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Research Communication

A Facile Synthesis of Cyclotriveratrylene[1]

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Abstract. Cyclotriveratrylene (CTV) can be readily synthesized by chloromethylation or bromomethylation of dimethoxybenzene with halomethyloctyl ether in the presence of $SnCl_4$. The reaction provides the trimer exclusively and in high yield. Recrystallizations from benzene or $CHCl_3$ yielded the solvent inclusion complexes and did not remove other inclusion impurities. Flash chromatography on silica yielded the pure CTV. ^{13}C NMR shows only five signals and no impurities

Key words. Cyclotriveratrylene, halomethyloctyl ethers, dimethoxybenzene.

Cyclotriveratrylene (CTV) [1] (Figure 1) attracts considerable attention for three main reasons: (a) existence in a 'crown' conformation with a high energy barrier for interconversion [2–15]; (b) the formation of stoichiometric inclusion compounds with small neutral molecules [13, 14]; and (c) the existence of chiral derivatives of CTV [12, 13].

The synthesis of CTV (m.p. 234°C) was first described by Robinson in 1915 [15], but the structure assigned to it was 2,3,6,7,-tetramethoxy-9,10-dihydroanthracene (m.p. 212–213°C) [6a]). Erdtman, Haglid and Ryhage [3], and later, Lindsey [5] pointed out this error. Erdtman *et al.* [3] showed, by mass spectrometry and NMR, that a tetramer was also present (m.p. 361°C [6b]).

Lindsey [5a] discusses the various reaction conditions and schemes leading to CTV. Warming 3,4-dimethoxybenzyl alcohol in glacial acetic acid, in the presence of H_2SO_4 as catalyst, results in the highest yield reported so far (87%). The reaction of veratrole with formaldehyde in 70% H_2SO_4 at 0°C, yields 70% CTV. Other reaction conditions, such as formaldehyde and HCl involve, as we know today, undesirable formation of bis-chloromethyl ether (BCME) [16]. In all methods, crystallization or sublimation techniques were used for separating CTV from other products.

During the course of investigations on safer halomethylating agents [16] we attempted halomethylation of veratrole with chloromethyloctyl ether and bromomethyl octyl ether. In these attempts, an unexpected producct, a solid, m.p. 229–230°C was obtained in 97% yields. Examination of the proton NMR, mass and IR spectra led us to conclude that this compound is cyclotriveratrylene [17]. Re-examination of CTV, m.p. 226–227°C, made by our procedure, shows the presence of some foreign bands at 6.62, 6.48, 4.42, 3.72, 3.68 (singlets) in the NMR spectrum. Continued recrystallizations from benzene do not remove these impurities, nor does it increase the melting point. Thus, CTV, m.p. 226–227°C was chromatographed on silica and a compound designated as *x* (not identical to the tetramer) less polar, was eluted first (2% of the CTV fraction). Next eluted was CTV ($R_f = 0.4$, hexane/EtOH 4 : 6) m.p. 228–229°C, mixed melting point of

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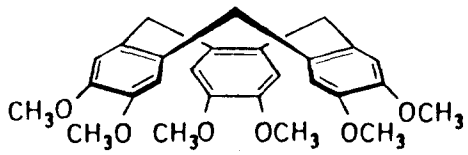


Fig. 1.

the 'precolumn' and 'postcolumn', CTV with authentic CTV made from veratryl alcohol (3,4-dimethoxybenzyl alcohol [3]) gave no depression in temperature. TLC shows one spot (4 : 5 hexane/EtOH, silica) by UV detection or with 25% phosphomolybdic acid in EtOH. Both the NMR and mass spectra show excellent agreement with reported values (see below). In the NMR, bands of the last solvent(s) used in crystallization are very strong and are attributed to the strong clathrating properties of CTV.

We have also tried sublimation of the CTV, m.p. 226–227°C, at 0.2 torr. The sublimation was very slow and the CTV decomposed as indicated by an increase in the m.p. of the residue.

It is believed that previous reports may have disregarded the tendency of CTV to include impurities, such as other reaction products. The melting point test is insensitive in indicating the presence of impurities. The flash column procedure provides a rapid route to high purity CTV and the combined detection by UV and 2.5% phosphomolybdic acid provides higher sensitivity for detection. From the results, the following further conclusions are derived.

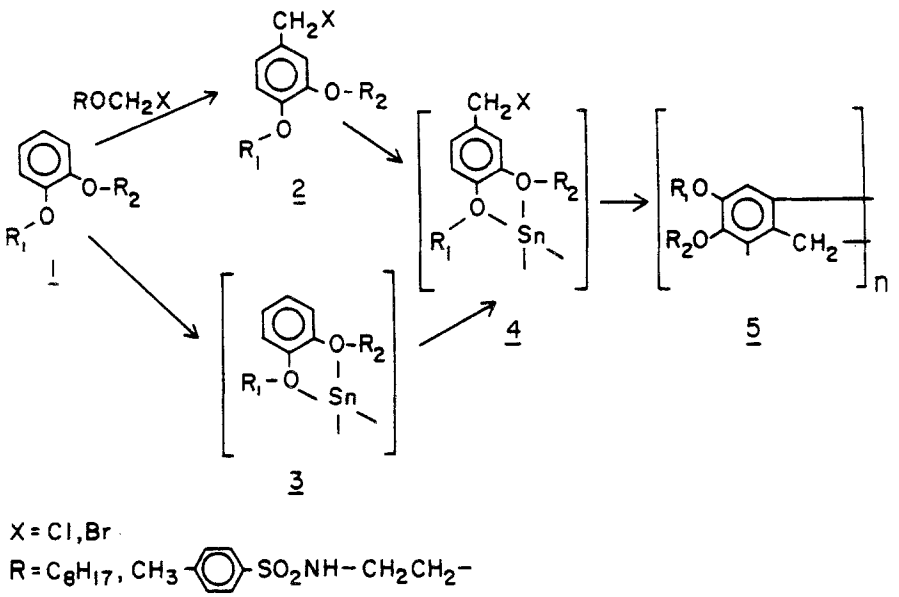
(1) Haloalkyl ethers, including chloromethyl ether, are reluctant to react with veratrole (even after 48 hours no CTV is observed).
(2) Lewis acids, e.g. $SnCl_4$, $ZnCl_2$, $AlCl_3$, catalyse the reaction, leading to CTV in high yields. $SnCl_4$ seems to provide the most convenient conditions and highest yields.
(3) The rate of the reaction depends on the ratio of veratrole to catalyst. If this ratio is 1 : 1, the conversion of veratrole to CTV is complete within a few minutes. The presence of catalytic amounts of Lewis acids results in slow rates (several days to complete conversion).
(4) The stoichiometric complex with $SnCl_4$ is insoluble in the reaction medium (1,2-dichloroethane) and can be isolated prior to reaction with the halomethylating agent. The exact structure of the complex has not yet been determined.

Scheme 1 summarizes these conclusions: the reaction of veratrole (**1**: $R_1 = R_2 = CH_3$) with halomethyloctyl ether is slow and the intermediate, 4-halomethylveratrole (**2**), can be detected only if $ROCH_2X$ is precomplexed with $SnCl_4$ and is present in a large excess relative to veratrole. On the other hand, complexation of **1** with $SnCl_4$ rapidly yields a complex **3** (as yet uncharacterized) leading to intermediate (**4**) and then to cyclotriveratrylene **5** ($n = 3$, $R_1 = R_2 = CH_3$).

Experimental

Cyclotriveratrylene: 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a*,*d*,*g*,]cyclononene.

Bromomethyl-*n*-octylether (4.46 g, 0.020 mol), and 1,2-dimethoxybenzene (veratrole)



Scheme 1.

(2.76 g, 0.02 mol) were dissolved in dry 1,2-dichloroethane (100 mL, over $CaCl_2$). Anhydrous $SnCl_4$ (5.4 g, 2.4 mL, 0.02 mol) was added dropwise with some evolution heat, of and the solution turned purple. After 10 min no veratrole could be detected by TLC (silica, ether–hexane 1 : 1). The reaction mixture was diluted with $CHCl_3$ (100 mL) and the organic layer was washed twice with 1M HCl (100 mL) and then with water to neutral pH. After drying, the solvent was evaporated and a brown semisolid (7.25 g) was obtained. Triturations with ether (5–6 times) removed the soluble and colored components in the reaction mixture and yielded 2.9 g (95%) solid (one spot on TLC). This was dissolved in 10 mL hot $CHCl_3$ and hot hexane added to the point of precipitation to yield 2.49 g solid. Recrystallization from $CHCl_3$/hexane yielded 2.2 g (72%) of pure cyclotriveratrylene, m.p. 229–230°C, recrystallized from benzene m.p. 226–227°C (*lit.* [5]; m.p. 230.5–231°C). TLC.: alumina (EtAc/hex. 1 : 1) $R_f = 0.4$.

NMR of cyclotriveratrylene crystals from $CHCl_3$: ($CDCl_3$, δ, ppm): 7.25 (4.8H, $CHCl_3$,S) 6.83 (S), (6H, Ar) 4.76 (*d*, 3H, CH_2, $J = 14$ Hz), 3.83 (S, 18H) 3.53 (*d*, 8H, CH_2, $J = 14$ Hz). NMR of crystals recrystallized, first from $CHCl_3$ and then from C_6H_6: ($CDCl_3$: δ ppm): 7.35 (2.06H, S, C_6H_6) 7.25 (2.41H, S, $CHCl_3$) the rest as above. *lit* [2]: 6.83, 4.67 (*d*, $J = 14$ Hz), 3.84 (S), 3.48 (*d*, $J = 14$ Hz). *lit* [3]: 6.78, 4.52, 3.84.

Mass spectrum: $M^+ = 450$ (I/base = 100%): $M - 15 = 435$ (34.02%) $M - 31 = 419$ (100%); $m/e = 404$ (8.82%); $m/e = 388$ (82%): $m/e = 312$ (20.3%); $m/e = 299$ (100%); $m/e = 281$ (36.15%); $m/e = 268$ (33.80%); $m/e = 151$ (66.2%) in complete agreement with mass spectrum of cyclotriveratrylene [2].

IR (KBr, cm^{-1}) in parentheses, from Lindsey [5]; 2920 (2915) 2830 (2825) 1608 (1605) 1512 (1508) 1465 (1460) 1450 (1447) 1396 (1390) 1346 (1346) 1264 (1260) 1250 (1220) 1200 (1190) 1152 (1142) 1090 (1085) 1040 (1025) 998 (990) 942 (948) 928 (923) 886 (877) 873 854 (847) 742 (738) 621 (614) cm^{-1}.

CHROMATOGRAPHIC PURIFICATION OF CRYSTALLIZED CTV*

Cyclotriveratrylene, m.p. 226–227°C contains impurity(ies) having the following NMR signals (δ) 6.62, 6.48, 4.42, 3.72, 3.62. This material has a mixed m.p. of 225.5–227°C with an authentic sample of cyclotriveratrylene, made from veratryl alcohol (m.p. 229.5–232°C) [5]. Repeated recrystallizations from benzene did not change the NMR spectrum, nor did it result in an increase in the melting point. Consequently, a sample of 180 mg dissolved in $CHCl_3$ was absorbed onto 3 g silica, the solvent evaporated, and added to 20 g silica and eluted with hexane : EtOAc 4 : 6. Fractions of 10 mL were collected. Fractions contained (after evaporation) 1 mg of a compound x, $R_f = 0.5$ (hexane : EtOAc 4 : 6) and fractions 8 and 9, a mixture of compound x and (CTV) cyclotriveratrylene (total, 4 mg). Fractions 10–22 contained CTV, $R^f = 0.4$ pure (UV detection and 2.5% phosphomolybdic acid in EtOH), m.p. 228–229.5°C, NMR spectrum as reported above, no impurities were detected.

Compound x, $R_f = 0.4$, shows bands at 6.82, 6.62, 3.88 and 3.83 ppm. No band at 3.6 ppm (tetramer) was detected. Sublimation of CTV, m.p. 226–227°C at 220°C (0.2 torr) produced very little sublimate and the residue changed, as indicated by the increase of the m.p. to > 260°C. The carbon-13 NMR (broad decoupling) of CTV, m.p. 226–227°C showed five bands: (1) 147.867 ppm (2C, C and C_2 on ring); (2) 131.899 (1C, C_4 on ring); (3) 113.287 (1C C_6 on ring); (4) 56.050 (6C, OCH_3) and (5) 36.467 ppm (2C, CH_2 on C_4). Impurities are present adjacent to bands 1 (at 147.382), 2 (at 131.899 and 131.629) and 5 (at 34.903 ppm). These impurities are absent in the chromatographed material.

SYNTHESIS OF CYCLOTRIVERATRYLENE WITH VARIOUS LEWIS ACID CATALYSTS

(*a*) *with* $ZnCl_2$

To chloromethyloctylether (178 mg, 1 mol) dissolved in 1,2-dichloroethane (DCE) (5 mL) and dry $ZnCl_2$ (26 mg, 0.2 mmol), a solution of veratrole (138 mg, 1 mmol) in 1.2 DCE (5 mL) was added with magnetic stirring. A bright violet color developed. TLC showed, after 2 hours, the presence of veratrole. After 48 hours, the usual work-up afforded cyclotriveratrylene. TLC corresponded with authentic cyclotriveratrylene. Chromatographic separation on silica provides 97 mg (65%) of CTV.

(*b*) *with* $AlCl_3$

As in (a), but with $AlCl_3$ (26.5 mg, 0.2 mmol). A very intense violet color developed. After 3 hours at room temp, TLC showed complete conversion to cyclotriveratrylene. The usual work up and chromatographic separation provides 121 mg (81%) of CTV.

VERATROLE-STANNIC CHLORIDE COMPLEX

To veratrole (1.38 g, 0.01 mol) dissolved in 1,2-dichloroethane (25 mL) was added $SnCl_4$ (2.7 g, 1.2 mL, 0.01 mol). A white precipitate began forming very rapidly. NMR (acetone-d_6) showed absorptions at 6.9 ppm (S, 4H) and 3.84 (S, 6H). The hygroscopic complex can be converted to veratrole by dissolution in $CHCl_3$ and treatment with 1 M HCl.

*We want to thank a referee for pointing out the need to review initial results.

ATTEMPTED SYNTHESIS OF CYCLOVERATRYLENE WITHOUT A LEWIS ACID

(a) Bromomethyloctyl ether (223 mg, 1 mmol) and veratrole (138 mg, 0.001 mmol) in dry 1.2 DCE (5 mL) were left at room temp for 48 hours. No reaction (TLC) took place. (b) Chloromethyl ethyl ether (0.16 mL, 2 mmol), veratrole (276 mg, 0.002 mmol) in $CHCl_3$ (dry, 5 mL) were left at room temp for 48 hours. Only starting material was observed (TLC).

Acknowledgement

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References and Notes

1. Cyclotriveratrylene is also named cycloveratril. Its IUPAC name is 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a*,*d*,*g*]cyclononene.
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