Cyclotrimerization versus Cyclotetramerization in the Electrophilic Oligomerization of 3,4-Bis(methyloxy)benzyl Derivatives

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Received September 5, 1990; Revised Manuscript Received December 10, 1990

ABSTRACT: The product distribution of cyclooligomerizations of 3,4-bis(methyloxy)benzyl chloride, 3,4-bis(methyloxy)benzyl alcohol, *N*-veratrylethanolamine-*N*-tosylate, and 1,2-bis(methyloxy)benzene with formaldehyde and with paraformaldehyde using a large variety of reaction conditions was determined in order to find conditions selective for either cyclotriveratrylene (CTV) or cyclotetraveratrylene (CTTV) formation. CTV, which is the kinetic cyclization product, is formed almost exclusively when 3,4-bis(methyloxy)-benzyl chloride is reacted stoichiometrically with $AgBF_4$ in methylene chloride. CTV is also formed in high yield when 3,4-bis(methyloxy)benzyl alcohol is cyclooligomerized with superacids ($HClO_4$ and CF_3SO_3H), especially if the reaction is performed in a nonsolvent. CTTV, which can be considered the thermodynamic product, is obtained in the highest yield when 3,4-bis(methyloxy)benzyl alcohol is cyclized by using a large excess of CF_3COOH and dilute CH_2Cl_2 solution. Higher molecular weight analogues were also obtained in almost all reactions.

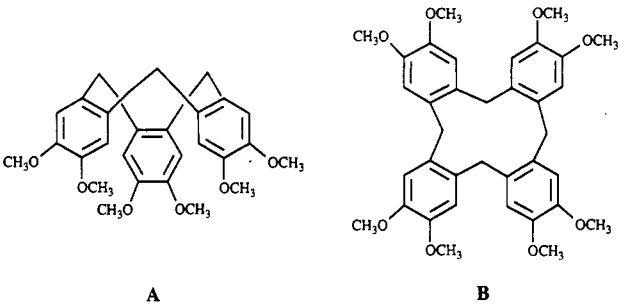
Introduction

Since the first conclusive evidence that the cyclic trimer, cyclotriveratrylene (CTV), is the condensation product of 3,4-bis(methyloxy)benzene and formaldehyde,[1-3] several other methods have been used for its synthesis.[4-7] These include the cyclotrimerization of 3,4-bis(methyloxy)-benzyl alcohol[2,4] and the cyclotrimerization of *N*-tosylates of veratrylamine.[5,6] In addition, cyclononatriene derivatives have been prepared from benzyl chloride based compounds.[1,7] Although the cyclic tetramer, cyclotetraveratrylene (CTTV), also forms as a byproduct in many of these reactions,[3-6] CTV was reported to be the main product in all cases.[3-6,8] All these cyclooligomerization reactions were performed under heterogeneous reaction conditions.

Our interest in this electrophilic cyclooligomerization reaction is in developing it as a polymerization reaction for the synthesis of liquid-crystalline polymers containing discotic mesogens. In this case, the mesogenic units based on CTV or on CTTV would be constructed during the polymerization process. Several laboratories have already reported that the alkyloxy and alkanoyloxy derivatives of both CTV[9-13] and CTTV[14-16] form columnar mesophases. A polymer based on the CTTV mesogen was also recently reported.[15] Because the CTV core is fixed in a rigid cone or crown conformation as shown in Chart I,[3,4,8] CTV-based mesogens form pyramidic[10] mesophases. In contrast, the CTTV core is conformationally flexible[3,4,8] (Chart I) and forms columnar mesophases different from the pyramidic mesophases of CTV derivatives.[14,15] However, a convenient procedure for the synthesis of CTTV[4,8] and its derivatives in high yield has not been developed yet.

In order to be successful as both a polymerization reaction and as a mesogen-forming reaction, the conversion must be quantitative and the reaction must occur in homogeneous phase and with a high selectivity toward either the CTV trimer or the CTTV tetramer. While the mesophases of the hexakis(*n*-alkyloxy)tribenzocyclononatriene (CTV-*n*) derivatives order very slowly to their rigid conelike conformation, those of the flexible octakis(*n*-alkyloxy)tetrabenzocyclododecatetraene (CTTV-*n*) derivatives form very fast. This is due to the difference between the slow dynamics of rigid versus the fast dynamics of flexible liquid-crystalline systems. The CTTV *n*-derivatives therefore tolerate impurities formed during the cyclotetramerization process.[16] However, because impurities retard CTV-*n* mesophase formation,[17] only cyclotetramerization reactions are suitable polymerization reactions for the in situ formation of disklike mesogens.

Chart I
Most Stable Conformations of CTV and CTTV: (A) Crown or Cone Conformation of CTV; (B) Sofa or Saddle Conformation of CTTV



This paper reports the distribution of products resulting from the condensation of 1,2-bis(methyloxy)benzene with formaldehyde and with paraformaldehyde, as well as from the cyclization of 3,4-bis(methyloxy)benzyl alcohol 3,4-bis(methyloxy)benzyl chloride, and *N*-veratrylethanolamine-*N*-tosylate, under a wide variety of reaction conditions. The main effort was devoted to cyclooligomerization reactions performed in CH_2Cl_2 solution. Only a few heterogeneous reactions were reported to compare the heterogeneous versus homogeneous reaction products. In addition to varying the leaving group, which ionizes and subsequently dissociates during the reaction to form a benzyl carbenium ion, we have considered the influence of acid strength, of the amount of acid used, of the reaction time, and of various solvents and solvent systems. These data reveal conditions that will result in either predominantly CTV or CTTV. Finally, a method for the large-scale synthesis of CTTV, and its extension to *n*-alkyloxy derivatives, is reported.

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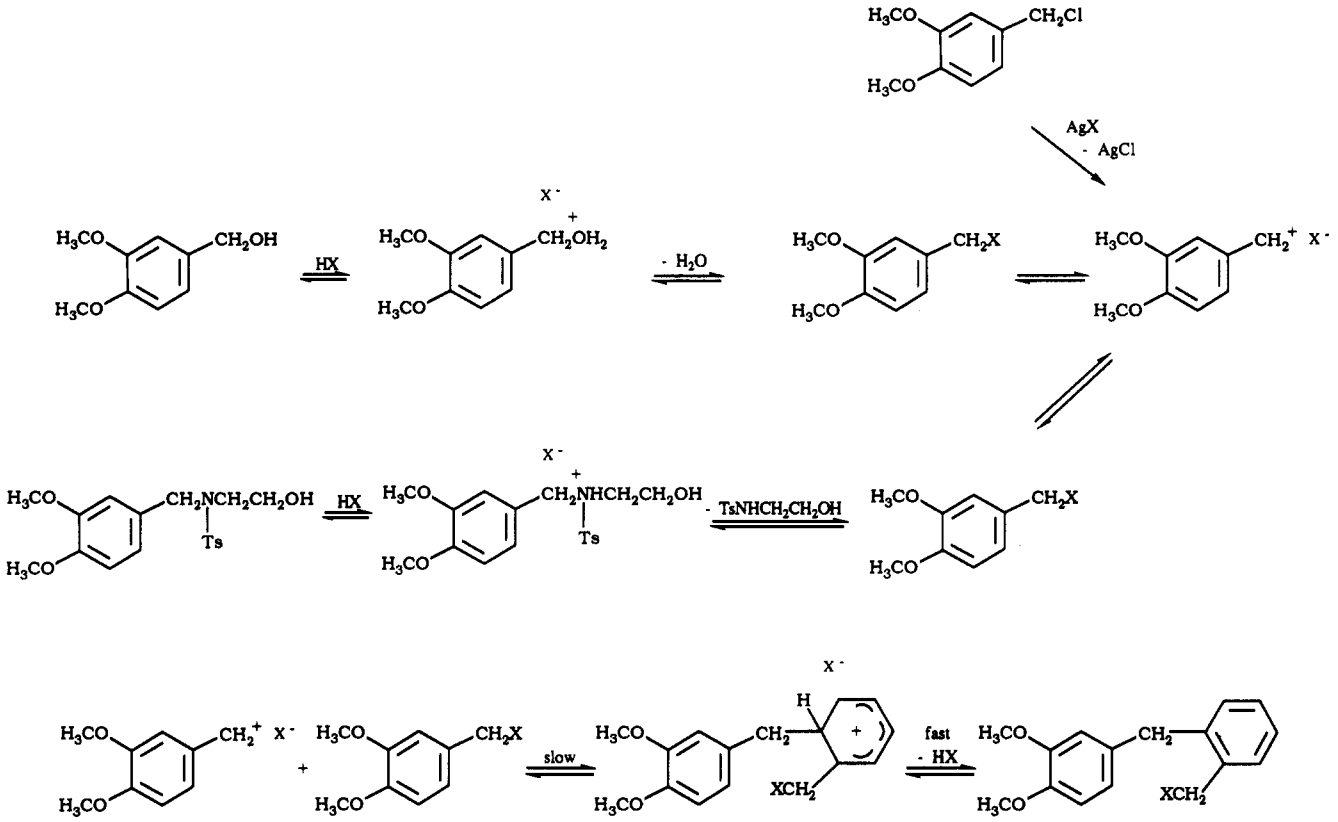
0024-9297/91/2224-3227$02.50/0

Scheme I
Generation of 3,4-Bis(methyloxy)benzyl Carbenium Ions and a Subsequent Electrophilic Aromatic Substitution Reaction



Results

The generally accepted mechanism(s) of aromatic carbenium ion generation and of two steps of the electrophilic aromatic substitution reaction are shown in Scheme I. In the presence of a protonic acid, both the benzyl alcohol and the veratrylamine are protonated to form an oxonium and an ammonium ion, respectively. Oligomerization of 1,2-bis(methyloxy)benzene with either formaldehyde or paraformaldehyde also involves oxonium ions. Because protonation results in a much more ionizable group, water or an amine is readily displaced by nucleophilic attack of the counteranion. The resulting benzyl ester ionizes to the corresponding benzyl carbenium ion pair. In contrast, the carbenium ion is most efficiently generated from 3,4-bis(methyloxy)benzyl chloride by reaction with the silver salt of a strong acid, in which case AgCl precipitates out of solution. In all cases, the resulting benzyl carbenium ion is stabilized by the two electron-donating methyloxy substituents, with the para substituent providing the primary stabilization through resonance. However, the nucleophilicity of the counteranion dictates the equilibrium ratio of the ester and ion pair. Oligomerization occurs by successive electrophilic aromatic substitution reactions of a benzyl carbenium ion with a neutral precursor to generate an arenium ion, which loses a proton to form a neutral substitution product.

The ease of ionization of a C–Y bond to form a carbenium ion pair follows the leaving group order of I > Br > Cl > F > CN > OH > OR ~ NH_2 > CH_3 > H.[18] In the case of *N*-veratrylethanolamine-*N*-tosylate, the tosylate reduces the basicity of the amine and therefore increases its ionizability. However, it should still be more basic than –OH. The ease of ionization of compounds considered here is therefore 3,4-bis(methyloxy)benzyl chloride > 3,4-bis(methyloxy)benzyl alcohol > *N*-veratrylethanolamine-*N*-tosylate.

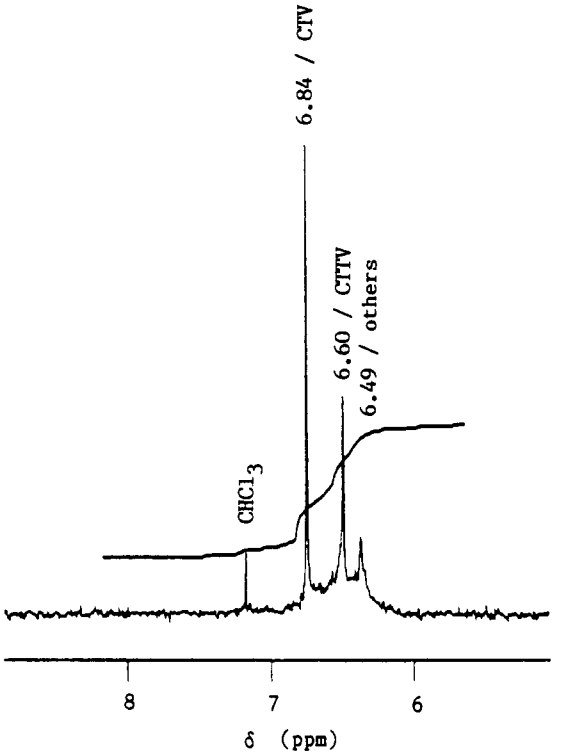


Figure 1. ^{1}H NMR ($CDCl_3$, 55 °C, δ) spectrum of the aromatic region of the products generated by cyclooligomerization of 3,4-bis(methyloxy)benzyl alcohol initiated by *p*-toluenesulfonic acid monohydrate (entry 11, Table II).

As shown in Figure 1, the product distribution from these cyclization reactions can be measured by integration of the ^{1}H NMR aromatic resonances at δ 6.84 (CTV), 6.60 (CTTV), and 6.49 (higher molecular weight analogues). The ^{1}H NMR resonances of CTV,[8] of CTTV,[4] and of higher

Table I
Product Distribution of the Cyclooligomerizations of 3,4-Bis(methyloxy)benzyl Alcohol[a]

no.	acid	mol of acid/mol of OH	solvent	mL of solvent/mmol of OH	mol of DMSO/mol of OH	temp	time, h	yield, %	product distribution CTV:CTTV:other
1	CF_3COOH	0.13	CH_2Cl_2	1.68	0	reflux	6	0	
2	CF_3COOH	2.18	CH_2Cl_2	1.51	0	ambient	2	98	27:49:24
3	CF_3COOH	2.18	CH_2Cl_2	1.51	0	reflux	2	99	24:48:28
4	CF_3COOH	2.18	H_2O	1.51	0	reflux	2	99	37:13:50
5[b]	CF_3COOH	10.9	CH_2Cl_2	16.0	0	ambient	4	90	10:65:25
6	CF_3COOH	10.9	H_2O	0.84	0	reflux	2	100	22:25:53
7	CF_3COOH	10.9	H_2O	0.84	0	reflux	6	100	22:26:52
8	CH_3SO_3H	0.13	CH_2Cl_2	1.68	0	reflux	6	100	40:33:27
9	CH_3SO_3H	0.13	CH_2Cl_2	1.68	0.21	reflux	6	76	35:35:30[c]
10	CH_3SO_3H	0.13	CH_2Cl_2	1.68	0.84	reflux	6	73	25:21:54[c]
11	$TsOH-H_2O$	0.13	CH_2Cl_2	1.68	0	reflux	2	99	48:30:22
12	$TsOH-H_2O$	0.62	CH_2Cl_2	1.68	0	reflux	2	98	53:29:18
13	H_2SO_4	0.13	CH_2Cl_2	1.68	0.21	reflux	6	76	40:22:38[c]
14	H_2SO_4	0.13	CH_2Cl_2	1.68	0.84	reflux	6	80	43:22:35[c]
15	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0	reflux	2	96	49:24:27
16	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0[d]	reflux	2	97	46:31:23
17	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0[e]	reflux	2	99	45:33:21
18	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0.21	reflux	2	97	47:35:18
19	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0.20[e]	reflux	2	90	32:24:44[c]
20	70% $HClO_4$	0.13	CH_2Cl_2	1.60	1.1	reflux	2	0	
21	70% $HClO_4$	0.13	CH_2Cl_2	1.18	4.1	reflux	2	0	
22	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0	reflux	6	99	44:31:25
23	70% $HClO_4$	0.13	CH_2Cl_2	1.68	0.21	reflux	6	93	41:37:22
24[b]	70% $HClO_4$	175	H_2O	1.68	0	ambient	2	83	66:10:24
25	CF_3SO_3H	0.12	CH_2Cl_2	1.67	0	ambient	2	97	53:31:16
26	CF_3SO_3H	0.12	CH_2Cl_2	1.68	0	reflux	6	95	48:28:24
27	CF_3SO_3H	0.12	CH_2Cl_2	1.68	0.20	reflux	6	99	41:34:25
28	$CF_3SO_3H + CF_3COOH$	0.12 + 13.0	CH_2Cl_2	1.51	0	ambient	2	98	25:48:27
29[b]	$CF_3SO_3H + CF_3COOH$	0.30 + 10.9	CH_2Cl_2	16.0	0	ambient	2	99	31:48:21

[a] 6.0 mmol $ArCH_2OH$. [b] 0.60 mmol $ArCH_2OH$. [c] Other products include some unreacted starting material. [d] Also contains 0.79 mmol of MeOH/mmol of $ArCH_2OH$. [e] Also contains 1.5 mmol of H_2O/mmol of $ArCH_2OH$.

molecular weight derivatives are described in the Experimental Section. Although it is known that CTV contains six aromatic protons and CTTV contains eight aromatic protons, the number of aromatic protons in the higher molecular weight analogue(s) is not known. Direct integration therefore yields the molar ratio of monomer units due to each of the three types of products, rather than the actual molar ratio of CTV:CTTV:other products.

The product ratios resulting from cyclization of 3,4-bis(methyloxy)benzyl alcohol using various reaction conditions are listed in Table I. The acids used and their relative strength are $CF_3COOH < CH_3SO_3H < p\text{-}CH_3PhSO_3H < H_2SO_4 < HClO_4 < CF_3SO_3H$. The acids range from a relatively weak acid, CF_3COOH, to the superacids, $HClO_4$ and CF_3SO_3H.[19] In general, the stronger the acid is, the faster the cyclooligomerization reaction. Because there is apparently no difference in the reactivity of an ion pair and that of the corresponding free carbenium ion in carbocationic polymerizations,[20] the differences in the rates of cyclooligomerization initiated by the different acids must result from differences in the concentration of electrophilic species. That is, the strongest acid evidently creates the highest concentration of electrophilic species. The concentration of electrophilic species is affected by both the strength and the concentration of the acid. Strong acids favor a higher equilibrium concentration of ionic carbenium species (Scheme I) because the conjugate bases of strong acids, and therefore the counteranions of the carbenium ions, are nonnucleophilic. However, because the conjugate bases of weak acids are more nucleophilic, formation of the esters of the 3,4-bis(methyloxy)benzyl alcohol is favored when the weak acid is present in low concentration. In this case, carbenium ions are formed by activation with excess acid.[21,22]

As shown in Table I, CF_3COOH is too weak an acid to catalyze cyclization (entry 1) because the formation of the covalent ester is favored by the high nucleophilicity of the trifluoroacetate anion. However, excess CF_3COOH is effective since the excess acid catalyzes ionization of the trifluoroacetate[21,22] (entries 2–7). A substantial amount of higher molecular weight products also forms. However, CTTV is the predominant product when both a large excess of CF_3COOH and high dilution conditions are used (entry 5). Using these conditions, we have developed a large-scale synthesis with which CTTV can be isolated in 55% yield.

As the acid strength increases to that of CH_3SO_3H (entries 8–10) and *p*-toluenesulfonic acid (TsOH) (entries 11 and 12), the reaction proceeds with only a catalytic amount of acid. Both $HClO_4$ (entries 15–24) and CF_3SO_3H (entries 25–27) also catalyze electrophilic cyclooligomerization.

The product precipitates out of the reaction mixture either when the acid itself or water is used as solvent or when CH_3SO_3H, H_2SO_4, $HClO_4$, or CF_3SO_3H is used to initiate cyclooligomerization in CH_2Cl_2 solutions. That is, CTV and possibly the other products apparently form complexes with these acids, which are insoluble in CH_2Cl_2; the neutral products are completely soluble. The CH_2Cl_2 reaction mixtures are also slightly turbid in the presence of *p*-toluenesulfonic acid but are homogeneous in the presence of CF_3COOH. In addition, all previous experiments using either the acid itself or CH_3COOH as solvent report that CTV is always the main product.[3-6,8] However, Umezawa[6] et al.'s results on *N*-veratrylethanolamine-*N*-tosylate cyclizations suggested that the use of solvent encourages CTTV formation, although it was always the minor product. These observations indicate that the

Table II
Product Distribution of the Cyclooligomerizations of 3,4-Bis(methyloxy)benzene with Formaldehyde and with Paraformaldehyde[a]

no.	mmol of $Ar(OMe)_2$	acid	mol of acid/mol of $Ar(OMe)_2$	solvent	mL of solvent/mol of $Ar(OMe)_2$	time, h	yield, %	product distribution CTV:CTTV:other
				37% Aqueous Formaldehyde				
1	7.2	CF_3COOH	9.0	H_2O	0.55	2	94	36:21:43[b]
2	7.2	H_2SO_4	12.3	H_2O	0.83	2	99	63:20:17
3	7.2	70% $HClO_4$	8.0	H_2O	0.55	2	97	28:22:50[b]
				Paraformaldehyde				
4	340	CF_3COOH	1.5	CH_2Cl_2	1.1	30	90	51:29:20
5	290	CF_3COOH	1.8	CH_2Cl_2	1.2	22	100	56:31:13
6	7.2	CF_3COOH	1.8	CH_2Cl_2	1.2	22	100	46:27:27
7	0.72	CF_3COOH	9.0	CH_2Cl_2	13	4	52	50:19:31[b]
8	7.8	H_2SO_4	2.6	H_2O	1.1	22	0	
9	7.8	70% $HClO_4$	2.5	H_2O	1.1	22	0	

[a] 1.1–1.8 mol of CH_2O/mol of $Ar(OMe)_2$; ambient reaction temperature. [b] Other products include a small amount of unreacted starting material.

product distribution is kinetically controlled, with the compound forming the fastest rather than the most thermodynamically stable compound being the major product.

We have found that the inhomogeneous reaction mixture becomes homogeneous by the addition of DMSO and have therefore studied its effect on the product distribution. In addition to solubilizing the reaction mixture, DMSO is basic enough to form relatively weak onium type complexes with aryl carbenium ions, which would slow the cyclization reaction and possibly favor CTTV formation.[18] Complexation by DMSO is confirmed by the fact that the colored reaction mixture becomes colorless upon addition of DMSO. As expected, when DMSO is added to reactions involving CH_3SO_3H, it decreases the rate of reaction and prevents it from going to completion (entries 9 and 10 vs entry 8). However, the ratio of CTV to CTTV is essentially the same. Incomplete conversions are also seen in reactions initiated by H_2SO_4 (entries 13 and 14) and $HClO_4$ (entries 18, 20, and 21). However, more DMSO is required to affect the $HClO_4$-initiated reactions although it eventually inhibits the reaction completely (entries 20 and 21). In the cases of $HClO_4$- and CF_3SO_3H-initiated cyclooligomerizations, addition of DMSO does seem to slightly increase the relative amount of CTTV formed (entries 18 vs 15, 23 vs 22, and 27 vs 26). Therefore, weak bases such as DMSO decrease the rate of electrophilic cyclooligomerization reactions but only affect the product distributions of reactions catalyzed by strong acids that involve a higher concentration of ion pairs. This agrees with the influence of weak bases such as DMSO and DMA on the carbocationic polymerization of olefins.[23]

The results in Table I also demonstrate that prolonged reaction times (entries 7 vs 6, 22 vs 15, 23 vs 18), changes in temperature (entry 2 vs 3), and the addition of small amounts of H_2O (entry 17 vs 15) and methanol (entry 16 vs 15) have very little effect on the product distribution. However, more CTV is produced in solvents that it is not soluble in such as H_2O (entries 4 vs 3, 24 vs 15–23), while more CTTV is produced in homogeneous reaction mixtures (entry 5).

In addition to causing differences in the ability to catalyze electrophilic cyclooligomerization, the strength of the acid affects the product distribution. Comparison of entries 8, 22, and 26 demonstrates that the amount of CTV increases while that of CTTV decreases when the acid strength increases from that of CH_3SO_3H to $HClO_4$ to CF_3SO_3H. In contrast, CTTV is the major product formed (entries 2, 3, and 5) in all reactions involving CF_3COOH in CH_2Cl_2 solutions. Therefore, if CF_3COOH is added in large excess to the CF_3SO_3H-initiated cyclooligomerizations, there is a substantial increase in the amount of CTTV formed (entries 28 and 29 vs 25), demonstrating that CTTV formation is favored not only by homogeneous reaction conditions but also by weak acids. Since only a low concentration of active species is produced by weak acids, CTTV is evidently the thermodynamic product.

Oligomerization of 1,2-bis(methyloxy)benzene with either formaldehyde or paraformaldehyde is similar to the 3,4-bis(methyloxy)benzyl alcohol cyclization in that both involve oxonium ions that are in equilibrium with the corresponding carbenium ions. However, as shown in Table II, the reactions involving formaldehyde and paraformaldehyde often do not go to completion, especially when water is used as solvent (entries 1, 3, and 7–9). This is probably due to differences in solubility of the starting components, although the leaving groups are also slightly different. That is, while 3,4-bis(methyloxy)benzyl alcohol is soluble in both H_2O and organic solvents, 1,2-bis(methyloxy)benzene is insoluble in H_2O, and two liquid layers result when H_2O is used as the solvent in reactions involving paraformaldehyde. In addition, paraformaldehyde is almost insoluble in CH_2Cl_2. However, CTV is the main product in all cases, even in reactions involving CF_3COOH.

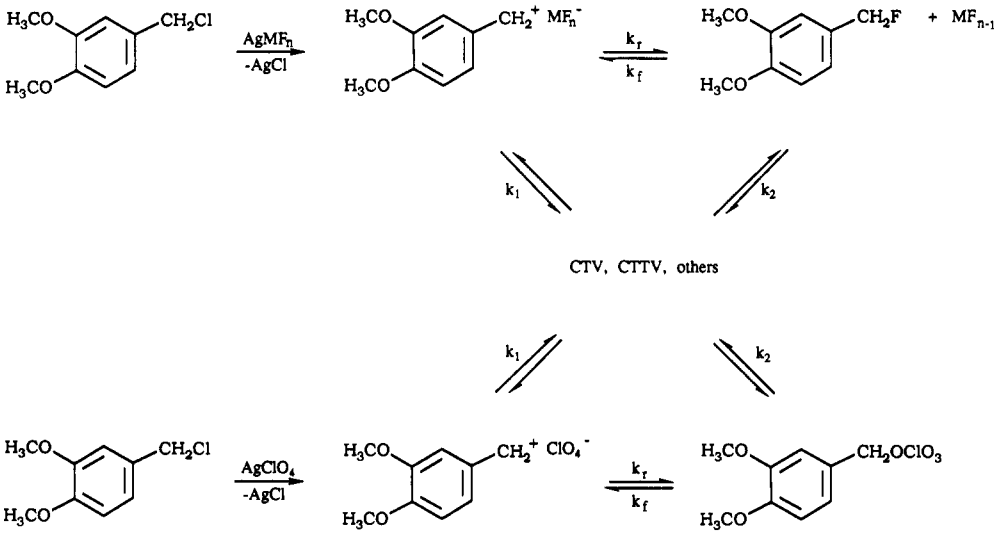
Two examples of *N*-veratrylethanolamine-*N*-tosylate cyclizations are presented in Table III. Umezawa[6] et al. have previously reported the results of *N*-veratrylethanolamine-*N*-tosylate cyclizations under a variety of reaction conditions. Compared to the 80% yield of CTV and the absence of any CTTV obtained when $HClO_4$ was used as both acid and solvent, the CTV:CTTV ratio dropped to 53:12 when the reaction mixture was diluted with CH_3COOH, 41:17 when H_2SO_4 was used as acid and CH_3COOH as solvent, and 25:14 when *p*-toluenesulfonic acid was the acid and CH_3COOH was the solvent. In addition, when *N*-veratrylethanolamine-*N*-tosylate was cyclized in the presence of *p*-toluenesulfonic acid in organic solvents, the CTV:CTTV ratio varied from 56:21 in benzene, 44:11 in $CHCl_3$, and 23:13 in toluene. These results suggested that the use of solvent increases CTTV formation and decreases CTV formation. Our results in Table III substantiate this. That is, when the $HClO_4$-catalyzed reaction is diluted with a nonsolvent (H_2O), the yield of CTV is still very high (entry 6), albeit lower than when only the acid is present.[6] Again, CTV formation drops dramatically while substantial CTTV is formed when the reaction is initiated by a weak organic acid in a CH_2Cl_2 solution (entry 1).

Table III
Product Distribution of the Cyclooligomerizations of *N*-Veratrylethanolamine-*N*-tosylate and 3,4-Bis(methyloxy)benzyl Chloride

no.	mmol of $ArCH_2R$	initiator	mol of initiator/mol of $ArCH_2R$	solvent	mL of solvent/mmol of $ArCH_2R$	temp	time, h	yield, %	product distribution CTV:CTTV:other
				R = $-N(Ts)CH_2CH_2OH$					
1	1.1	CF_3COOH	11.9	CH_2Cl_2	8.2	reflux	4	88	33:38:29
2	0.27	70% $HClO_4$	381	H_2O	3.7	ambient	4	69	65:12:23
				R = –Cl					
3	1.3	$AgBF_4$	1.1	CH_2Cl_2	8.4	ambient	2	77	91:9[a]
4	1.3	$AgPF_6$	1.1	CH_2Cl_2	8.5	ambient	2	88	33:29:38
5	1.1	$AgClO_4$	1.2	CH_2Cl_2	9.0	ambient	2	76	52:23:25

[a] 9% CTTV and higher molecular weight products whose ^1H NMR resonances are not resolved.

Scheme II
Generation of 3,4-Bis(methyloxy)benzyl Carbenium Ions and Other Intermediates from 3,4-Bis(methyloxy)benzyl Chloride and Silver Salts



As stated previously, we have used silver salts to generate benzyl carbenium ions from 3,4-bis(methyloxy)benzyl chloride. However, benzyl chlorides can also be ionized by hydrogen bonding of the electron-rich chloride with an acidic proton.[18] The silver salts could therefore potentially be used catalytically since protons are generated during the reaction. However, we have used at least stoichiometric amounts of the silver salts in all cases in order to encourage reaction through a single mechanism. The results of these cyclooligomerizations are presented in Table III. Surprisingly, CTV is formed almost exclusively when $AgBF_4$ is used. In contrast, both $AgClO_4$ and $AgPF_6$ result in substantial amounts of CTTV and higher molecular weight products. Each of these three reactions was performed three times with nearly identical results.

Because there is no difference in the reactivity of an ion pair and that of the free carbenium ion in carbocationic polymerizations,[20] the counteranion should theoretically have little influence on the rate of electrophilic substitution. However, the nucleophilicity of the counteranion does influence the overall rate of reaction by influencing the rate at which the ion pair collapses back to a covalent species and therefore the concentration of carbenium ions available.[18] Because Lewis acids function here primarily as halide acceptors, PF_6^- and BF_4^- reduce the rate of collapse of the ionic species. As shown in Scheme II, these counteranions can, however, donate a halide to re-form a covalent species. In contrast, the perchlorate salt cannot donate a halide but can rearrange to form a perchlorate ester.[18,22,24]

Because BX_3 is 1 order of magnitude more ionizing than PX_5,[18] k_1 in Scheme II is evidently greater than k_r when MF_n^- is BF_4^- and less than or equal to k_r when MF_n^- is PF_6^-. These results again indicate that CTV is the kinetic product of electrophilic cyclooligomerization. When $AgClO_4$ is used, k_1 and k_r are apparently comparable to those of $AgPF_6$ reactions. In addition, $AgClO_4$ goes into solution much slower than either $AgBF_4$ or $AgPF_6$, with a correspondingly slow development of color characteristic of carbenium ion formation. Both $AgPF_6$ and $AgClO_4$ produce violet solutions, whereas $AgBF_4$ produces a pinkish purple solution.

Discussion

The ease of ionization to form a benzyl carbenium ion, and therefore the reactivity of the 3,4-bis(methyloxy)-benzyl derivatives is 3,4-bis(methyloxy)benzyl chloride > 3,4-bis(methyloxy)benzyl alcohol > *N*-veratrylethanolamine-*N*-tosylate. Because only 3,4-bis(methyloxy)benzyl alcohol was cyclooligomerized by an ample variety of conditions, it is not possible to directly compare the three reagents. However, there are a number of indications that CTV is the kinetic product of cyclization. First, superacids, which generate a high concentration of carbenium ions and therefore fast reaction rates, favor CTV formation, whereas more CTTV is formed when weaker acids, which generate a low concentration of carbenium ions and therefore slow reaction rates, are used. Second, more CTV is formed when no solvent[6] or when nonsolvents such as H_2O are used. Last, CTV is formed almost exclusively when the most reactive 3,4-bis(methyloxy)benzyl chloride is cyclized with $AgBF_4$, in which case a high concentration of the pure benzyl carbenium ion apparently forms. In addition, CTTV is the predominant product (65% con-

Table IV
Product Distribution of the Cyclooligomerizations of 3,4-Bis(*n*-heptyloxy)benzyl Alcohol[a]

no.	mol of CF_3COOH/ mol of $ArCH_2OH$	mL of solvent/ mmol of $ArCH_2OH$	temp	time, h	product distribution CTV-7: CTTV-7:other
1	2.18	16.7	ambient	4	31:53:16[b]
2	10.9	16.0	5 °C	5	12:64:24
3	10.9	16.0	ambient	4	21:66:13
4	10.9	16.0	reflux	5	17:58:25
5	45.2	13.5	ambient	4	20:64:16

[a] 0.59 mmol of $ArCH_2OH$; quantitative conversion except where noted. [b] Other products include a small amount of unreacted $ArCH_2OH$.

version) when the less reactive 3,4-bis(methyloxy)benzyl alcohol is cyclized with a large excess of a weak acid (CF_3COOH) under dilute reaction conditions. In this way, CTTV was isolated from a large-scale synthesis in 55% yield.

Table IV demonstrates that the optimum synthesis of CTTV can also be extended to 3,4-bis(*n*-alkyloxy)benzyl alcohols with similar results. That is, approximately 65% of 3,4-bis(heptyloxy)benzyl alcohol is converted to CTTV-7 when a large excess of CF_3COOH and dilute reaction conditions are used (entries 2, 3, and 5). Slightly higher yields of the cyclotetramer are obtained at lower reaction temperatures (entries 2, 3, and 5 vs entry 4).

As shown in Chart I, CTTV is flexible. It rapidly interconverts between two sofa conformations at room temperature and above but can be frozen into a rigid crown conformation at −10 °C.[4] In contrast, CTV exists in the rigid crown conformation shown in Chart I[1-3] and does not become conformationally mobile even at 200 °C.[25] Therefore, CTTV is evidently the more thermodynamically stable cyclization product compared to CTV. Since CTV appears to be the kinetic product, an important question is whether it is possible for the product distribution to reach its thermodynamic equilibrium. In order for a thermodynamic equilibrium to be reached, there must be a kinetic pathway through which a given cycle can either gain or lose a monomer unit. This kinetic pathway would obviously involve ring cleavage. Ring cleavage occurs when either halogenation or nitration of CTV is attempted.[26] In addition, because CTV rather than CTTV is the main product from condensation of bis[3,4-bis(methyloxy)phenyl]methane with formaldehyde, bis[3,4-bis(methyloxy)phenyl]methane is thought to undergo a reverse Friedel–Crafts reaction to produce 1,2-bis(methyloxy)benzene and a 3,4-bis(methyloxy)benzyl carbenium ion.[4b] We have therefore attempted to equilibrate pure CTV and CTTV in NMR sample tubes in the presence of CF_3COOH and in the presence of CF_3SO_3H.

Table V summarizes the ^1H NMR analysis of CTTV and CTV equilibrated with excess CF_3COOH and with catalytic CF_3SO_3H for 1 week at room temperature and for up to 9 h at 50 °C. CF_3COOH has no effect on CTTV. However, a 10% of CTV's monomer units have been converted to CTTV after 9 h at 50 °C in the presence of CF_3COOH. CF_3SO_3H has a more dramatic effect on both CTTV and CTV. After 9 h at 50 °C, approximately 31% of CTTV's repeat units have been converted to CTV, with an unresolved shoulder due to higher molecular weight products. CTV's repeat units are converted to CTV: CTTV:others in the ratio of 68:11:21 after 4 h at 50 °C without any further rearrangement up to 9 h. Although CF_3SO_3H has only a slight effect on CTTV at room temperature, CTV is rearranged to approximately the same extent after 1 week at room temperature as it is after 9 h at 50 °C. These results demonstrate that ring cleavage is possible, especially if a superacid such as CF_3SO_3H is used. The results also confirm that CTV is less thermodynamically stable than CTTV since it is much more easily converted to other products than CTTV is. As expected, the higher molecular weight analogue(s) is more stable than both CTV and CTTV since more CTV is converted to it than to CTTV by CF_3SO_3H. However, since the product ratios from CTV and CTTV do not approach each other under similar equilibration conditions, thermodynamic equilibrium is not reached with either CF_3COOH or CF_3SO_3H at 50 °C in up to 9 h.

Table V
Equilibration of CTTV and CTV with CF_3COOH and CF_3SO_3H

no.	acid	mol of acid/ mol of repeat unit	mL of CH_2Cl_2/ mmol of repeat unit	temp	time	product distribution CTV: CTTV:other
			CTTV			
1	CF_3COOH	7.52	4.29	50 °C	9 h	0:100:0
2	CF_3SO_3H	0.33	3.00	ambient	1 week	9:91:0
3	CF_3SO_3H	0.33	3.00	50 °C	4 h	20:80[a]
					9 h	31:69[a]
			CTV			
4	CF_3COOH	7.52	4.29	50 °C	9 h	90:10:0
5	CF_3SO_3H	0.33	3.00	ambient	1 week	60:13:27
6	CF_3SO_3H	0.33	3.00	50 °C	4 h	68:11:21
					9 h	67:11:22

[a] Includes an unresolved shoulder due to higher molecular weight analogue(s).

These results further demonstrate that CF_3COOH is a superior acid for cyclotetramerization of 3,4-bis(methyloxy)benzyl alcohol since it can cleave the CTV ring system as it forms but does not affect CTTV. In contrast, while CTV formation is favored by fast reactions using superacids, the CTV ring system is also more easily cleaved under the same conditions. Therefore, cyclotrimerization of 3,4-bis(methyloxy)benzyl alcohol should be performed by using superacids in a nonsolvent in which CTV completely precipitates out of solution as it forms. Cyclotrimerization of 3,4-bis(methyloxy)benzyl chloride using $AgBF_4$ is even more effective, apparently because $AgBF_4$ provides not only fast reaction kinetics involving a high concentration of benzyl carbenium ions but also a less oxidizing medium. The synthesis and characterization of branched polymers containing CTTV units based on the cyclotetramerization reaction elaborated in this paper are reported in a subsequent paper from our laboratory.[17]

Experimental Section

Materials. CH_3SO_3H (Aldrich, 99%), CF_3COOH (Fisher Scientific, >99%), CF_3SO_3H (Aldrich, 98%), 3,4-bis(methyloxy)benzaldehyde (veratraldehyde) (Aldrich, 99%, or Lancaster Synthesis, 98%), 1,2-bis(methyloxy)benzene (veratrole) (Lancaster Synthesis, 97%), 3,4-bis(methyloxy)benzyl alcohol (veratryl alcohol) (Aldrich, 96%, or Lancaster Synthesis, 97%), formaldehyde (Fisher Scientific, 37 wt % in water), HCl (Fisher Scientific, 37% in H_2O), $HClO_4$ (Fisher Scientific, 70%), H_2SO_4 (Fisher Scientific, 98%), paraformaldehyde (Aldrich, 95%), pyridine (Fisher Scientific), and *p*-toluenesulfonic acid monohydrate (Aldrich, 99%) were used as received. Diethyl ether was distilled from $LiAlH_4$, and $SOCl_2$ was distilled from pyridine. CH_2Cl_2 used as the cyclooligomerization solvent was distilled from CaH_2. Doubly deionized and distilled H_2O was also used as solvent. The synthesis of 3,4-bis(*n*-heptyloxy)benzyl alcohol was described previously.[16]

Techniques. ^1H NMR spectra (δ, 200 MHz) were recorded on a Varian XL-200 spectrometer. All spectra were recorded in

$CDCl_3$ with TMS as the internal standard. Unless noted otherwise, all spectra from the cyclooligomerization experiments were recorded at 55 °C; all other spectra were recorded at room temperature.

Purity and relative elution volumes were determined by gel permeation chromatography (GPC) with a Perkin-Elmer Series 10 LC instrument equipped with an LC-100 column oven (40 °C), an LC-600 autosampler, and a Nelson Analytical 900 Series data station. Measurements were made with a UV detector with $CHCl_3$ as solvent and a 100-Å PL gel column (0.9 mL/min).

Synthesis of *N*-Veratrylethanolamine-*N*-tosylate. *N*-Veratrylethanolamine-*N*-tosylate was prepared as described in the literature from 3,4-bis(methyloxy)benzaldehyde.[6] Mp: 122–123 °C (from benzene) (lit.[6] mp 122–123 °C). Purity: >99.9%. ^1H NMR: 1.81 (1 H, bs, $-OH$), 2.44 (3 H, s, $-ArCH_3$), 3.22 (2 H, t, $-CH_2OH$), 3.50 (2 H, t, $-CH_2N(Ts)-$), 3.81 and 3.87 (6 H, 2s, $-OCH_3$), 4.29 (2 H, s, $ArCH_2-$), 6.81 (3 aromatic H of the veratryl ring, 2 overlapping s), 7.36 (2 aromatic H ortho to $-CH_3$, d), 7.76 (2 aromatic H ortho to $-SO_2-$, d).

Synthesis of 3,4-Bis(methyloxy)benzyl Chloride. 3,4-Bis(methyloxy)benzyl chloride was prepared following a literature procedure and then stored at 4 °C in a desiccator.[22] If prolonged reaction times are used in the absence of pyridine, the product cyclooligomerizes either before or after it is isolated. In addition, pyridine should be used only stoichiometrically relative to $SOCl_2$ to prevent formation of the pyridinium–benzylic chloride salt.

A solution of $SOCl_2$ (9.1 mL, 0.13 mol) in dry diethyl ether (70 mL) was added in four portions over 10 min via an addition funnel to a solution of 3,4-bis(methyloxy)benzyl alcohol (10 g, 61 mmol) and pyridine (1 mL, 12 mmol) in dry diethyl ether (150 mL) under an argon atmosphere. After the reaction mixture was stirred at room temperature for 15 min, H_2O (100 mL) was added, and the two layers were separated. The organic layer was washed four times with aqueous $NaHCO_3$. The combined aqueous layers were then extracted two times with diethyl ether, and the combined ether extracts were washed one time with H_2O. After the organic layers were dried over Na_2SO_4, the solvent was removed on a rotary evaporator, and the resulting liquid was distilled. The fraction distilling at 120–124 °C (ca. 10 mm Hg) was collected. The slightly yellow distillate solidified on standing to yield 7.0 g (61%) of 3,4-bis(methyloxy)benzyl chloride as a white solid. Mp: 48–50 °C. Purity: 99.6%. ^1H NMR: 3.83 (6 H, s, $-OCH_3$), 4.53 (2 H, s, $-CH_2Cl$), 6.80 and 6.89 (3 aromatic H, two s).

Cyclooligomerizations and Analysis of the Product Distributions. Cyclooligomerization of 3,4-Bis(methyloxy)benzyl Alcohol and 3,4-Bis(*n*-heptyloxy)benzyl Alcohol. In a typical procedure (entry 9, Table I), CH_3SO_3H (0.072 g, 0.75 mmol) was added dropwise to a solution of 3,4-bis(methyloxy)-benzyl alcohol (1.0 g, 5.9 mmol) in CH_2Cl_2 (10 mL) in a 25-mL round-bottomed flask equipped with a reflux condenser and a drying tube. The reaction mixture immediately turned purple, and a precipitate formed. DMSO (0.16 g, 1.3 mmol) was added dropwise, and the reaction mixture became homogeneous and colorless. After refluxing 6 h, the reaction was quenched with triethylamine, and the solvent was removed by rotary evaporation. The residue was then dissolved in acetone (15 mL), precipitated in H_2O (100 mL), collected, and dried in vacuo to yield 0.68 g (76%) of a waxy solid. ^1H NMR analysis: CTV:CTTV:other products = 40:22:38.

3,4-Bis(*n*-heptyloxy)benzyl alcohol was cyclooligomerized similarly by using CF_3COOH in the absence of DMSO. The results are presented in Table IV.

Condensation of 1,2-Bis(methyloxy)benzene with Formaldehyde. Using entry 3 of Table II as an example, 70% $HClO_4$ (5 mL, 58 mmol) was added to a mixture of 1,2-bis(methyloxy)-benzene (1.0 g, 7.2 mmol) and 37% aqueous formaldehyde (1 mL, 13 mmol) in H_2O (4 mL). The reaction mixture soon became a white paste but was stirred at room temperature for 2 h. Additional H_2O was then added to completely precipitate the product mixture. This was collected and dried to yield 1.1 g (97%) of white powder. ^1H NMR analysis: CTV:CTTV:other products = 28:22:50.

Condensation of 1,2-Bis(methyloxy)benzene with Paraformaldehyde. In a typical procedure (entry 4, Table II), 1,2-bis(methyloxy)benzene (60 g, 0.34 mol) in CH_2Cl_2 (60 mL) was added to a mixture of paraformaldehyde (18 g, 0.60 mol) and CF_3COOH (40 mL, 0.52 mol) in CH_2Cl_2 (300 mL). After the mixture was stirred at room temperature for approximately 6 h, a blue-green color and a white dispersion had developed. The reaction mixture was stirred at room temperature for 30 h, and the solvent was removed by rotary evaporation. A slurry of the residue in acetone (200 mL) was precipitated in H_2O (1000 mL), collected, washed with additional H_2O, and dried in vacuo to obtain 70 g (90%) of white solid. ^1H NMR analysis: CTV:CTTV: other products = 51:29:20.

The above product was combined with the product from entry 5 of Table II and recrystallized in several fractions from benzene–$CHCl_3$ (initially 2:1 v/vol). All CTV fractions were combined, and all CTTV fractions were combined. Two additional fractions of higher molecular weight, i.e., shorter GPC elution times, were obtained. The aromatic ^1H NMR chemical shifts, melting points, and GPC elution times are listed.

	ppm	mp, °C	elution time, min
CTV	6.84	281	14.02
CTTV	6.61 (50 °C)	339	13.38
3rd fraction	6.46	198	12.80
4th fraction	6.49	318	12.73

Cyclooligomerization of *N*-Veratrylethanolamine-*N*-tosylate. Using entry 2, Table III, as an example, 70% $HClO_4$ (9 mL, 0.10 mol) was added to a solution of *N*-veratrylethanolamine-*N*-tosylate (0.10 g, 0.27 mmol) in H_2O (1 mL), resulting immediately in a violet color and a turbid solution. After stirring at room temperature for 4 h, the pinkish purple reaction was quenched with NEt_3 (0.5 mL). The solvent was removed on a rotary evaporator, resulting in 29 mg (69%) of product. ^1H NMR analysis: CTV:CTTV:other products = 65:12:23.

Cyclooligomerization of 3,4-Bis(methyloxy)benzyl Chloride. 3,4-Bis(methyloxy)benzyl chloride was cyclized by using stoichiometric $AgBF_4$, $AgPF_6$, and $AgClO_4$ as in the following example (entry 3, Table III). 3,4-Bis(methyloxy)benzyl chloride (0.22 g, 1.2 mmol) and $AgBF_4$ (0.25 g, 1.3 mmol) were placed in a 25-mL round-bottomed flask equipped with a septum and an air-cooled condenser with an argon inlet/outlet. CH_2Cl_2 (10 mL) was added, and the mixture immediately became blue in color, purple within 4 min, and pinkish purple after 10 min. As the $AgBF_4$ went into solution and the mixture became almost homogeneous, AgCl began to precipitate out. After the mixture was stirred at room temperature for 2 h, much precipitate had collected, and the color was quenched with NEt_3 (0.5 mL). AgCl was filtered off and washed three times with CH_2Cl_2 (75 mL total). The yellow CH_2Cl_2 solution was washed three times with H_2O and dried over Na_2SO_4, and the solvent was then removed on a rotary evaporator. After the residue was dried in vacuo, 0.15 g (77%) of product was scraped out of the flask. ^1H NMR analysis: CTV:other products including CTTV = 91:9.

Large-Scale Synthesis and Isolation of Cyclotetraveratrylene (CTTV). A solution of 3,4-bis(methyloxy)benzyl alcohol (5.0 g, 30 mmol) in CH_2Cl_2 (20 mL) was added dropwise to an ice-cooled solution of trifluoroacetic acid (25 mL, 0.32 mol) in CH_2Cl_2 (200 mL). This resulted in an immediate purple color. After the reaction mixture was stirred for 4 h in an ice–water bath, it was neutralized with aqueous NaOH and the two layers were separated. The solvent was removed on a rotary evaporator, and the residue was washed several times in a fritted glass funnel with H_2O and twice with acetone. The resulting white solid was then recrystallized from $CHCl_3$–benzene (80 mL:30 mL) to yield 2.5 g of CTTV (55%) in two fractions. Purity: 99.1%. Mp: 342 °C (lit.[4b] mp 319–321 °C). ^1H NMR: 3.62 (8 H, s, $ArCH_2Ar$), 3.80 (24 H, s, $-OCH_3$), 6.60 (8 aromatic H, s). The ^1H NMR of CTV[8] is as follows: 3.56 (H_{eq}) and 4.78 (H_{ax}) (6 H, AB q, $ArCH_2Ar$), 3.84 (18 H, s, $-OCH_3$), 6.84 (6 aromatic H, s).

Equilibration of CTV and CTTV with CF_3COOH and CF_3SO_3H. In a typical experiment, 2 drops of CF_3SO_3H (approximately 15 mg, 0.15 mmol) was added to a solution of CTV (70 mg, 0.47 mmru) in $CDCl_3$ (1.4 mL) in an NMR sample tube. The solution immediately became turbid and purple. While the solution was maintained at 50 °C, the ^1H NMR spectra were recorded after 5 and 9 h. Separate experiments were also recorded

after 1 week at room temperature. The product analysis of CTV and CTTV equilibrations in the presence of CF_3SO_3H and in the presence of CF_3COOH are listed in Table V.

Acknowledgment. Financial support from the U.S. Army Research Office is gratefully acknowledged.

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Registry No. CTV, 1180-60-5; CTV-7, 96189-54-7; CTTV, 17873-58-4; CTTV-7, 126948-24-1; CF_3CO_2H, 1493-13-6; CH_3SO_3H, 75-75-2; TsOH, 104-15-4; H_2SO_4, 7664-93-9; $HClO_4$, 7601-90-3; $AgBF_4$, 14104-20-2; $AgPF_6$, 26042-63-7; $AgClO_4$, 7783-93-9; (formaldehyde)(veratrole) (copolymer), 133165-71-6; *N*-veratryletheanolamine-*N*-tosylate (homopolymer), 133165-73-8; 3,4-bis(methyloxy)benzyl chloride (homopolymer), 133165-74-9; 3,4-bis(*n*-heptyloxy)benzyl alcohol (homopolymer), 133165-76-1; 3,4-bis(methyloxy)benzyl alcohol (homopolymer), 133165-77-2.