Cascade molecules. Part 6. Synthesis and characterization of two-directional cascade molecules and formation of aqueous gels

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Synthesis and Characterization of Two-Directional Cascade Molecules and Formation of Aqueous Gels[1a]

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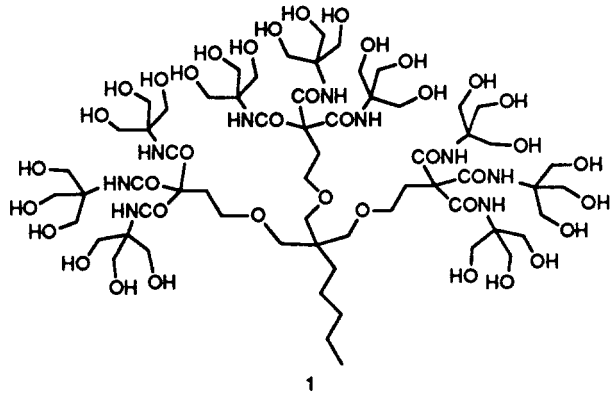
Abstract: Numerous two-directional cascade molecules (arborols) have been prepared via a simple two-step procedure. These cascade molecules have been abbreviated as [*m*]-*n*-[*m*] arborols, where *m* is the number of hydroxyl moieties on the cascade spherical surface and *n* is the number of methylenes connecting the cascade spheres. Several of the arborols in the [9]-*n*-[9] and [6]-*n*-[6] series form thermally reversible aqueous gels; properties of these gels are discussed. An aggregation model is proposed for the gel-forming molecules; preliminary molecular modeling calculations and electron micrograph data support this model.

Introduction

The synthesis of the model arborol **1**[2] provided the foundation for the synthesis of other cascade molecules. We consider arborol **1** to be a "one-directional" cascade polymer in that it possesses a central "trunk" (core) attached to a single cascade sphere. An obvious extension of this concept was the attachment of additional cascade spheres to the hydrocarbon backbone (or central core).



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Addition of a second sphere should affect the aggregation of the arborols by changing the overall topology; attachment of additional spheres may eventually lead to a *unimolecular* micelle, i.e. a highly branched, specifically shaped structure with an aggregation number of one. The attachment, or construction, of cascade spheres onto each end of a hydrocarbon chain forms a *two-directional* arborol.

In following an organic "tree" analogy,[3] the lipophilic core of these two-directional molecules should solubilize hydrocarbons in an aqueous environment. The chemical and physical properties of these arborols will depend upon several factors: the length of the hydrocarbon backbone, the incorporation of functionality along the backbone, the flexibility of the backbone, the size of the cascade spheres, and the size, shape, and functionality of the organic species itself. For example, an arborol possessing a central unsaturated moiety should permit chemical modification within the lipophilic region. Construction of the arborol with a catalytic moiety appended to the lipophilic backbone should provide an enzymatic model where catalysis occurs at a lipophilic site within a hydrophilic environment.[4]

The synthesis of a series of two-directional arborols was undertaken to explore their properties, and herein we report the results. Attachment of the molecular spheres was shortened[2] to a two-step procedure: reaction of an α,ω-dibromoalkane with either ethyl sodiomethanetricarboxylate or methyl sodiomalonate, followed by amidation with tris(hydroxymethyl)aminomethane ("Tris"). This shortened procedure gave high overall yields while providing sufficient surface hydroxyl moieties per sphere to impart the desired water solubility. These spheres are not as highly branched or extended as those of arborol **1**, or those of Tomalia and co-workers;[5] however, CPK molecular models show that each terminal sphere has a radius of ca. 12 Å. We have abbreviated the nomenclature for this family of cascade molecules as [*m*]-*n*-[*m*] arborols, where *m* designates the number of terminal groups for each sphere and *n* denotes the length of the hydrocarbon bridge. The hydrocarbon (lipophilic) backbone connecting the two spheres generates an inner region, which should be highly compressed in aqueous solution, in the absence of aggregation (see Figure 1). This concept was verified by molecular modeling[6] of a [9]-10-[9] arborol. Several of the arborols formed thermally reversible aqueous gels ([9]-*n*-[9]: $10 \le n \le 13$; [6]-*n*-[6]: $8 \le n \le 13$), which were characterized via optical and electron microscopy, and light scattering techniques.

Synthetic Aspects

The first series of two-directional arborols was prepared by a two-step nucleophilic substitution-amidation procedure. The hexaethyl esters **2a-k** were prepared (72-82%) by the reaction of the appropriate α,ω-dibromoalkane with $NaC(CO_2Et)_3$ in a C_6H_6-DMF (1:1) solvent mixture at 90 °C for 24 h; shorter reaction times resulted in the recovery of some unchanged starting material. Because of the essentially hydrocarbon backbone of **2a-k**, the ^1H NMR spectra were quite simple: a triplet (δ 1.21, J = 7.1 Hz) and a quartet (δ 4.20, J = 7.1 Hz) for the ester methyl and methylene, respectively, and a broad singlet (δ 1.50) for the

(1) (a) Cascade Molecules Part 6. For Part 5, see: Newkome, G. R.; Moorefield, C. N.; Theriot, K. J. *J. Org. Chem.* **1988**, *53*, 5552. (b) Department of Chemistry, University of South Florida. (c) Visiting scholar from the Tokyo Metropolitan University, Tokyo, Japan. (d) Department of Biology, University of South Florida. (e) Louisiana State University. (f) Undergraduate.

(2) Newkome, G. R.; Yao, Z.-Q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.

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(6) Preliminary calculations using QUANTA/CHARMm: Polygen Corporation, 200 Fifth Avenue, Waltham, MA 02254. For a description of the CHARMm force field, see: Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187-217.

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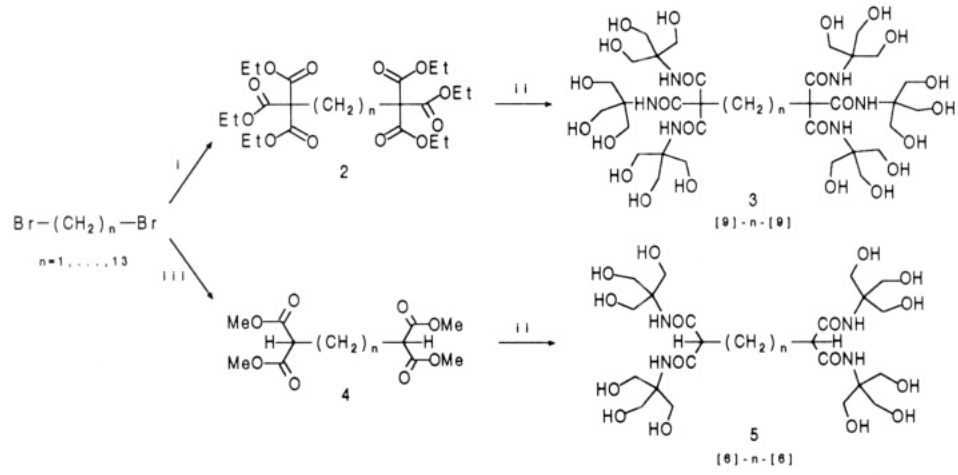
Scheme I[a]



[a] (i) $NaC(CO_2Et)_3$, C_6H_6–DMF, 90 °C; (ii) $H_2NC(CH_2OH)_3$, Me_2SO, K_2CO_3, 25 °C; (iii) $H_2C(CO_2Me)_2$, K_2CO_3, DMF, 25 °C.

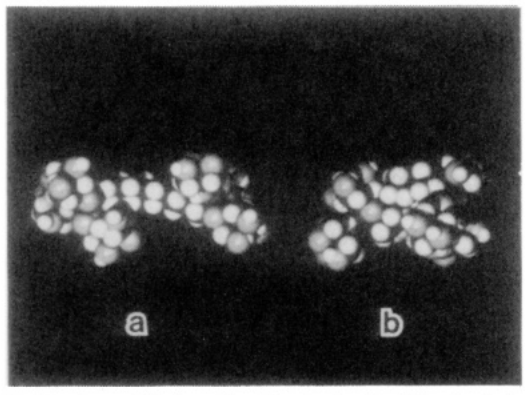


Figure 1. Topology of the two-directional arborols: (a) extended and (b) compressed conformations.

bridging methylenes. The infrared spectra of these hexaesters are all similar, characterized by a C=O stretch at ca. 1740 cm^{-1} and C—O stretches at 1267 and 1223 cm^{-1}.

The ^{13}C NMR spectra confirmed the proposed structures of **2a–k**, since unique resonances were obtained for each of the carbons. The triester moiety has four characteristic peaks: ca. δ 14 for the OCH_2CH_3; ca. δ 62 for the OCH_2CH_3; ca. δ 65.8 for the C_{quat}; and ca. δ 168 for the C=O. The methylene adjacent to the triester has a chemical shift of ca. δ 33.5. The bridging methylene carbons have chemical shifts in agreement with empirical values.[7,8]

Hexaethyl esters **2a–k** were converted to the desired [9]-*n*-[9] arborols **3a–k** by reaction with Tris in Me_2SO at 70 °C via the previously described procedure (Scheme I);[2] however, purification of the products proved extremely difficult. Similar solubility properties of the [9]-*n*-[9] arborols and Tris made separation by precipitation impossible; thus, a modification of reaction conditions was deemed appropriate and several variations were investigated. On the basis of the results of Prelicz et al,[9] reaction of **2d** with Tris neat at 120–140 °C was attempted; however, only a paucity of **3d** was obtained with the remainder of the material as intractable brown solid.

The next variation was the attempted amidation of hexaester **2d** in a suitable solvent without added base; Me_2SO was again chosen since it solubilized both reagents (hexaester and Tris) and allowed reaction temperatures above 100 °C. When a Me_2SO solution of hexaester **2d** and Tris was stirred for 15 h at 25 °C, unreacted ester **2d** and amine were recovered (>90%), as determined from the ^{13}C NMR spectra of the CH_2Cl_2 and water soluble components, respectively. Similar results were obtained when this reaction was repeated at higher temperatures (up to 130 °C); however, addition of anhydrous K_2CO_3 to the reaction at 130 °C caused a color change (clear to light yellow) in approximately 30 min. NMR analysis of the crude product mixture showed the presence of the desired arborol **3d**, some unreacted Tris, and *no trace of unreacted ester*. Decreasing the reaction temperature to 25 °C and using an exact 6:1 molar ratio of Tris to ester afforded (88–93%) the [9]-*n*-[9] arborols, which were free of unreacted Tris. Reaction of Tris with these triesters has been erratic, and sometimes results in extensive decarbalkoxylation to give the corresponding [6]-*n*-[6] arborol and several byproducts.

The ^1H NMR spectra of **3** were quite simple, each consisting of a broad singlet (δ 1.5) for bridging methylenes, a broad singlet (δ ~3.7) for exterior hydroxymethylenes, and a broad singlet (δ ~5.2) for amide hydrogen. Complete transformation from **2** to **3** was verified by ^{13}C NMR spectroscopy: an 8 ppm downfield shift of C=O (**2** (δ ~167) to **3** (δ ~175)), disappearance of the OCH_2CH_3 resonances (**2** (δ 62.2 and 14.0, respectively)), and appearance of NHC and CH_2OH resonances (**3** (δ 64.8 and 63.2, respectively)).

Acceptable elemental analyses of **3** proved difficult partly due to their hygroscopicity; attempted drying (70 °C, 1 mm) did not improve the results. Thus, the purities of **3** were established by the absence of extraneous peaks in the ^{13}C NMR spectra (>95%) and reversed-phase HPLC (>97%). Further proof of their structures was obtained by preparation of the acetate derivatives via standard conditions;[10] the [9]-*n*-[9] arborols (**3**) decarboxamidate under the reaction conditions to give an acetate identical (^{13}C NMR spectra) with that formed by the corresponding [6]-*n*-[6] arborol (**5**). The ^{13}C NMR spectra have signals at ca. δ 20.5 for $COCH_3$, ca. δ 55.7 for CH, ca. δ 57.7 for NHC, ca. δ 62.0 for CH_2OAc, and ca. δ 170.2 and 171.2 for CO_2 and CONH, respectively.

The IR spectra of arborols **3** are practically superimposable; there is a broad O–H stretch at ca. 3320 cm^{-1} and C–H stretches at 2953, 2924, 2855 cm^{-1}. The presence of the amide moiety was indicated by amide I (1651 cm^{-1}) and amide II (1628 cm^{-1}) bands and the absence of an ester carbonyl stretch (1740 cm^{-1}). The ultraviolet spectra of these arborols show only one absorption (e.g., **3h** λ = 212 nm, ϵ = 4674 L mol^{-1} cm^{-1}). Attempted melting point determinations for the [9]-*n*-[9] arborols **3** resulted in effervescent decomposition over a broad temperature range (ca. 120–160 °C). Heating the arborols at these temperatures probably causes ox-

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(9) Prelicz, D.; Sucharda-Sobczyk, A.; Kolodziejczyk, A. *Rocz. Chem.* **1970**, *44*, 49; *Chem. Abstr.* **1970**, *73*, 24873v.

(10) The arborol (0.2 mmol) was added to acetic anhydride (5.0 mL) and pyridine (0.5 mL) and then warmed to 50 °C for 15 h. The mixture was concentrated in vacuo to give a thick oil, which was purified by HPLC (ODS, MeCN) to give the acetate derivative.

azoline formation via loss of water;[11] oxazoline formation will be discussed in more detail later.

All [9]-*n*-[9] arborols are slightly hygroscopic, water soluble solids and their aqueous solutions foam upon agitation. From this series, the [9]-*n*-[9] arborols with connecting hydrocarbon chains of 10 or more carbons ($10 \leq n \leq 13$) have the distinction of forming thermally reversible, thixotropic[12] aqueous gels[13] at concentrations as low as 1.0 wt %. The gel formed by [9]-10-[9] arborol (**3h**) was subsequently studied to elucidate its structural properties.

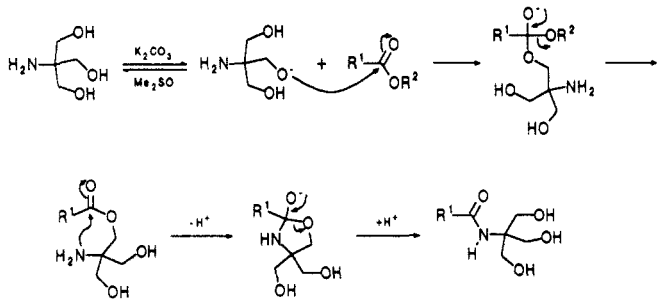
The analogous series of [6]-*n*-[6] arborols (**5**) was prepared to investigate the relationship between cascade sphere size, linkage distance, and gel formation. The tetraesters **4** were prepared by the reaction of a α,ω-dibromoalkane with an excess of dimethyl malonate in DMF with K_2CO_3. The ^1H NMR spectra of **4** consist of a broad singlet (ca. δ 1.3) for the central backbone methylenes, a multiplet (ca. δ 1.9) for the methylene adjacent to the malonate methine, a triplet (ca. δ 3.35) for the malonate methine, and a singlet (ca. δ 3.73) for the methyl ester. The infrared spectra of the tetraesters are characterized by a C=O stretch at 1757 and 1736 cm^{-1} and C—O stretches at 1202 and 1157 cm^{-1}. The ^{13}C NMR spectra verified the structure of **4**: an upfield shift of the substituted methylene [CH_2Br, ca. δ 33; $CH_2CH(CO_2Me)_2$, ca. δ 29] and appearance of the three peaks characteristic of the methyl malonate moiety (δ ca. 51.5, 52.5, and 170.2 for the methine, methyl ester, and carbonyl, respectively). The peaks for the remaining methylenes had chemical shifts in agreement with predicted values.[7,8]

The reaction of 1,2-dibromoethane with excess methyl malonate gave *only* the expected methyl 1,1-cyclopropanedicarboxylate,[14] which arises via dialkylation. Similarly, the reaction of 1,4-dibromobutane with excess methyl malonate gave dimethyl 1,1-cyclopentanedicarboxylate and a paucity (7%) of the desired **4c**.

Tetraesters **4** were converted to the [6]-*n*-[6] arborols **5** by the procedure described for [9]-*n*-[9] arborols. The ^1H NMR spectra of **5** consisted of two broad singlets (ca. δ 1.15 and 1.60) for bridging methylenes, a broad singlet (ca. δ 3.54) for hydroxymethylenes, and a broad singlet (ca. δ 7.41) for amide hydrogen. ^{13}C NMR verified the complete amidation of the tetraester: there was a 1.0 ppm downfield shift of *C*=O (**4** (δ 170) to **5** (δ 171)), disappearance of OCH_3 resonances (**4** (ca. δ 52.5)), and appearance of NH*C* and *C*H_2OH resonances (**5** (ca. δ 62.2 and 60.5, respectively)). The IR spectra of arborols **5** are all similar: a broad O–H stretch at 3312 cm^{-1} and C–H stretches at 2949, 2926, and 2857 cm^{-1}. The amide moiety was confirmed by the presence of amide bands (1655 and 1632 cm^{-1}). As with **3**, attempted melting point determinations of **5** resulted in effervescent decomposition at temperatures of 120–160 °C. Gelation was also observed with **5**, *but with shorter hydrocarbon chains* ($8 \leq n \leq 13$) than observed with **3**. The corresponding acetate derivatives were prepared and shown to be spectrally identical with samples prepared from **3**, and also afforded correct elemental analyses.

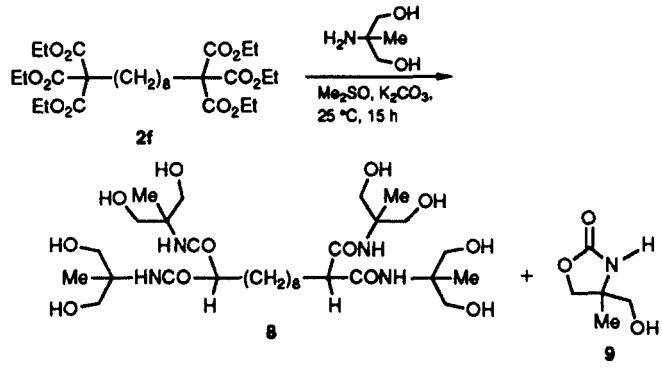
Three representative [3]-*n*-[3] arborols were prepared to evaluate the relationship between cascade sphere size and gel formation at the lower limit of cascade sphere size. Dimethyl pimelate and dimethyl dodecane-1,12-dioate were prepared from the corresponding diacids via Fischer esterification and gave physical and spectral properties in agreement with literature data. These diesters and dimethyl glutarate were treated with Tris via the standard conditions to give the bisamides **6**. The ^1H NMR spectra of **6** consisted of upfield signals indicative of the hydrocarbon backbone and downfield singlets at ca. δ 3.5, 4.75, and 7.0 for the hydroxymethylene, hydroxyl, and amide hydrogens, respectively. ^{13}C NMR spectra gave peaks for each unique carbon; signals characteristic of the amide functionalities were δ 35.0 for

Scheme II. Amidation of an Ester by Tris



CH_2CONH, δ 60.7 for *C*H_2OH, δ 62.0 for C_{quat}, and δ 174.0 for *C*=O. The infrared spectra also confirmed the amide functionality: ca. 1630 cm^{-1} (amide I), ca. 1570 cm^{-1} (amide II), and absence of an ester carbonyl stretch at 1740 cm^{-1}. Unfortunately, these bisamides showed very little or no water solubility.

The generality of these amidation conditions was examined via reaction of hexaester with several other amines. The hexaester **2f** (n = 8) was treated with *tert*-butylamine (**7a**), 2-amino-1-ethanol (**7b**), 2-amino-2-methyl-1-propanol (**7c**), and 2-amino-2-methyl-1,3-propanediol (**7d**), employing the same conditions used for Tris. There are three possible scenerios: no reaction, amide formation, or triester monodecarbalkoxylation, which is a major side reaction with triesters.[15] The crude products from each reaction were analyzed by ^{13}C NMR spectroscopy; the occurrence of amidation or decarbalkoxylation was discerned by comparison with the ^{13}C NMR spectra of **2f**, **3f**, **4g**, and **5g**. Reaction of *tert*-butylamine (**7a**) with hexaester **2f** gave an oil, whose ^{13}C NMR spectra were identical with starting hexaester **2f** with *no indication of either decarbalkoxylation or amidation.* The reaction of **2f** with aminoethanol **7b** gave an oil, whose ^{13}C NMR spectrum indicated extensive monodecarbalkoxylation. The reaction of **2f** with aminopropanol **7c** gave an oil with a small amount of decarbalkoxylation. The ^{13}C NMR spectrum of the material from the reaction with aminodiol **7d** indicated no hexaester **2f** or malonic ester moieties; purification via HPLC gave two major products **8** and **9**.



Reactions of several esters with $H_2NC(CH_2CH_2CH_2OH)_3$ [bis(homotris)][1a,16] failed to give the desired amides under these reaction conditions; ^{13}C NMR spectral data indicated the presence of partially transesterified bis(homotris). However, the desired amide was obtained by use of NaOEt in Me_2SO; details will be presented in a future publication.

Amidation of esters usually proceeds by the $B_{AC}2$ mechanism[17] and is general base catalyzed,[17-19] where a second molecule of the amine[20] (or other suitable base) accepts a proton in the rate-de-

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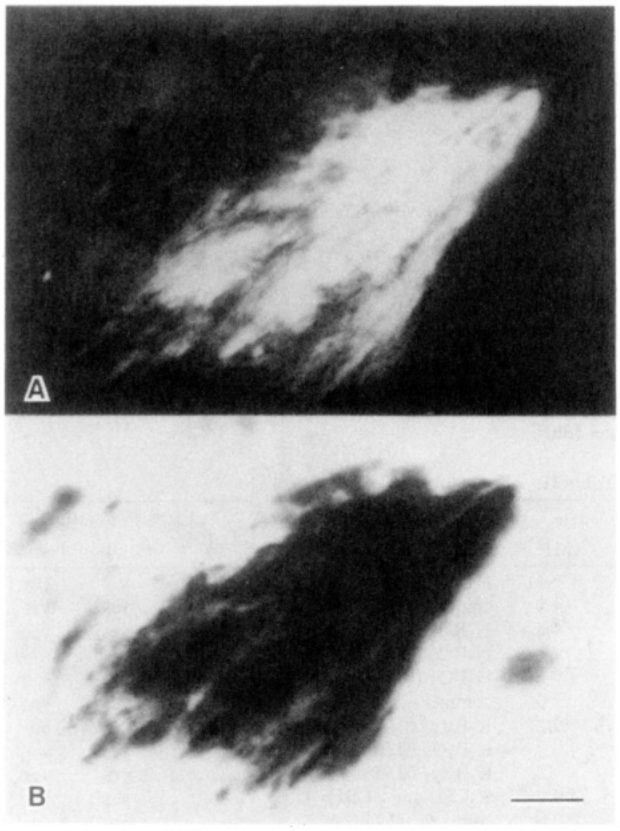
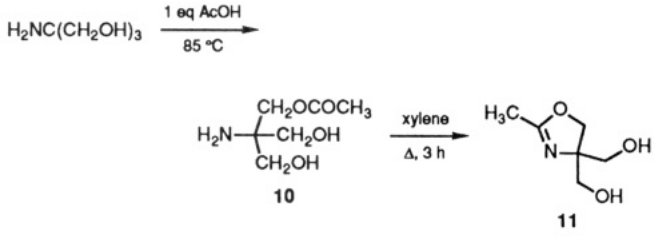


Figure 2. Birefringence of the [9]-10-[9] arborol (**3h**) gel: (a) viewed between cross-polarized filters; (b) viewed between plane polarized filters. Bar = 100 μm.

termining step. The need for added base (anhydrous K_2CO_3) could result from the steric bulk of both ester and attacking amine, which precludes proton abstraction by a second amine molecule. The reactions of these β-aminoalcohols reveal several mechanistic aspects of the reaction of an ester and Tris: initial N attack of the carbonyl is unlikely, since *tert*-butylamine did not react with **2f**, under similar conditions; the observed decarbalkoxylations probably arise from initial O attack of the carbonyl (note: reactions with **7b** and **7c**); decarbalkoxylation was a predominate side reaction; and little or no amidation was observed unless the aminoalcohol possessed a second hydroxyl. This suggests that Tris reacts via the mechanism shown in Scheme II, which proceeds by formation of the alkoxide of Tris; subsequent transesterification with the triester (or decarbalkoxylation); and amide formation (or decarbalkoxylation) via an intramolecular rearrangement.

Such an intramolecular process should be rather facile. Similar reactions were previously observed by Nys and Libeer.[11] Azeotropic removal of water from a refluxing xylene solution of acetate **10** gave a paucity of oxazoline **11**; related reactions were also reported.[11]



Characteriztion of the Gels

The thermally reversible aqueous gels formed by [9]-10-[9] arborol (**3h**) and [6]-10-[6] arborol (**5i**) were studied by several techniques: viscometry, optical and electron microscopy, and light scattering. In general, gelation was observed at concentrations of 2–10 wt % and the solutions exhibited pseudoplastic behavior during gelation. Arborols **3h** and **5k** also gelled in MeOH–H_2O mixtures (up to a 4:1 ratio); these gels appeared much stiffer than their aqueous counterparts.

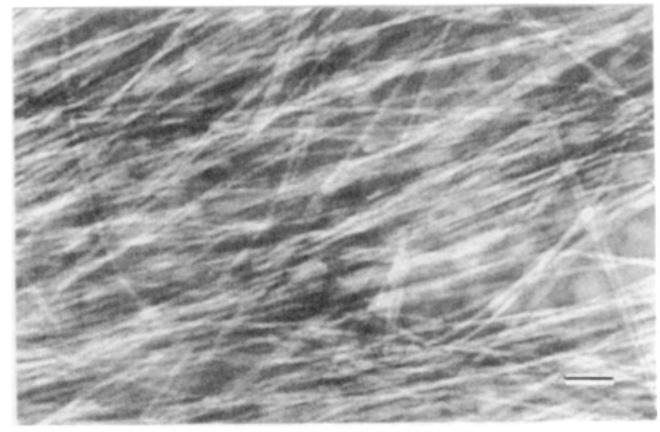


Figure 3. Negatively stained transmission electron micrograph of the [9]-10-[9] arborol (**3h**) gel. Bar = 300 Å. Diameter of individual aggregate strands is ca. 35 Å.

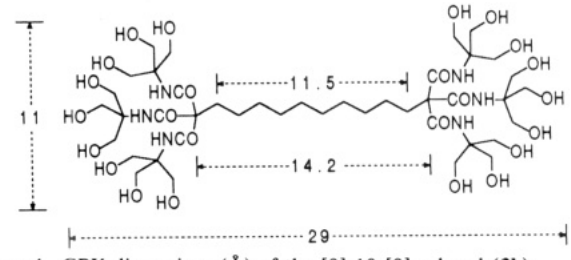


Figure 4. CPK dimensions (Å) of the [9]-10-[9] arborol (**3h**).

Since by definition a gel has no zero shear flow,[13] i.e. it exhibits no steady flow under conditions of zero shear, viscosity is an appropriate experimental method. The viscosity of an aqueous solution of **3h** was measured during gelation. A 5.0 wt % aqueous solution of **3h** was prepared at 80 °C, transferred to a viscometer at 25 °C, and the viscosity was measured (at various shear rates) as the solution gelled. At the onset of gelation the viscosity showed pseudoplastic behavior and then *quickly* increased as the solution gelled. The elapsed time was approximately 45 min.

Optical microscopy of gelled solutions of **3h** was investigated to detect the presence of any macroscopic structure. A gelled solution of arborol **3h** was lyophilized and observed through crossed polarizing filters; the dried gel showed no discernable structure. However, a sample of the original gel exhibited birefringence, indicative of an extended ordered structure or multiple scattering. Addition of water to the aqueous gel caused dilution of the sample until only limited areas of birefringence were visible (Figure 2). Further dilution of the sample led to complete disappearance of birefringence.

The relatively small size and low molecular weight (FW = 1052) of **3h** compared to a typical polymer gel[13] implies probable aggregation of **3h** into a larger structure prior to or during gelation. In order to discern the aggregate size and shape, the gel was negatively stained and examined by transmission electron microscopy. The long fibrous rod structure of the aggregates is clearly visible in Figure 3. These rods have uniform diameters (34–36 Å) and variable lengths (ca. >2000 Å). The dimensions of a single molecule of **3h** were determined by examination of CPK space filling models and molecular modeling (Figure 4). The most interesting dimension of Figure 4 is the end-to-end distance of ca. 29 Å, which compares favorably with the observed rod diameter of 34–36 Å. The slight difference between the measured rod diameter and the end-to-end distance of **3h** can be attributed to some degree of hydration of the cylindrical aggregate surface and the thickness of the stain used for the transmission electron microscopy. The agreement between end-to-end distance and rod

(20) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638. Bruice, T. C.; Felton, S. M. *J. Am. Chem. Soc.* **1969**, *91*, 2799. Felton, S. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 6721.

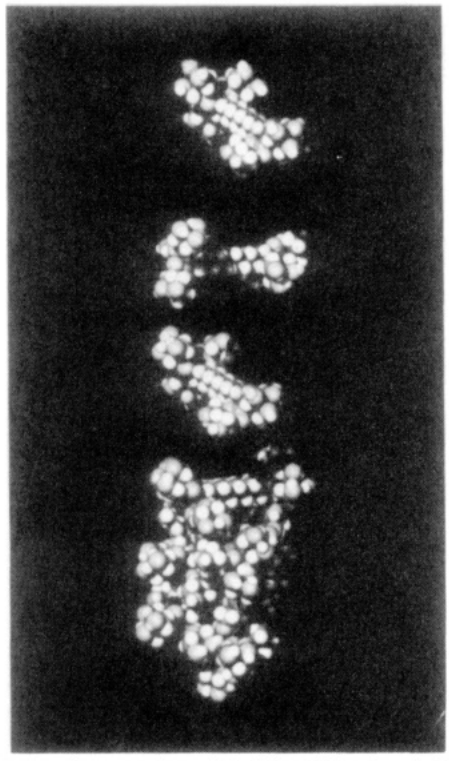


Figure 5. Proposed aggregation of the [9]-10-[9] arborol (**3h**).

Table I. Phase-Transition Temperatures (Gel to Solution) for Aqueous Solutions of [9]-10-[9] Arborol (**3h**)

concentration, wt %	temperature (g → s), °C
2.12	48–49
4.34	54–55
6.22	65–66
8.15	69–70

diameter suggests that molecules of **3h** pack in a cross-over fashion (Figure 5) where the dumbbell-shaped molecules form an interlocking network. This arrangement maximizes intermolecular lipophilic as well as hydrophilic interactions and generates a rod structure of appropriate diameter. Preliminary molecular modeling of the aggregation of six molecules of **3h** (without solvation) verify the favorable energetics of this molecular organization. The minimized energy of a six molecule aggregate was 79.7 kcal/mol while the energy of six noninteracting (ca. 20 Å separation) arborol molecules was 305 kcal/mol. The outer surface of these rods is covered by the terminal hydroxy groups which permit the rods to "cross-link" via hydrogen bonding through adjacent water molecules. Organization of the molecules into the cylindrical aggregates occurs at shorter chain lengths for [6]-*n*-[6] arborols because the smaller spherical size and lipophilic relationship favors the diminished aggregate diameter for maximized interactions cascade spheres are smaller.

The gel structure was also visualized by fluorescence microscopy. The hydrophobic dye chlortetracycline (CTC), which is soluble and nonfluorescent in aqueous solution, fluoresces at 520–530 nm (excitation <450 nm) *only in a hydrophobic environment*.[21] In very dilute solutions, fluorescence from individual molecules was undetectable; however, at higher concentrations **3h** aggregated, forming a gel, a CTC fluorescence from the hydrophobic cores was observed (Figure 6). Thus, the CTC dye must have intercalated into the lipophilic region of these cylindrical aggregates.

The concentration dependence of the phase transition temperature (Table I), i.e. from gel (G) to solution (S), was determined by (1) light microscopy (disappearance of birefringence) and (2) light scattering (decrease of scattered intensity). Gelation

(21) Saunders, M. J.; Helper, P. K. *Planta* **1981**, *152*, 272.

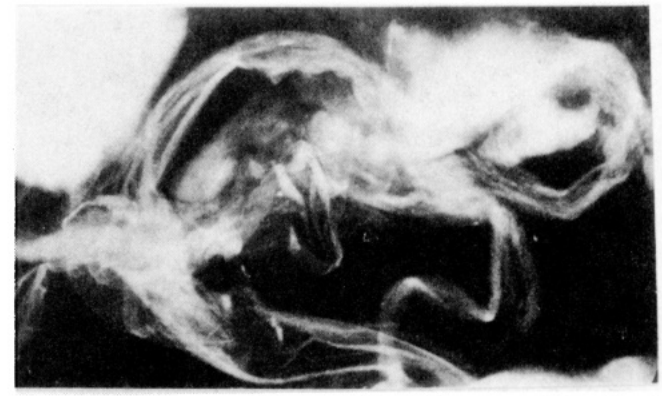


Figure 6. Fluorescence of chlortetracycline in the presence of the arborol gel (**3h**).

Table II. pH Stability of the Arborol Gels

		gelation[a]	
pH[b]	solution	**3h**	**5i**
2.1	HCl (0.25 M)	yes	yes
4.0	commercial buffer[c]	yes	yes
4.4	H_3BO_3 (0.1 M)	yes	yes
	H_3BO_3 (0.75 M)	yes[d]	–
	H_3BO_3 (0.1 M) and NaCl (0.1 M)	yes	–
7.0	commercial buffer[c]	yes	yes
9.2	$K_2B_4O_7$ (0.1 M)	no	no
	$K_2B_4O_7$ (0.01 M)	yes	yes
	$K_2B_4O_7$ (0.001 M)	yes	yes
9.9	K_2CO_3 and H_3BO_3	yes[d]	–
10.0	commercial buffer[c]	no	yes
10.2	NH_4OH (0.25 M)	yes	yes
11.5	K_2CO_3 (0.25 M)	yes	yes
11.6	KOH (0.25 M)	yes	yes
11.6	NaOH (0.25 M)	yes	yes

[a] The arborol (20 mg) was dissolved in the solution (0.4 mL) at 80–90 °C, cooled to 25 °C, and allowed to gel. [b] pH was measured by a Corning Model 7 pH meter with a combination electrode. [c] The pH 4.0 and 7.0 buffers were obtained from Mallinckrodt Inc. (composition unknown); the pH 10.0 buffer obtained from Fisher Scientific contained KOH, K_2CO_3, and $K_2B_4O_7$ in unknown amounts. [d] Very slowly formed a soft gel.

was observed for concentrations below 2.0 wt. %; however, prolonged heating of these solutions above the phase transition temperature causes a reorganization into another aggregate, which very slowly (2–14 days) reverts to the original gel.

The pH stability of these two-directional arborols and their associated gels was of interest for several potential applications. Arborols **3h** and **5i** were dissolved in a solution with the desired pH at 80–90 °C, allowed to cool to 25 °C, and the formation of a gel was noted. Table II summarizes the results for dissolution of **3h** and **5i** in various acid, base, and buffer solutions. Both arborols formed gels in the pH range of 2–12 in solutions containing various inorganic ions; the resulting gels were stable for more than 2 months. As noted, the solution of **3h** in a pH 10 buffer did not form a gel. The pH 10 buffer also inhibited gelation of **5g** and **5h**, but did not affect gelation of the other gel-forming arborols. The pH 10 buffer utilized for this study contained KOH, K_2CO_3, and $K_2B_4O_7$; further experiments with KOH, K_2CO_3, and $K_2B_4O_7$ confirmed that *potassium borate inhibits gel formation.* Both arborols readily dissolved in $K_2B_4O_7$ solutions even at 25 °C. When a gelled solution of **3h** was heated above the phase transition temperature and $K_2B_4O_7$ was added, the solution did not revert to the original gel upon cooling.

The interaction of potassium borate with **3h** was investigated by ^{13}C NMR spectroscopy. The ^{13}C NMR of **3h** in D_2O (2% w/v) showed the following signals: 27.2 (*C*-2), 29.2 (*C*-3), 31.3 (*C*-1, *C*-4 and *C*-5), 55.1 (C_{quat}), 61.4 (CH_2OH), 62.9 [$C(CH_2OH)_3$], and 173.8 (*C*=O). The ^{13}C NMR was repeated with a sample of **3h** (2% w/v) dissolved in a D_2O solution of $K_2B_4O_7$ (0.1 M, 0.4 mL); the ratio of $K_2B_4O_7$ to **3h** was 2:1. The presence of borate ion resulted in a broad signal at δ 63.8 with concomitant disap-

pearance of the signals at δ 61.4 and 62.9. The chemical shifts of the other carbons were little affected by addition of borate ion. Increasing the $K_2B_4O_7$ to **3h** ratio to 18:1 caused the broad resonance to sharpen. For comparison purposes the simple model $CH_3CONHC(CH_2OH)_3$ (**12**) was prepared and showed similar behavior. The ^{13}C NMR of amidetriol **12** in D_2O gave the expected four signals: 23.6 (CH_3), 61.4 (CH_2OH), 62.8 [$C(CH_2OH)_3$], and 175.8 (C=O). In the presence of $K_2B_4O_7$, signals at δ 61.4 and 62.8 were replaced by a broad signal at δ 63.6. The CH_3 and C=O signals were only slightly affected.

The amount of borate ion present is important since gelation was observed for 0.01 M and 0.001 M $K_2B_4O_7$ solutions of the arborols. Borate salts hydrolyze in water to form a boric acid-borate [$[B(OH)_3] \rightleftharpoons [B(OH)_4^-]$] buffer (pH ~9);[22] $B(OH)_4^-$ can interact with up to four hydroxy groups. Complex formation between polyols and boric acid and borate ion is well known.[22-25] Addition of sodium borate to a 4% solution of poly(vinylalcohol) results in formation of a semisolid gel;[22] gelation is attributed to cross-linking of different polymer chains by borate ion. Pentaerythritol[23] and $CH_3C(CH_2OH)_3$[24] form 1:1 or 1:2 complexes with boric acid. Nickerson[25] examined the complexation of mannitol by borate ion and boric acid, and concluded that: complexation is mainly a borate ion phenomenon; polyols undergo a strongly exothermic reaction with borate ion, *but not with boric acid*; and the equilibrium constant for polyol–boric acid complexation is small.

Summary

Two-directional arborols were easily prepared via a two-step procedure. The manipulation of the ratio of inner surface size (and character) to cascade sphere volume afforded insight to the structural relationship necessary for gelation. The [6]-*n*-[6] arborols are most suited for future studies of these gels, since the reaction of Tris and a triester is unreliable and sometimes gives the malonamide product; however, even these products are useful for gel formation. The preparation and properties of gels have become active areas of investigation, since their utility has been demonstrated for various applications.[26] The gel formed by arborol **3h** is interesting due to the relatively low concentration of **3h** required for formation of the gel and its thermal reversibility. The fluorescence of CTC within the rod-shaped aggregates verifies the lipophilic character of the interior, and illustrates the ability of these arborols to solubilize other molecules. The geometric arrangement of the borate complex of the arborol is not certain; however, the borate ion must interact with the terminal hydroxyls which disrupts the hydrogen-bonding network of the gel. We are currently studying the properties of two-directional arborols which possess central unsaturated moieties; preassembly (aggregation) of these monomers via gelation may permit a facile polymerization, which will be described in detail in a future publication.

Experimental Section

General Comments. All melting points were taken in capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were determined at 80, 100, 200, or 400 MHz with use of $CDCl_3$ as solvent, or Me_2SO-d_6 for the arborols **3** and **5**. Infrared (IR) spectra were recorded on either a Perkin-Elmer 621 spectrophotometer or an IBM Instruments IR/38 Fourier transform spectrophotometer. Mass spectral (MS) data were determined at LSU by Mr. D. Patterson or Mr. H. Land on a Hewlett-Packard HP 5985 GC/mass spectrometer and reported herein as (assignment, relative intensity).

Reported R_f values were determined by a standard thin-layer chromatography (TLC) procedure: Baker-flex silica gel IB2-F plates eluted with the stipulated solvent system. Preparative thick-layer chromatography (ThLC) utilized 2-mm Brinkmann silica gel PF-254-366 plates. Baker silica gel (60–200 mesh) was used for column chromatography. Dry flash chromatography was performed by the method of Harwood[27] with use of preparative grade silica gel (Brinkmann PF-254-366) and a quartz funnel. Elemental analyses were obtained from Micanal Organic Microanalyses, Tucson, AZ.

Reagents. Triethyl methanetricarboxylate was prepared via literature procedures.[28] α,ω-Dibromoalkanes, dimethyl glutarate, and dimethyl undecane-1,11-dioate and tris(hydroxymethyl)aminomethane (Tris) were obtained from Aldrich Chemical Co. and used without purification.

Solvents. Unless specified, solvents were purified by simple distillation. Acetonitrile was stirred over CaH_2 for 24 h, refluxed over P_2O_5 for 2 h then distilled, and then refluxed over CaH_2 for 1 h followed by distillation, discarding the first and last 10% of the distillate. The product so obtained was pure by GC/MS *except for a trace of oxazole*. Benzene was washed with H_2SO_4, then water, dried over $CaCl_2$, distilled, and then stored over 3A molecular sieves. *tert*-Butyl alcohol was purified by distillation from CaO and multiple crystallizations. *N*,*N*-Dimethylformamide (DMF) was purified by the method of Trisler et al.[29] and Newkome et al.[30] Me_2SO was dried and stored over 3A molecular sieves. Pyridine was dried over solid KOH then distilled and stored over KOH. Tetrahydrofuran was refluxed over metallic sodium and then distilled from benzophenone ketyl immediately prior to use. Diethyl ether was refluxed over $LiAlH_4$ then distilled immediately prior to use.

HPLC. Reversed-phase HPLC was performed with a Perkin-Elmer Series 4 pump and Isco UA-5 absorbance detector with type 10 optical unit at either 214 nm (analytical) or 254 nm (preparative). An Altex Ultrasphere-ODS column (4.6 mm × 25 cm) was used for method development and analytical separations while a DuPont Zorbax ODS column (21.2 mm × 25 cm) was used for preparative separations. Solvents were obtained from Aldrich (HPLC grade) and used without further purification.

Hexaethyl α,α,α,ω,ω,ω-Alkanehexacarboxylate (2a–k). General Procedure. The appropriate α,ω-dibromoalkane (15 mmol) was added to a stirred solution of $NaC(CO_2Et)_3$ (33 mmol) in C_6H_6–DMF (40 mL; 1:1) at 90 °C. After 24 h, the solution was cooled and C_6H_6 (100 mL) was added. This solution was washed with water (3 × 100 mL) and saturated aqueous $NaHCO_3$ (2 × 100 mL), then dried over anhydrous $MgSO_4$, concentrated in vacuo, and vacuum distilled (Kugelrohr) to give the respective hexaesters **2**. ^1H NMR, mass spectral, infrared, and elemental analysis data, as well as complete ^{13}C NMR spectral data (Table III), are given in the supplementary material.

2a (*n* = 3): 72%; bp 185–190 °C (2.0 mm); ^{13}C NMR δ 33.6 (β-CH_2), 65.8 (α-C), 167.3 (C=O). **2b (*n* = 4)**: 80%; bp 190–195 °C (2.0 mm); ^{13}C NMR δ 33.0 (β-CH_2), 65.8 (α-C), 167.4 (C=O). **2c (*n* = 5)**: 80%; bp 210–220 °C (2.0 mm); ^{13}C NMR δ 34.9 (β-CH_2), 66.6 (α-C), 168.9 (C=O). **2d (*n* = 6)**: 77%; bp 210–215 °C (2.0 mm); ^{13}C NMR δ 33.4 (β-CH_2), 65.8 (α-C), 167.5 (C=O). **2e (*n* = 7)**: 80%; bp 210–220 °C (2.0 mm); ^{13}C NMR δ 33.5 (β-CH_2), 65.8 (α-C), 167.5 (C=O). **2f (*n* = 8)**: 81%; bp 210–220 °C (2.0 mm); ^{13}C NMR δ 33.5 (β-CH_2), 65.9 (α-C), 167.5 (C=O). **2g (*n* = 9)**: 82%; bp 215–220 °C (2.0 mm); ^{13}C NMR δ 33.5 (β-CH_2), 66.3 (α-C), 167.5 (C=O). **2h (*n* = 10)**: 78%; bp 220–225 °C (2.0 mm); ^{13}C NMR δ 33.5 (β-CH_2), 65.9 (α-C), 167.6 (C=O). **2i (*n* = 11)**: 80%; bp 230–240 °C (1.0 mm); ^{13}C NMR δ 33.2 (β-CH_2), 65.6 (α-C), 167.2 (C=O). **2j (*n* = 12)**: 75%; bp 235–240 °C (3.0 mm); ^{13}C NMR δ 33.2 (β-CH_2), 65.5 (α-C), 167.2 (C=O). **2k (*n* = 13)**: 81%; bp 235–240 °C (1.0 mm); ^{13}C NMR δ 33.1 (β-CH_2), 65.5 (α-C), 169.2 (C=O).

***N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗′-Hexakis[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-α,α,α,ω,ω,ω-alkanehexacarboxamide [3(a–k), [9]-*n*-[9] Arborols]. General Amide Formation.** The hexaester **2** (2.0 mmol) and Tris (12.0 mmol) were dissolved in Me_2SO (10 mL) and stirred over anhydrous K_2CO_3 (13.0 mmol) for 10 h at 25 °C. The mixture was filtered and evaporated in vacuo. The pure alcohols **3** were obtained via dissolution of the oily residue in water and precipitation by the slow addition of acetone to give a white solid. Purity (>97%) of **3** ascertained by analytical HPLC (Zorbax ODS, detection at 214 nm) by gradient elution with MeCN–H_2O (0–100% MeCN, 10 min) and by preparation of the decarboxamidated acetate derivative.[10] ^1H NMR and infrared data, as well as complete ^{13}C NMR spectral data for the arborols **3** (Table IV) and their acetate derivatives (Table VII), are given in the supplementary material. Attempted melting point determinations of the arborols **3** resulted in effervescent decomposition at temperatures from 120–160 °C,

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and, thus, no melting points are reported.

3a (n = 3): 88%; ^{13}C NMR δ 32.4 (β-CH_2), 63.4 (CH_2OH), 175.3 (C=O). **3b** (n = 4): 92%; ^{13}C NMR δ 32.6 (β-CH_2), 63.3 (CH_2OH), 175.5 (C=O). **3c** (n = 5): 91%; ^{13}C NMR δ 32.9 (β-CH_2), 63.4 (CH_2OH), 175.7 (C=O). **3d** (n = 6): 90%; ^{13}C NMR δ 32.9 (β-CH_2), 63.3 (CH_2OH), 175.5 (C=O). **3e** (n = 7): 89%; ^{13}C NMR δ 33.1 (β-CH_2), 63.3 (CH_2OH), 175.7 (C=O). **3f** (n = 8): 91%; ^{13}C NMR δ 32.5 (β-CH_2), 63.2 (CH_2OH), 175.5 (C=O). **3g** (n = 9): 92%; ^{13}C NMR δ 32.9 (β-CH_2), 63.2 (CH_2OH), 175.5 (C=O). **3h** (n = 10): 93%; ^{13}C NMR δ 33.0 (β-CH_2), 63.3 (CH_2OH), 175.5 (C=O). **3i** (n = 11): 91%; ^{13}C NMR δ 33.0 (β-CH_2), 63.3 (CH_2OH), 175.6 (C=O). **3j** (n = 12): 90%; ^{13}C NMR δ 33.1 (β-CH_2), 63.3 (CH_2OH), 175.6 (C=O). **3k** (n = 13): 88%; ^{13}C NMR δ 32.9 (β-CH_2), 63.3 (CH_2OH), 175.5 (C=O).

Tetramethyl $\alpha,\alpha,\omega,\omega$-Alkanetetracarboxylate (4a). General Procedure. A mixture α,ω-dibromoalkane (10 mmol), dimethyl malonate (24 mmol), and K_2CO_3 (24 mmol) in DMF (10 mL) was stirred at 25 °C for 24 h and heated to 100 °C for 2 h. The mixture was filtered, and the solid was washed with DMF (10 mL). The combined filtrate was concentrated to give a residue, which was dissolved in C_6H_6 (100 mL), then washed sequentially with water (2 × 50 mL), 15% NaOH (2 × 25 mL), and water (2 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the respective tetraesters **4**. ^{1}H NMR, mass spectral, infrared, and elemental analysis data, as well as complete ^{13}C NMR spectral data (Table V), are given in the supplementary material. The reaction with 1,2-dibromoethane gave (87%) dimethyl 1,1-cyclopropanedicarboxylate. Distillation of the crude material obtained from the reaction with 1,4-dibromobutane gave (70%) dimethyl 1,1-cyclopentanedicarboxylate; a paucity of the desired **4c** was isolated (7%) from the pot residue via thick-layer chromatography [SiO_2, $C_6H_6H_{12}$–EtAc (4:1)].

4a (n = 1): 70%; ^{13}C NMR δ 27.5 (β-CH_2), 49.2 (α-C), 169.2 (C=O). **4b** (n = 3): 67%; ^{13}C NMR δ 28.2 (β-CH_2), 51.2 (α-C), 169.7 (C=O). **4c** (n = 4): 7%; ^{13}C NMR δ 28.6 (β-CH_2), 51.7 (α-C), 170.1 (C=O). **4d** (n = 5): 73%; ^{13}C NMR δ 28.5 (β-CH_2), 51.5 (α-C), 169.9 (C=O). **4e** (n = 6): 95%; mp 47.0–47.1 °C; ^{13}C NMR δ 28.8 (β-CH_2), 51.6 (α-C), 170.0 (C=O). **4f** (n = 7): 95%; ^{13}C NMR δ 28.8 (β-CH_2), 51.8 (α-C), 170.2 (C=O). **4g** (n = 8): 80%; mp 45.0–45.4 °C; ^{13} NMR δ 28.9 (β-CH_2), 51.8 (α-C), 170.2 (C=O). **4h** (n = 9): 87%; ^{13}C NMR δ 28.9 (β-CH_2), 51.5 (α-C), 170.0 (C=O). **4i** (n = 10): 94%; mp 51.3–52.7 °C; ^{13}C NMR δ 28.9 (β-CH_2), 51.9 (α-C), 170.2 (C=O). **4j** (n = 11): 94%; bp 235–240 °C (0.4–3.5 mm); ^{13}C NMR δ 28.9 (β-CH_2), 51.5 (α-C), 169.9 (C=O). **4k** (n = 12): 92%; mp 59.0–59.3 °C; ^{13}C NMR δ 28.9 (β-CH_2), 51.8 (α-C), 170.2 (C=O). **4l** (n = 13): 81%; ^{13}C NMR δ 29.0 (β-CH_2), 51.5 (α-C), 170.0 (C=O).

N,N',N'',N'''-Tetrakis[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-$\alpha,\alpha,\omega,\omega$-alkanetetracarboxamide [5a–l, [6]-n-[6] Arborols]. General Amide Formation. A mixture of Tris (8.0 mmol), tetraester **4** (2.0 mmol), and anhydrous K_2CO_3 (8.64 mmol) in Me_2SO (5 mL) was stirred at 25 °C for 24 h. The solution was filtered, the solid washed with Me_2SO (10 mL), and the combined filtrate concentrated in vacuo. The residue was dissolved in water, precipitated by the addition of acetone, and then filtered to give the desired tetraamide **5**, as a white solid; the solid was washed with anhydrous EtOH. Purity (>97%) of these arborols was determined by analytical HPLC (Zorbax ODS, detection at 214 nm) by gradient elution with MeCN–H_2O (0–100% MeCN, 10 min) and by preparation of the acetate derivative.[10] ^{1}H NMR and infrared data, as well as complete ^{13}C NMR spectral data for the arborols **5** (Table VI) and their acetate derivatives (Table VII), are given in the supplementary material. Attempted melting point determinations of **5** caused effervescent decomposition at temperatures of 140–180 °C and, thus, no melting points are reported.

5a (n = 1): 66%; ^{13}C NMR δ 24.1 (β-CH_2), 51.5 (α-CH), 60.4 (CH_2OH), 170.4 (C=O). **5b** (n = 3): 69%; ^{13}C NMR δ 24.5 (β-CH_2), 53.5 (α-CH), 60.4 (CH_2OH), 171.0 (C=O). **5c** (n = 4): 65%; ^{13}C NMR δ 26.6 (β-CH_2), 53.5 (α-CH), 60.6 (CH_2OH), 171.1 (C=O). **5d** (n = 5): 72%; ^{13}C NMR δ 26.4 (β-CH_2), 53.5 (α-CH), 60.5 (CH_2OH), 171.1 (C=O). **5e** (n = 6): ^{13}C NMR δ 26.6 (β-CH_2), 53.6 (α-CH), 60.6 (CH_2OH), 171.2 (C=O). **5f** (n = 7): 60%; ^{13}C NMR δ 26.6 (β-CH_2), 53.7 (α-CH), 60.4 (CH_2OH), 171.1 (C=O). **5g** (n = 8): 86%; ^{13}C NMR δ 26.6 (β-CH_2), 53.4 (α-CH), 60.6 (CH_2OH), 171.2 (C=O). **5h** (n = 9): 84%; ^{13}C NMR δ 26.6 (β-CH_2), 53.6 (α-CH), 60.6 (CH_2OH), 171.2 (C=O). **5i** (n = 10): 62%; ^{13}C NMR δ 26.7 (β-CH_2), 53.8 (α-CH), 60.5 (CH_2OH), 171.3 (C=O). **5j** (n = 11): 69%; ^{13}C NMR δ 26.7 (β-CH_2), 53.7 (α-CH), 60.5 (CH_2OH), 171.3 (C=O). **5k** (n = 12): 61%; ^{13}C NMR δ 26.6 (β-CH_2), 53.7 (α-CH), 60.5 (CH_2OH), 171.2 (C=O). **5l** (n = 13): 68%; ^{13}C NMR δ 26.6 (β-CH_2), 53.7 (α-CH), 60.8 (CH_2OH), 171.2 (C=O).

N,N'-Bis[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-α,ω-alkanedicarboxamide (6a–c). General Amide Formation. A mixture of Tris (16.0 mmol), diester (8.0 mmol), and anhydrous K_2CO_3 (25 mmol) in Me_2SO (25 mL) was stirred at 25 °C for 24 h. The solution was filtered, the solid washed with Me_2SO (10 mL), and the combined filtrate concentrated in vacuo. The residue was dissolved in water, precipitated by the addition of acetone, and then filtered to give the desired diamide **6**, as a white solid.

6a (n = 3): 1.78 g (66%); mp 120–122 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.67 (m, $CH_2CH_2CH_2$, 2 H), 2.12 (t, $CH_2CH_2CH_2$, J = 6.4 Hz, 4 H), 3.52 (s, CH_2OH, 12 H), 4.74 (s, OH, 6 H), 7.06 (s, NH, 2 H); ^{13}C NMR (Me_2SO-d_6)) δ 21.6 (CH_2), 35.1 (CH_2CONH), 60.7 (CH_2OH), 62.2 (C_{quat}), 173.6 (C=O); IR (KBr) 3278, 2998, 2996, 2941, 2896, 1648 (amide I), 1636 (amide II), 1036 cm^{-1}. Anal. Calcd for $C_{13}H_{26}N_2O_8$: C, 46.15; H, 7.75; N, 8.28. Found: C, 46.22; H, 7.60; N, 8.18.

6b (n = 5): 2.40 g (82%); mp 131–133 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.3 (m, $CH_2(CH_2)_3CH_2$, 6 H), 2.12 (t, $OCCH_2$, J = 6.4 Hz, 4 H), 3.50 (s, CH_2OH, 12 H), 4.76 (s, OH, 6 H), 7.09 (s, NH, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 25.0 (CH_2), 28.1 (CH_2CH_2CONH), 35.7 (CH_2CONH), 60.9 (CH_2OH), 62.2 (C_{quat}), 174.0 (C=O); IR (KBr) 3261, 31001, 2941, 1627 (amide I and amide II), 1043 cm^{-1}. Anal. Calcd for $C_{15}H_{30}N_2O_8$: C, 49.17; H, 8.25; N, 7.65. Found: C, 48.92; H, 8.35; N, 7.58.

6c (n = 10): 2.68 g (77%); mp 143–145 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.23 (s, $(CH_2)_6$, 12 H), 1.43 (m, $OCCH_2CH_2$, 4 H), 2.12 (t, $OCCH_2$, J = 6.4 Hz, 4 H), 3.50 (s, CH_2OH, 12 H), 4.74 (s, OH, 6 H), 7.06 (s, NH, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 25.3 (CH_2), 28.5, 28.7, 28.9, 35.9 (CH_2CONH), 60.9 (CH_2OH), 62.2 (C_{quat}), 174.0 (C=O); IR (KBr) 3316, 2936, 2923, 2874, 2852, 1623 (amide I and amide II), 1045 cm^{-1}. Anal. Calcd for $C_{20}H_{40}N_2O_8$: C, 55.03; H, 9.24; N, 6.42. Found: C, 54.96; H, 9.07; N, 6.33.

Reaction of Hexaethyl 1,1,1,10,10,10-Decanehexacarboxylate with Other Amines. Hexaester **2f** (250 mg, 435 μmol) and *tert*-butylamine (**7a**; 230 mg, 3.14 mmol) [or 2-amino-1-ethanol (**7b**; 193 mg, 3.16 mmol), or 2-amino-2-methyl-1-propanol(**7c**; 281 mg, 3.15 mmol)] were dissolved in Me_2SO (5 mL), and anhydrous K_2CO_3 (100 mg) was added. The reaction was stirred for 15 h at 25 °C and filtered, and the Me_2SO removed in vacuo. The *tert*-butylamine (**7a**) and 2-amino-2-methyl-1-propanol (**7c**) reactions gave oils (230 mg and 232 mg, respectively), whose ^{1}H and ^{13}C NMR spectra were identical with pure **2f**.

The 2-amino-1-ethanol (**7b**) reaction gave an oil (193 mg); ^{13}C NMR spectral data indicated [triester, C-3(8)], 26.9 [malonate; C-3(8)], 28.4 [mal; C-2(9))], 28.8 [mal; C-4(7) and C-5(6); tri; C-4(7)], 29.5 [tri; C-5(6)], 33.0 [tri; C-2(9)], 51.8 (mal; CH), 60.9 (mal; OCH_2CH_3), 61.6 (tri; OCH_2CH_3), 65.6 (tri; C_4•), 167.1 (tri; $CONH$), 169.5 (mal; $CONH$).

The reaction with 2-amino-1-ethanol was repeated with heating to 85 °C for 15 h; the relative peak intensities for the triester and malonate moieties in the ^{13}C NMR spectrum indicated that this material was highly decarbalkoxylated.

Reaction of Hexaethyl 1,1,1,10,10,10-Decanehexacarboxylate with 2-Amino-2-methyl-1,3-propanediol. Hexaester **2f** (250 mg, 435 μmol) and 2-amino-2-methyl-1,3-propandiol (**7d**, 275 mg, 2.61 mmol) were dissolved in Me_2SO, and anhydrous K_2CO_3 (100 mg) was added. The reaction was stirred at 25 °C for 15 h, filtered, and evaporated in vacuo to give a light yellow oil, which was purified by HPLC (Zorbax-ODS) with 100% water as eluant until the first peak was collected, and then gradient elution with MeCN–H_2O (0–50% MeCN, 20 min) gave a second fraction. The first fraction contained 5-(hydroxymethyl)-5-methyl-2-oxazolidone (**9**): 111 mg (97%); mp 109–111 °C; ^{1}H NMR δ 1.13 (s, CH_3, 3 H), 3.24 (s, CH_2OH, 2 H), 3.34 (s, CH_2OH, 1 H), 3.83 (d, $CO_2CH_aH_b$, $J_{a,b}$ = 8.34 Hz, 1 H), 4.15 (d, $CO_2CH_aH_b$, $J_{a,b}$ = 8.34 Hz, 1 H), 7.45 (NH); ^{13}C NMR δ 22.4 (CCH_3), 58.1 (C_{quat}), 66.4 (CH_2OH), 72.0 (CH_2O_2CNH), 158.6 (C=O); IR (KBr) 3285, 2976, 2931, 2876, 1743, 1475, 1400, 1302, 1261, 1193, 1046, 1008, 969, 934, 826, 771, 711 cm^{-1}. Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.57; H, 6.93; N, 10.69.

The second fraction was N,N',N'',N'''-tetrakis[1,1-bis(hydroxymethyl)ethyl]-1,1,10,10-decanetetracarboxamide (**8**): 235 mg (81%); ^{1}H NMR δ 1.12 (s, CH_3 and $(CH_2)_6$, 24 H), 1.61 (m, CH_2CH, 4 H), 3.02 (t, CH, J = 7.1 Hz, 2 H), 3.42 (s, CH_2OH, 16 H), 4.78 (s, CH_2OH, 8 H), 7.45 (s, NH, 4 H); ^{13}C NMR δ 18.4 (CH_3), 26.7 (*C*-2 and *C*-9), 28.7 and 28.8 (*C*-4, *C*-5, *C*-6, and *C*-7), 30.4 (*C*-3 and *C*-8), 53.9 (CH), 58.2 (C_{quat}), 63.7 (CH_2OH), 170.4 (C=O). Anal. Calcd for $C_{30}H_{58}N_4O_{12}$: C, 54.04; H, 8.77; N, 8.40. Found: C, 53.84; H, 8.68; N, 8.20.

Microscopy. The [9]-10-[9] arborol (**3h**) (20 mg) was dissolved in deionized distilled water (1 mL) at 80 °C, then allowed to gel at 25 °C. A portion of the gel was transferred onto a parlodion support film on a 50-mesh copper EM grid (Polaron Instruments Inc.) and air-dried for 1 h. The gel was stained by addition of a drop of 2% aqueous phosphotungstic acid (pH = 6.8); excess solution was drawn off with filter paper, and the grid was air-dried for 1 h. Grids were viewed on a JEOL 100-CX TEM at an accelerating voltage of 80 kV. Size comparisons

were made by using tobacco mosaic virus (diameter = 180 Å), as a reference.

Arborol **3h** (20 mg) was dissolved in deionized water (1 mL) at 80 °C, allowed to gel at 25 °C, and then lyophilized for 24 h. A portion of the dried gel was transferred into a drop of water on a microscope slide. The reconstituted gel was viewed on a Leitz Ortholux II microscope equipped with polarized light optics. A λ-plate and λ/4-plate were inserted in the light path for color contrast; photographs were taken on Ektachrome film (Kodak) and are reproduced in black and white.

Viscometry. The solution was transfered into a Wells-Brookfield cone and plate, steady shear viscometer (Model LVDCP). Shear rates were adjusted from 450 to 2.25 Hz.

Gel-Solution Phase Transition. Aqueous solutions of **3h** (2.12, 4.34, 6.22, and 8.15 wt %) were prepared with use of water from a three-stage Millipore R/Q water purifier. The gels were heated above the phase transition (ca. 80 °C) filtered through Durapore 0.22-μm filters into precleaned fluorimeter cells. Portions of these samples were used for polarized light microscopy. Gel melting points were determined by the disappearance of birefringence between crossed polars on an Olympus BH-2 microscope using a Mettler FP800 thermally controlled stage, increasing the temperature 2 °C/min. The phase-transition temperatures were also observed by light scattering experiments performed at a scattering angle of 90°. The instrument consisted of a Hughes helium-neon laser, Pacific Precision Instruments Model 126 photon counting system, and Hamamatsu R928P photomultiplier. Temperature regulation was accomplished either by a Lauda RCS-6 bath or an Omega CN-2010 electrical temperature controller using a temperature ramp of 2 °C/min. Phase-transition temperatures were taken as a decrease of the scattered intensity to 10% of its initial value.

pH Stability of Gels. The pH of the solutions was measured with a Corning Model 7 pH meter with a combination electrode. The arborol (20 mg) was added to the solution (0.40 mL) and the mixture warmed until a homogeneous solution was obtained (ca. 80–90 °C). After solution was cooled to 25 °C, the occurrence of gel formation was noted. For data, see Table II.

Molecular Modeling. Calculations were performed on a Silicon Graphics IRIS 4D/50GT superworkstation with use of Polygen's QUANTA/CHARMm software.[6] Preliminary structures were input via CHEMNOTE and minimized by using initially the conjugate gradient and then the adopted-basis Newton-Raphson methods until the RMS deviation was <0.001 kcal/Å. Molecular dynamics were performed with 2000 steps (2.0 ps) of heating to 298 °C, 3000 steps (3.0 ps) of equilibration, and 20000 steps (20.0 ps) of stimulation. The lowest energy structures from molecular dynamics were minimized via adopted-basis Newton-Raphson until the RMS deviation was <0.001 kcal/Å.

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Supplementary Material Available: The experimental procedures for 1,13-tridecanediol, 1,13-dibromotridecane, dimethyl pimelate, dimethyl dodecanedioate, and *N*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]acetamide (**12**), spectral and analytical data for hexaesters **2**, [9]-*n*-[9] arborols **3**, tetraesters **4**, and [6]-*n*-[6] arborols **5**, and ^{13}C NMR data for the acetate derivatives (18 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-*epi*-Jatrophone and (±)-Jatrophone Using Palladium-Catalyzed Carbonylative Coupling of Vinyl Triflates with Vinylstannanes as the Macrocycle-Forming Step

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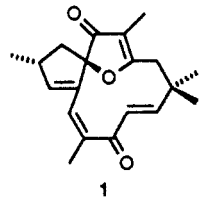
Abstract: Jatrophone is a macrocyclic diterpene which exhibits significant inhibitory activity in vivo and in vitro against various carcinomas. The synthesis of (±)-jatrophone and its epimer was completed with use of a palladium-catalyzed carbonylative coupling of a vinylic triflate with an organostannane as the key step. The synthesis of *epi*-jatrophone was first completed to establish the chemistry for jatrophone. The overall sequence for each synthesis required 16 steps starting from 4-methyl-2-cyclopenten-1-one. The overall yields were 0.83% and 0.28%, respectively.

Introduction

Jatrophone (**1**) is a macrocyclic diterpene first isolated from extracts of *Jatropha gossypiifolia* in 1970.[1] The structure of jatrophone was determined by NMR and X-ray studies.[2] This



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diterpene exhibits significant inhibitory activity in vivo against various carcinomas.[1,3] Jatrophone was first synthesized in 1981 by Amos B. Smith III and co-workers,[4] and this to date has been the only total synthesis reported. The key step in this synthesis of jatrophone involved a Mukaiyama titanium tetrachloride mediated cyclization of an acetal with a silyl enol ether.

As part of an ongoing study of palladium-catalyzed carbon-carbon bond-forming processes, an efficient carbonylative coupling

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