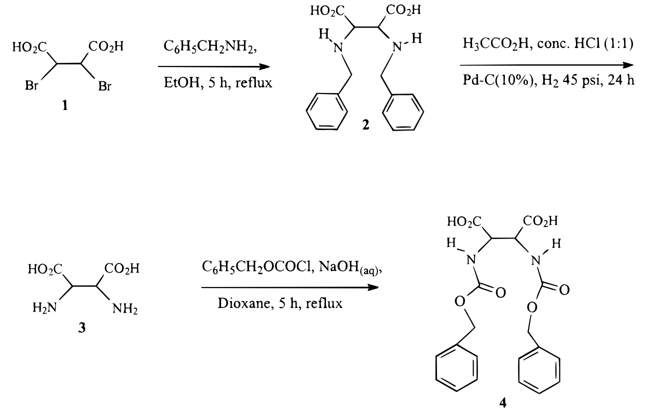
In medicine, it is advantageous to have multiple targeting and reporter moieties. Dendrimers,[1] which are synthetic macromolecules that possess various terminal functional groups, have been used by many researchers to develop diagnostic and therapeutic agents.[2] Monofunctional dendritic metallomacromolecules have interesting magnetic, electronic, photooptical, electrochemical, or catalytic properties.[3] By mixing and matching the appropriate dendrons, dendritic metallomacromolecules offer the potential to prepare multifunctional compounds. The goal of our research is to develop molecules with multiple targeting moieties to study the tumor environment in vivo. We have chosen a Co(III) metal core and ethylenediamine-based dendrons because of the potential biological compatibility, the low dissociation constant, and the temperature sensitivity of the Co(III) chemical shift observed for the model ion−ligand complex, Co(en)$_3$Cl$_3$.[4] The potential biocompatibility depends on dose and arises from the nutritional requirement for Co and the observations that cobalt (III) is a cofactor in vitamin B$_{12}$ and that EDTA is used in treating heavy metal poisoning and as a food additive.[5] While these observations outline the biocompatibility of the building blocks and bode well for the combination, it does not guarantee the biocompatibility of the complex.

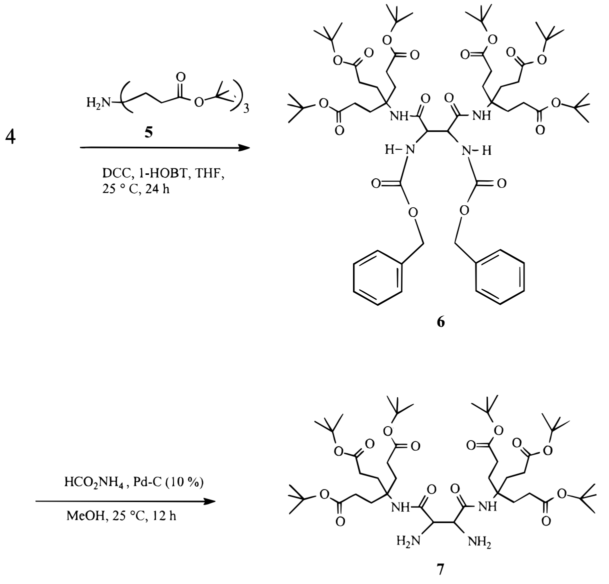
A major interest exists in the self-assembly of dendrons into dendrimers.[6] In this communication, we present our initial efforts in preparing a Co(III)-based self-assembling metallodendrimer using a convergent approach. We used a six-arm ethylenediamine backbone-based dendron, although the two- and four-arm versions can also be prepared. Three of these dendron bidentate ligands self-assemble around a Co(III) center. We followed the procedure described by Liao and co-workers[7] to construct diacid **4** starting from *meso*-dibromosuccinic acid **1** (Scheme 1). Refluxing a 2:1 mixture of benzylamine and **1** in ethanol afforded **2** (80%), which provided (88%) diamine **3** upon hydrogenation (3 atm of H$_2$) in a 1:1 HOAc/HCl medium over Pd/C. Compound **3** on treatment with carboxybenzyl chloride in a mixture of dioxane and aqueous NaOH solution produced **4** (62%).

Treatment of the diacid **4** with amine **5** under DCC-coupling conditions[8] afforded (60−65%) dendron **6**. We followed the procedure reported by Newkome and co-workers[9] to obtain building-block **5** in two steps from nitromethane and *tert*-butyl acrylate. Purification of **6** was easily achieved using column chromatography (SiO$_2$, CH$_2$Cl$_2$/EtAc). Evidence for the formation of **6** was obtained from the signals observed at δ 28.2 (CH_3); 29.5, 29.6 ($CH_2CH_2CO_2$); 56.4 ($NH^{4\circ}C$); 58.0 (CH); 67.8 ($C_6H_5CH_2$); 80.6 [$C(CH_3)_3$]; 128.4, 128.7, 128.5, 135.9 (C_{Ar}); 156.4 ($NHCO_2$); 170.6 ($CONH$); and 172.8 ($CH_2CH_2CO_2$) ppm in its ^{13}C (DCCl$_3$) spectrum and also from the intense peaks seen in its mass spectrum (MALDI-TOF-MS) at 1233.5 (M$^+$+Na) and 1249.44 (M$^+$+K).

Scheme 1. Synthesis of Diacid 4



Scheme 2. Synthesis of First-Generation EDA−Dendron 7



Deprotection of the carboxybenzyl protecting groups in **6** was smoothly achieved (95%) by overnight stirring of its methanolic solution with Pd−C (10%) and anhydrous ammonium formate.[10] Formation of diamine **7** (Scheme 2) was verified by signals at δ 28.1 (CH_3); 29.67, 29.73 (CH_2CH_2); 57.27 ($CHNH_2$); 57.48 ($^{4\circ}CNH$); 80.56 (CO_2C); 172.55 ($CONH$); and 172.64 (COO) ppm in its ^{13}C NMR spectrum (DCCl$_3$) and the absence of aromatic protons was also confirmed in its ^{1}H spectrum. An intense molecular ion peak in the mass spectrum (FAB, calcd MW: 943.2) at 943.6 amu provided further proof for the formation of the diamine macromolecule **7**.

Self-assembly of the first generation dendrimer was achieved by a modified procedure of Work for the preparation of Co(en)$_3$Cl$_3$.[11] Three equivalents of **7** were treated with 1 equiv of CoCl$_2$·6H$_2$O in methanol with

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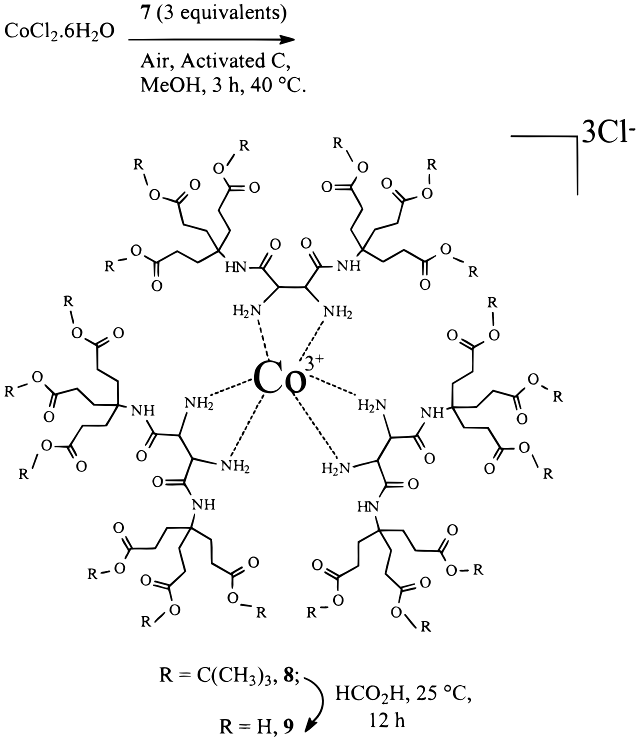
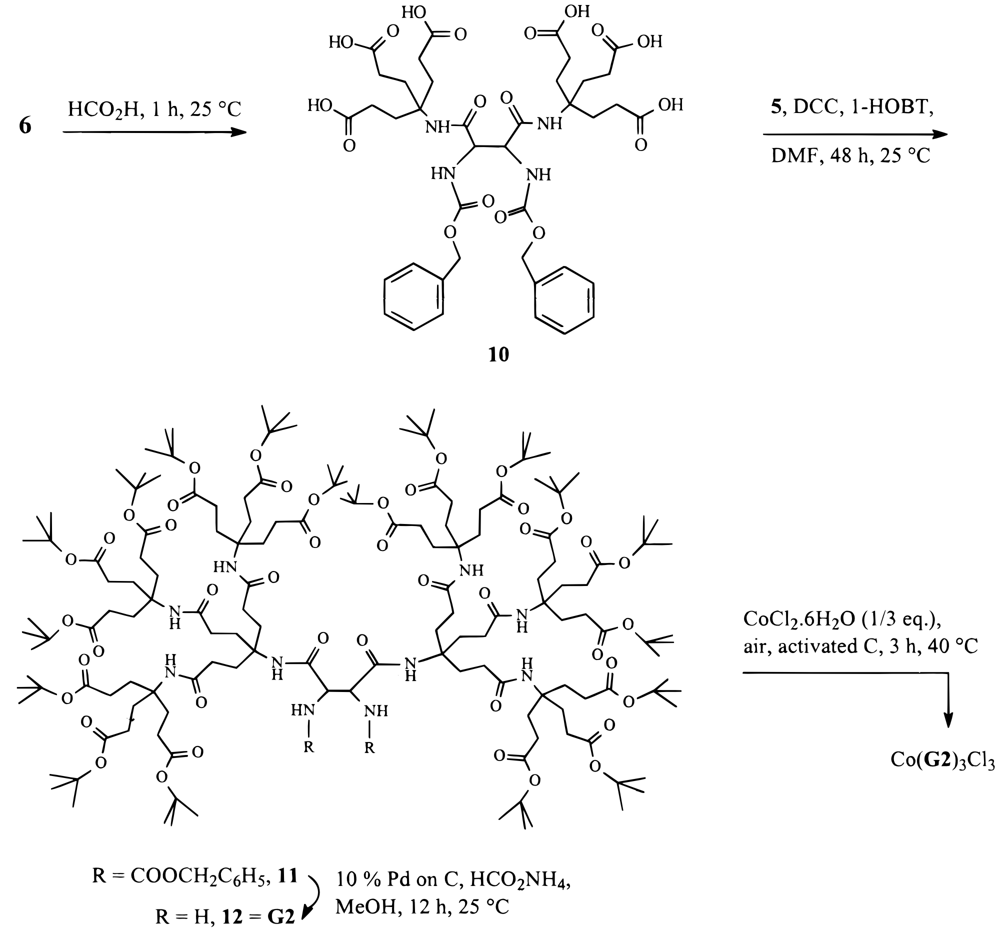
Scheme 3. Syntheses of First-Generation Dendritic Cobalt Complexes 8 and 9



some activated charcoal (Scheme 3). The mixture was heated in an open round-bottom flask at 40 °C for 3 h with air being bubbled into the mixture during the reaction. The crude product after purification on a short column (SiO_2, CH_2Cl_2/EtAc) afforded (98%) an orange-brown, lustrous powder **8**. The NMR spectrum ($DCCl_3$, ^1H) of **8** was similar to that of diamine **7**. The ^{13}C NMR spectrum of **8**, however, showed a downfield shift (δ 64.9 ppm) for the carbon atoms bearing the amine moieties when compared to the same in **7** (δ 57.3 ppm). This shift can be attributed to the free electrons on the amines being shared by the Co core in **8**. The absorption for the NH_2 stretching in the FT-IR spectrum of **7** was seen as a broad band (3200−3500 cm^{-1}) instead of a doublet. As **7** is moisture-sensitive, this could be due to the hydrogen bonding with water molecules. This absorption was absent in the FT-IR spectrum of **8**, suggesting association of the amine electrons with the Co core. Additional evidence for the formation of self-assembled dendrimer **8** was obtained from elemental analysis data.[12] The mass spectral data obtained by both FAB and ESI methods displayed clusters of peaks to account for species obtained by loss of chloride ions and *tert*-butyl groups attached to **8** and for species obtained by loss of one and two of the dendrons attached to **8**. (The MS-data for all the dendritic Co-complexes synthesized showed similar disintegration patterns). This dendritic metal complex **8** is extremely soluble in organic solvents, even petroleum ether. The diamine **7**, however, was insoluble in petroleum ether. Compound **8** was further characterized by UV−vis spectroscopy (Figure 1). The UV−vis spectrum of the dendrimer shows both the broad shoulder of the dendron and the characteristic d−d absorption bands at wavelengths 339 and 466 nm as expected for a Co(III) complex ligated by amine

Scheme 4. Construction of Second-Generation EDA−Dendron 12 and Its Cobalt Complex Co(G2)$_3$Cl$_3$



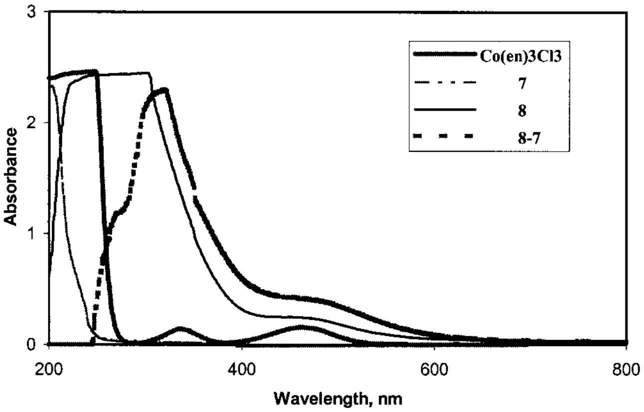


Figure 1. UV spectra of Co(en)$_3$Cl$_3$ in H$_2$O: **7**, **8**, and **8**−**7** in MeOH.

ligands [e.g., Co(en)$_3$Cl$_3$]. Treatment of **8** with formic acid hydrolyzed the terminal *tert*-butyl ester groups, affording (80%) polyacid **9** which could be rendered water soluble (pH = 7.5). Both ^{13}C and ^{1}H NMR (D$_2$O, KOH) spectra of **9** confirmed the loss of the *tert*-butyl ester groups.

Compound **6** on treatment with formic acid (12 h, 25 °C) afforded hexaacid **10** (80%). (Scheme 4) The absence of the intense peaks (^{13}C NMR, D$_2$O/KOH) due to the *tert*-butyl ester moiety at 28.2, 80.6, and 172.8 ppm and the appearance of a peak at 182.2 ppm accounting for the new carboxylic acid carbon provided evidence for the formation of **10**. This was also verified by the^{1}H NMR signals. An intense peak at *m*/*z* 875.2 (FAB-MS, calcd mass 874.9 amu) in the mass spectrum provided additional supporting evidence for the purported structure of **10**. Treatment of hexaacid **10** with amine **5** under DCC coupling conditions afforded (65%) **11** [FAB-MS 3260, calcd MW 3260 amu]. Deprotection of the carboxybenzyl groups on **11** yielded (90%) second-generation dendron (**12** = **G2**, FAB-MS 2992, calcd MW 2992). Second-generation cobalt complex Co(**G2**)$_3$Cl$_3$ (structure not shown) was obtained (90%) from **12** using the procedure that was followed for **8**. The NMR and UV−vis spectra for the second-generation dendrons and the Co complex possess features similar to their first-generation cousins. All new compounds gave satisfactory spectral, elemental, and mass data.

Currently we are focusing our attention toward the construction of higher generation dendrons and testing the limits of "steric" effects by the dendritic branches on the availability of the free amino groups for Co^{3+} complexation. Additionally, attaching chosen target molecules to the surface functional groups of these dendrons before complex formation is also under intense investigation. It should be noted that dendron **7** and its higher generation analogue **12** could be resolved into their optically active enantiomers. However, in this study their racemic mixtures were used.

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(12) Selected data for **8**, $C_{144}H_{258}N_{12}O_{42}CoCl_3$. Found: C, 57.73; H, 8.58; N, 5.63; Cl, 3.65; Co, 1.92. Requires: C, 57.75; H, 8.68; N, 5.61; Cl, 3.55; Co, 1.97. ^{1}H NMR (400 MHz, DCCl$_3$): δ 1.42 (s, 162 H, CH_3), 1.98 (t, 36 H, CH_2CO$_2$), 2.22 (t, 36 H, CH_2CH$_2$), 2.40 (s, br, 12 H, NH_2), 3.6 (s, 6H, NH), 3.8 (s, 6H, CH). ^{13}C NMR: δ 28.2 CH$_3$, 29.8, 29.9 (CH$_2$$CH_2$), 57.4 CNH, 65.0 CHNH$_2$, 80.7 C(CH$_3$)$_3$, 172.6 CONH, 172.7 COO. **Elem. Anal. (C, H, N) data for all new compounds.** ***6***, $C_{64}H_{98}N_4O_{18}$. Found: C, 63.23; H, 7.97; N, 4.49. Requires: C, 63.45; H, 8.15; N, 4.62. ***7***, $C_{48}H_{86}N_4O_{14}$. Found: C, 60.98; H, 9.18; N, 6.02. Requires: C, 61.12; H, 9.19; N, 5.94. ***9***, $C_{72}H_{114}N_{12}O_{42}CoCl_3$. Found: C, 43.59; H, 5.67; N, 8.35. Requires: C, 43.57; H, 5.79; N, 8.47. ***10***, $C_{40}H_{50}N_4O_{18}\cdot H_2O$. Found: C, 53.97; H, 5.78; N, 6.28. Requires: C, 53.81; H, 5.87; N, 6.27. ***11***, $C_{172}H_{284}N_{10}O_{48}$. Found: C, 63.75; H, 8.76; N, 4.30. Requires: C, 63.37; H, 8.78; N, 4.30. ***12***, $C_{156}H_{272}N_{10}O_{44}$. Found: C, 62.57; H, 9.00; N, 4.63. Requires: C, 62.63; H, 9.16; N, 4.68. *Co(G2)$_3$Cl$_3$*, $C_{468}H_{816}N_{30}O_{132}CoCl_3$. Found: C, 61.27; H, 8.94; N, 4.62. Requires: C, 61.49; H, 9.00; N, 4.60.

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