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Synthesis of C-unalkylated calix[4]resorcinarene from 1,3-dimethoxybenzene-formaldehyde condensation

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Summary

We proposed a convenient method for the synthesis of C-unalkylated calix[4]resorcinarene octamethyl ether by the HCl-catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol. The conformation of the C-unalkylated calix[4]resorcinarene was preferentially chair-like and it changed to a boat-like by heating it in bulk and solution.

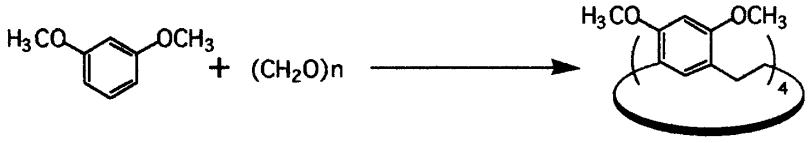
Introduction

The acid-catalyzed condensation of resorcinol with alkyl or aryl aldehydes has been investigated for the synthesis of macrocyclic host compounds. For example, the H_2SO_4 catalyzed condensation of resorcinol with acetaldehyde readily leads the formation of C-methyl calix[4]resorcinarene in good yield, which was reported by Niederl and Vogel in 1940[1]. However, the C-unalkylated calix[4]resorcinarene was not formed when formaldehyde was used as aldehyde under the same condition. In this case, polymer and gel were preferentially formed due to high reactivity of formaldehyde under the condition. The formation of calix[4]resorcinarene must be influenced by the reactivity of resorcinols and aldehydes. Thus, C-unalkylated calix[4]resorcinarene will be obtained when lower reactive resorcinols are used to avoid the formation of polymer and gel.

In this paper, we propose a convenient method for the synthesis of C-unalkylated calix[4]resorcinarene octamethyl ether by the HCl catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol. The formation condition of the C-unalkylated calix[4]resorcinarene is investigated and the stereostructure of the calix[4]resorcinarene is elucidated by ^{1}H NMR.

Results and discussion

Synthesis



Scheme 1. Synthesis of C-unalkylated calix[4]resorcinarene

The synthesis of C-unalkylated calix[4]resorcinarene was carried out by the condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol at 100 °C under acidic condition (Scheme 1). The formation of the calix[4]resorcinarene was monitored by GPC chromatograms of the crude products. The typical GPC chromatogams for the reaction of 1,3-dimethoxybenzene with paraformaldehyde with a molar ratio of 1,3-dimethoxybenzene/formaldehyde of 1:2 are shown in Figure 1. In the GPC

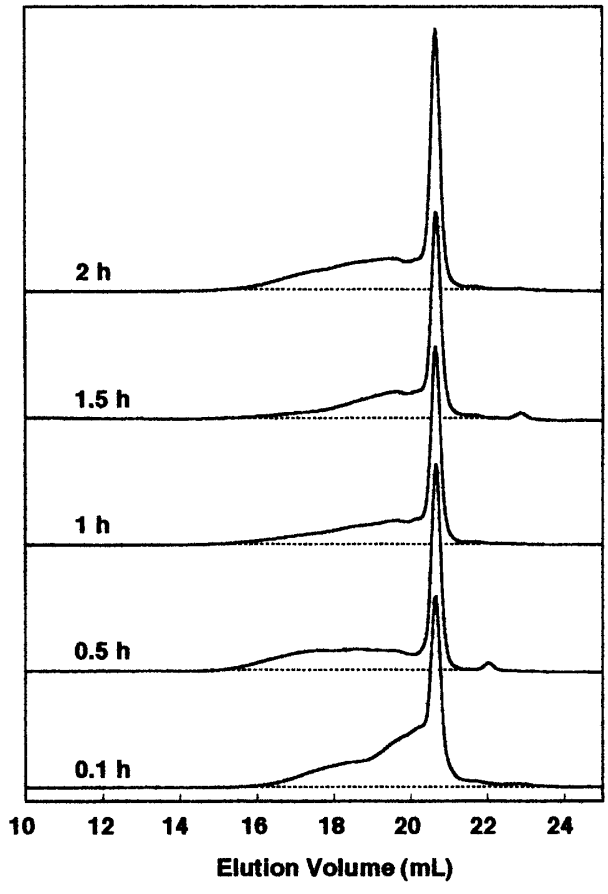


Figure 1. GPC chromatograms of crude products obtained during the reaction of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol at 100 °C with a molar ratio of 1,3-dimethoxybenzene/formaldehyde of 1:2.

chromatogram at the reaction time of 0.1 h, a peak corresponding to monomer (1,3-dimethoxybenzene) already disappeared and peaks corresponding to the calix[4]resorcinarene and linear oligomers were observed. It was found that the reaction rate of 1,3-dimethoxybenzene with paraformaldehyde was very rapid in 2-ethoxyethanol at 100 °C. No macrocycle larger than the calix[4]resorcinarene was found in the reaction.

In order to determine the formation mechanism of C-unalkylated calix[4]resorcinarene, the effect of molar ratio of 1,3-dimethoxybenzene to formaldehyde on the yield of the calix[4]resorcinarene was examined. The plot of the yield of C-unalkylated calix[4]resorcinarene against the reaction time as a function of molar ratio of 1,3-dimethoxybenzene to formaldehyde is shown in Figure 2. In the plot, the yield was calculated from the fraction of the peak area of C-unalkylated calix[4]resorcinarene to that of the crude product in GPC chromatogram. Obviously, the highest yield of the calix[4]resorcinarene was obtained when a molar ratio of 1,3-dimethoxybenzene/formaldehyde of 1:2 was used. The yield with the molar ratio was increasing with increasing of reaction time, and reached to the saturation beyond reaction time of 4h. In other molar ratios, the yield was decreasing with increasing of reaction time. This is because a cyclisation to form the calix[4]resorcinarene and a ring opening reaction to consume the calix[4]resorcinarene occur at the same time. In the reaction with the molar ratio of 1,3-dimethoxybenzene/formaldehyde of 1:2, the cyclisation is faster than the ring opening reaction.

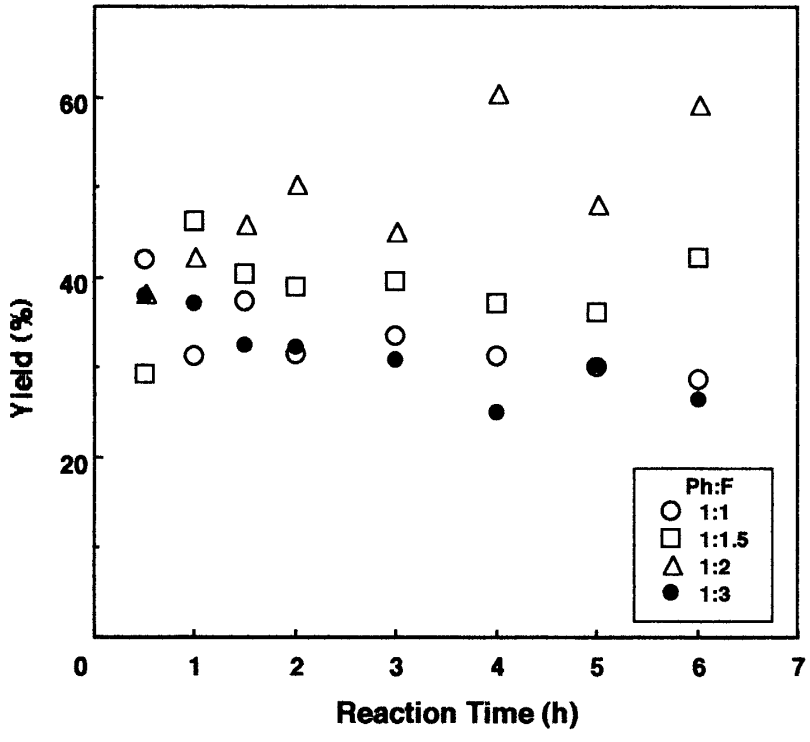


Figure 2. Plot of yield in the reaction of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol at 100 °C against reaction time as a function of molar ratio of 1,3-dimethoxybenzene (Ph) to formaldehyde (F).

The effect of reaction temperature on the cyclisation was examined. The reaction of 1,3-dimethoxybenzene with paraformaldehyde was carried out at 55 °C. In the GPC chromatogram of crude products, peaks corresponding to linear oligomers were observed, but a peak corresponding to the calix[4]resorcinarene was not observed. This is because a chain growth reaction preferentially occurred at lower temperature.

In the reports concerning the macrocyclic resorcinol-aldehyde condensation, the reaction temperature was lower that that in this study. For example, the reaction of resorcinol with acetaldehyde was carried out with a molar ratio of resorcinol/acetaldehyde of 1:1 in methanol under reflux for 1h and C-methyl calix[4]resorcinarene was obtained in 88% yield. In this reaction, a cyclisation preferentially occurs. The cyclisation is due to hydrogen bonds between the phenolic OH groups of adjacent resorcinol units, because no calixarene was obtained under the same condition when 1,3-dimethoxybenzene was used instead of resorcinol. [2]

In this study, the preparation of C-unalkylated calix[4]resorcinarene required 1) a molar ratio of 1,3-dimethoxybenzene/formaldehyde of 1:2 and 2) higher reaction temperature (100 °C). The formation of the C-unalkylated calix[4]resorcinarene was independent of hydrogen bonds between the phenolic OH groups of adjacent resorcinol units.

Characterization

The characterization of the purified C-unalkylated calix[4]resorcinarene was carried out by EI-MS and ^{1}H NMR spectrosopies. The quasi-molecular peak at *m/z* 600 in the EI-MS spectrum was in agreement with the structure of a C-unalkylated calix[4]resorcinarene octamethyl ether. Figure 3 a) shows ^{1}H NMR spectrum of the purified calix[4]resorcinarene. The signals at 6.62 and 6.29 ppm were corresponded to inner and outer aromatic protons, H_{b_v} and H_{a_v} in the vertical resorcinol units and the signals at 6.41 and 6.18 ppm corresponded to inner and outer aromatic protons, H_{a_h} and H_{b_h} in the horizontal resorcinol units. The signals at 3.78 and 3.61 ppm were methoxyl protons, H_{c_v} and H_{c_h} in the vertical and horizontal resorcinol units, respectively, and that at 3.69 ppm corresponded to methylene linkage protons, H_d between resorcinol units. The signals of aromatic protons, H_a and H_b, and the methoxy protons H_c were each split into a pair, indicating that the resorcinol units of the macrocycle occurred pairwise in two different environments. On the other hand, the signal of four methylene linkage groups appeared as a broad single, indicating that the methylene protons are in identical positions. This situation has been found in an analogous compound (C-methyl calix[4]resorcinarene octapropionate) [3,4] and has been attributed to a chair-like conformation.

In addition, we have found that the conformation of the calix[4]resorcinarene changed by heating it in bulk at 230 °C and also in DMSO at 90 °C. The ^{1}H NMR spectrum of the heated calix[4]resorcinarene is shown in Figure 3 b). The signals at 6.41 and 6.19 ppm were corresponded to outer and inner aromatic protons, H_a and H_b, respectively. The signal at 3.78 ppm was corresponded to methoxyl protons, H_c and that at 3.69 ppm corresponded to methylene linkage protons, H_d between resorcinol units. These assignments

were confirmed by the NOE effect. The assignments were not agreed with those of C-unalkylated calix[4]resorcinarene octamethyl ether obtained by the reaction of 2,4-dimethoxybenzyl alcohol with trifluoroacetic acid in $CHCl_3$[5].

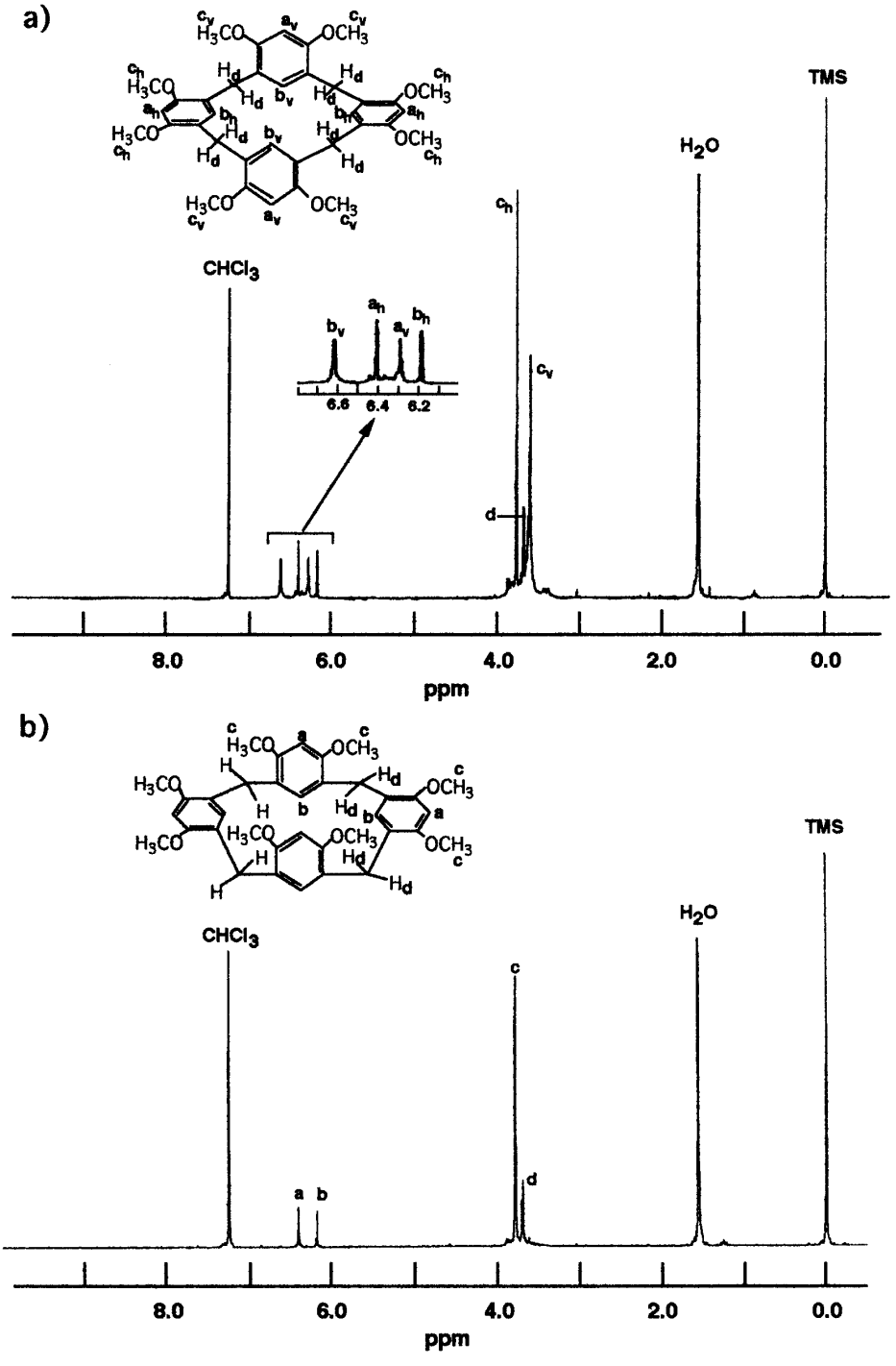
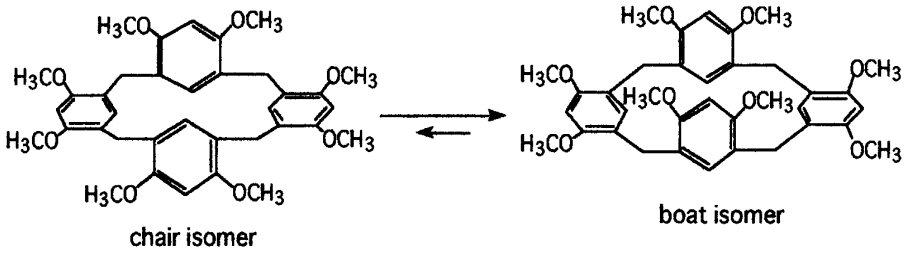


Figure 3. ^1H NMR spectra of C-unalkylated calix[4]resorcinarene octamethyl ether in $CDCl_3$ at 25 °C.



Scheme 2. Conformation change from a chair-like to a boat-like by heating.

In the report, the C-unalkylated calix[4]resorcinarene had a rigid saddle conformation. The conformation for the C-unalkylated calix[4]resorcinarene in this study will differ from the saddle. From the equivalency of each methylene linkage protons, and the four inner and outer aromatic protons in the macrocycle in ^{1}H NMR, the conformation has been assigned to a flexible boat-like one.[3,4] Thus, the chair-like conformation for the C-unalkylated calix[4]resorcinarene has changed to the boat like by heating (Scheme 2). The boat-like conformation for the C-unalkylated calix[4]resorcinarene was more stable than that of the chair-like one. This is supported by the molecular model consideration.[6]
From EI-MS and ^{1}H NMR results the isolated product obtained by the HCl catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde was confirmed to be a C-unalkylated calix[4]resorcinarene octamethyl ether.

In conclusion, a C-unalkylated calix[4]resorcinarene was obtained in high yield by the HCl-catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde. The chair-like conformation isomer was preferentially obtained under the condition. The conformation changed from a chair-like to a boat-like by heating the calix[4]resorcinarene in bulk and also in solution. Details on the conformation change of C-unalkylated calix[4]resorcinarene will be reported in the near future.

Experimentals

Materials

Commercially available 1,3-dimethoxybenzene, paraformaldehyde, conc.HCl, N,N-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) (all from Nacalai Tesque Inc.) were used without further purification. Tetrahydrofuran (THF) (Nacalai Tesque Inc.) was distilled and then used for measurements of gel permeation chromatography (GPC). 2-Ethoxyethanol (Nacalai Tesque Inc.) was distilled and then used.

Preparation

A solution of 0.70 g (0.005 mol) of 1,3-dimethoxybenzene and 0.54 g (0.01 mol as formaldehyde) of paraformaldehyde in 20 mL of 2-ethoxyethanol was charged in a three-necked flask equipped with a reflux condenser. 2 mL of

conc. HCl, as a catalyst, was added and the mixture was heated at 100 °C for 5 h. After cooling to room temperature, the resulting precipitate was filtered off and dried in vacuum. The crude product was washed with hot THF and then acetone. Yield : 0.45 g (59.1%).
^{1}H NMR ($CDCl_3$ at 25 °C): chair-like isomer: δ 6.62 (s, 2, H_{b_v}), 6.41(s, 2, H_{a_h}), 6.29(s, 2, H_{a_v}), 6.18(s, 2, H_{b_h}), 3.78(s, 12, H_{c_v}), 3.69(br s, 8, Hd), 3.61(s, 12, H_{c_h}); boat-like isomer: δ 6.41(s, 4, Ha), 6.19(s, 4, Hb), 3.78(s, 24, Hc), 3.69(s, 8, Hd).
IR (KBr) : 2900 cm^{-1}(-OCH_3)
mp (DSC) : chair-like isomer : can not determined; boat-like isomer:355 °C
Anal. Calcd for $C_{36}H_{40}O_8$ (600.28) : C, 71.98; H, 6.71. Found: C, 71.48; H, 6.75.
EI-MS : m/z=600 (M^+).

Measurements

GPC measurements were carried out by a Shimadzu HPLC LC-6A equipped with two TSKgel GMHXL columns and a TOSOH UV-8011 spectrophotometer (270 nm) as detector, and THF as an eluent at 1.0 mL/min. The chromatograms were analyzed by a Shimadzu C-R7A data processor. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 FT-NMR spectrometer at 270 MHz. $CDCl_3$ and acetone-d_6 were used as solvents and tetramethylsilane (TMS) was used as a reference. FT-IR spectra were obtained by a Jasco FT/IR-III spectrophotometer with a KBr disk. DSC measurements were carried out by a Shimadzu DSC-50 at a heating rate of 10 °C/min under N_2 atmosphere.

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