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Two stereoisomers of C-unalkylated calix[4]resorcinarene and the conformation change

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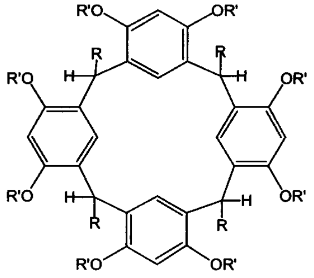
Summary

C-unalkylated calix[4]resorcinarene octamethyl ether was prepared 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 when the large amount of conc.HCl was used. The conformation changed from a chair-like to a boat-like isomer by heating in the temperature range from 240 to 250 °C in bulk.

Introduction

The acid-catalyzed condensation of resorcinol with alkyl or aryl aldehydes has been investigated for the synthesis of macrocyclic host compounds, since Niederl and Vogel studied the reaction of resorcinol with aliphatic aldehydes in 1940[1]. They obtained calix[4]resorcinarenes with the general structure as shown in Scheme 1 (R = alkyl, R’ = H). However, C-unalkylated calix[4]resorcinarene (R = H) 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. Recently, C-unalkylated calix[4]resorcinarene octamethyl ether (R = H, R’ = Me) has been formed by the HCl-catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol.[2]



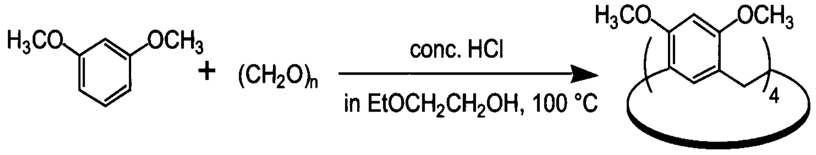
Scheme 1. General structure of calix[4]resorcinarene

The calix[4]resorcinarene showed two stereoisomers, one is a chair-like isomer and the other is a boat-like one. The yield of each stereoisomer was dependent on the reaction conditions. Thus, the stereoselectivity will be synthetically controllable.

In this paper, we study the stereoselective synthesis of chair-like and boat-like isomers for C-unalkylated calix[4]resorcinarene octamethyl ether and also study the conformation change from a chair-like to a boat-like isomer to elucidate the stereochemistry of the calix[4]resorcinarene.

Results and discussion

Stereoselective Synthesis



Scheme 2. Synthesis of C-unalkylated calix[4]resorcinarene

The C-unalkylated calix[4]resorcinarene octamethyl ether was obtained by the condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol at 100 °C under HCl-acidic condition (Scheme 2). The yield of the calix[4]resorcinarene was influenced by the molar ratio of 1,3-dimethoxybenzene/formaldehyde and the reaction temperature.[2] The C-unalkylated calix[4]resorcinarene consisted of two stereoisomers : chair-like isomer and boat-like one. The chair-like isomer was obtained by recrystallization from chloroform. The boat-like one was less soluble in chloroform than the chair-like one, so that it was obtained by washing the product with hot chloroform. The structure and ^{1}H NMR spectrum of each stereoisomer are shown in Figure 1. In the spectrum of chair-like isomer (Figure 1a), the signals at 6.62 and 6.29 ppm were assigned to inner and outer aromatic protons Hb_v and Ha_v in the vertical resorcinol units and the signals at 6.41 and 6.18 ppm were assigned to inner and outer aromatic protons Ha_h and Hb_h in the horizontal resorcinol units. The signals at 3.78 and 3.61 ppm were methoxyl protons Hc_v and Hc_h in the vertical and horizontal resorcinol units, respectively, and that at 3.69 ppm assigned to methylene linkage protons Hd between resorcinol units. In the spectrum of boat-like isomer (Figure 1b), the signals at 6.41 and 6.19 ppm were assigned to outer and inner aromatic protons Ha and Hb. The signal at 3.78 ppm was assigned to methoxyl protons Hc and that at 3.69 ppm assigned to methylene linkage protons Hd between resorcinol units. These assignments were confirmed by the NOE effect.[2]

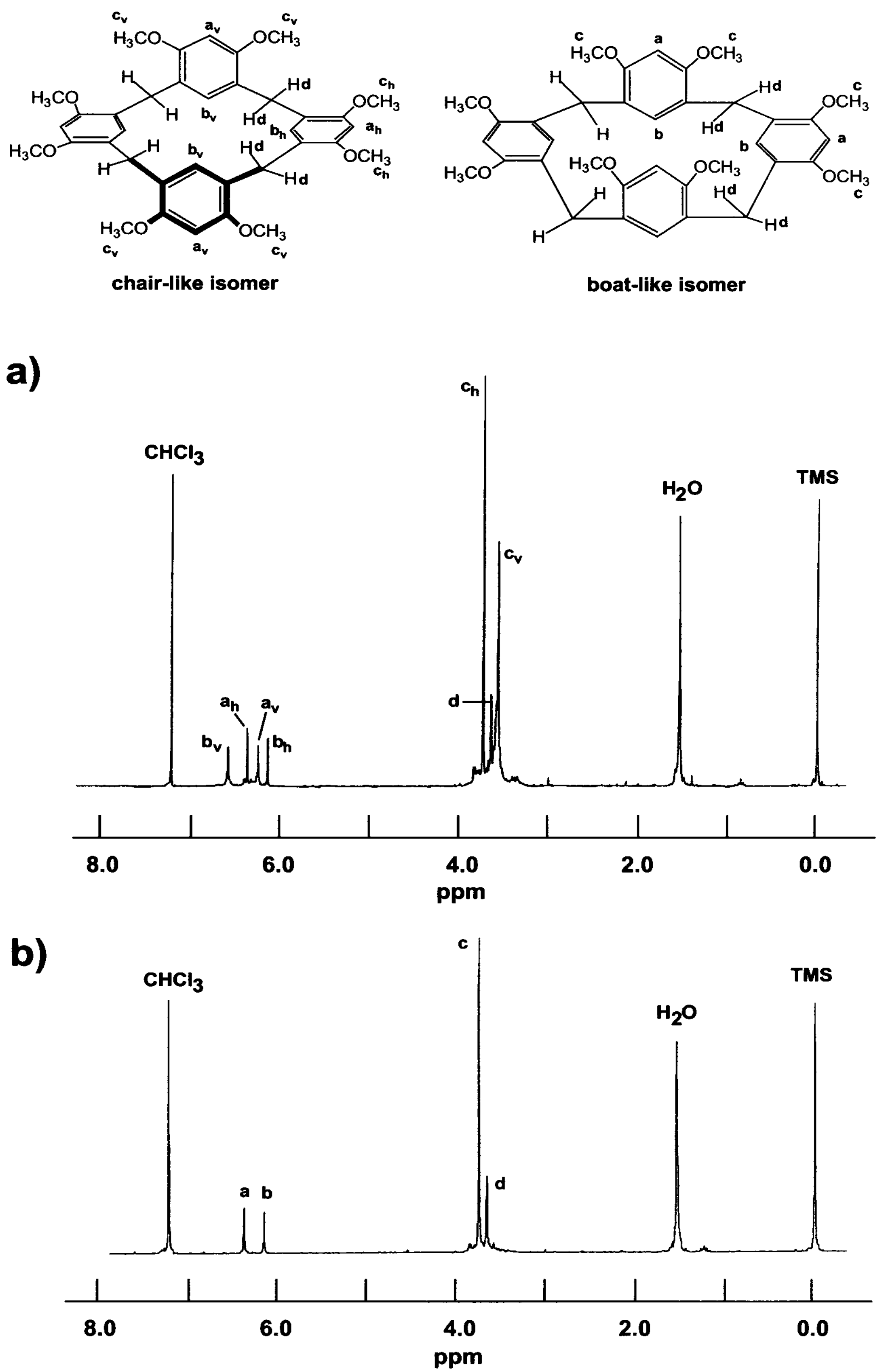


Figure 1. ^{1}H NMR spectra of a) chair-like and b) boat-like isomers for C-unalkylated calix[4]resorcinarene octamethyl ether in $CDCl_3$ at 25 °C.

The effect of the amount of conc.HCl on the isolated yield of each stereoisomer was examined. The yield was determined by comparing ^{1}H NMR signal areas of inner and outer aromatic protons Hb_v and Ha_v in the vertical resorcinol units of the chair-like isomer to those of all aromatic protons. The plot of the isolated yield of each stereoisomer against the amount of conc.HCl is shown in Figure 2. Obviously, the yield was influenced by the amount of conc.HCl. The yield of chair-like isomer was increasing with increasing amount of conc.HCl. To the contrary, the yield of boat-like isomer was increasing with decreasing amount of conc.HCl. Thus, the chair-like and boat-like stereoisomers were selectively formed depending on the amount of conc.HCl.

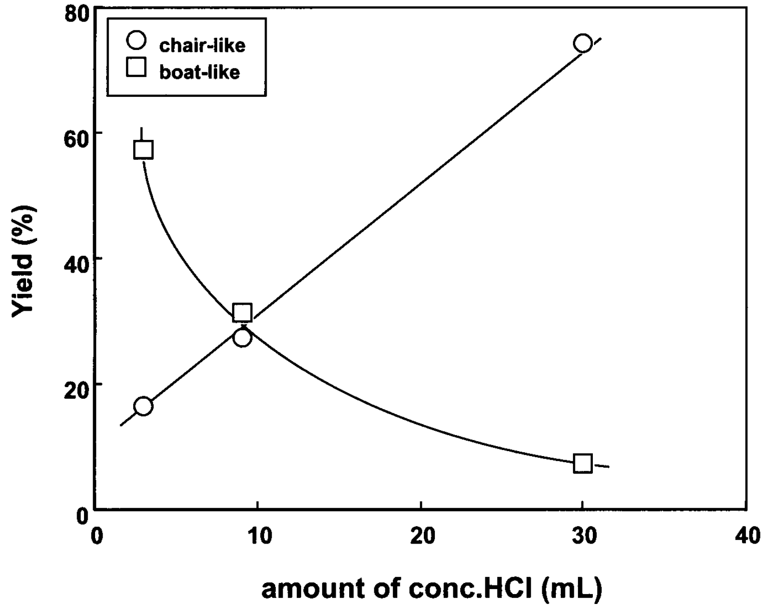


Figure 2. Plot of stereoisomer yield in the reaction of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol at 100 °C against the amount of conc.HCl.

Conformation change

The conformation of C-unalkylated calix[4]resorcinarene changed from a chair-like isomer to a boat-like one by heating it in bulk. The conformation change was examined by DSC measurements. The results are shown in Figure 3. The DSC thermogram of boat-like isomer was different from that of the chair-like one. The boat-like isomer showed a sharp peak of melting point at 370 °C. On the other hand, the chair-like one showed a broad exothermic peak in the temperature range of 230-300 °C, due to the conformation change from chair-like isomer to boat-like one. Details on the conformation change were followed by the ^{1}H NMR spectra of chair-like isomers, which were slowly heated in bulk from 230 to 250 °C by 5 °C intervals and then dissolved in $CDCl_3$ at room temperature. The ^{1}H NMR spectra are shown in Figure 4. In Figure 3, **a)** - **e)** arrows showed the temperatures, at which the chair-like isomers were heated in bulk.

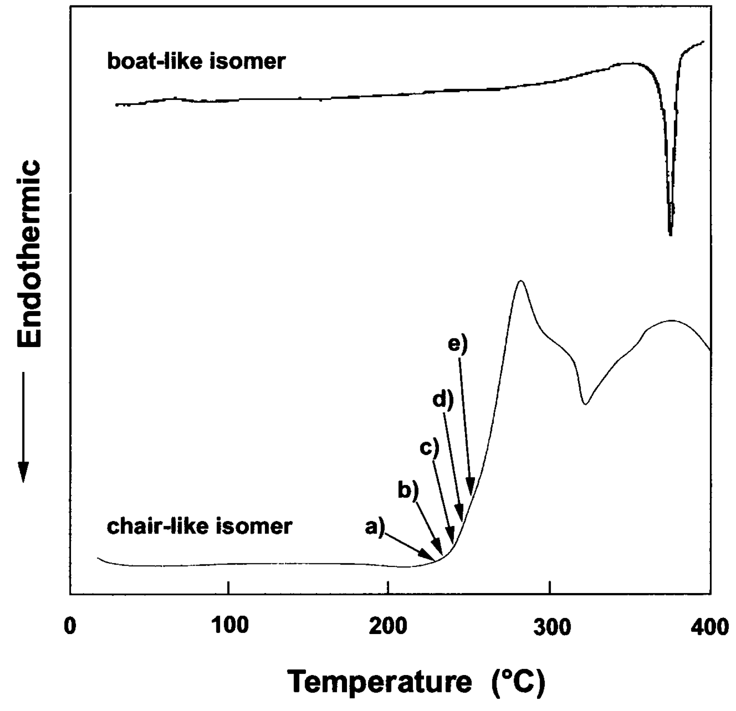


Figure 3. DSC thermograms of the chair-like and boat-like isomers for C-unalkylated calix[4]resorcinarene octamethyl ether at a heating rate of 10 °C/min under N_2 atmosphere.

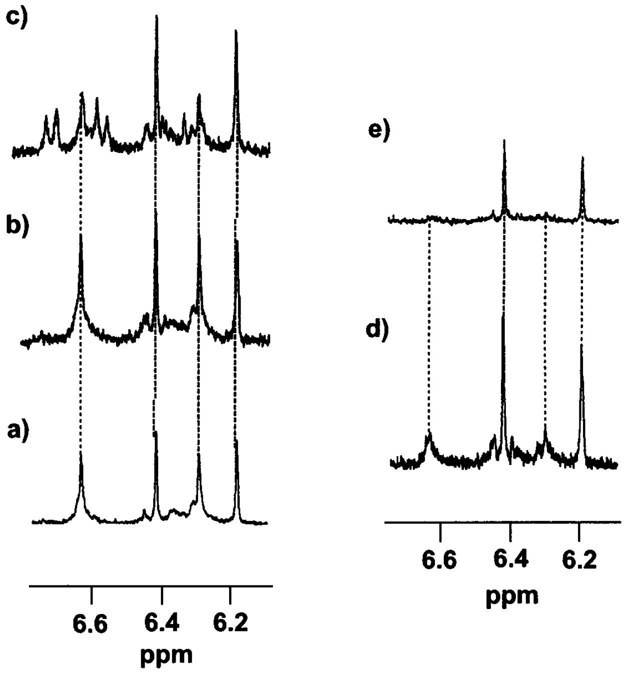


Figure 4. ^1H NMR spectra of the chair-like isomer heated at a) 230, b) 235, c) 240, d) 245 and e) 250 °C.

The ^{1}H NMR spectrum at 240 °C showed the signals of aromatic protons assigned to the chair-like isomer and also new signals, indicating that the chair-like isomer slightly changed to another stereoisomer (**Figure 4c**). At last the ^{1}H NMR spectrum at 250 °C only showed the signals of aromatic protons assigned to the boat-like isomer (**Figure 4e**). From the ^{1}H NMR spectra it was found that the chair-like conformation started to change to the boat-like one at 240 °C and it completely changed at 250 °C. Conformation changes for C-alkylated calix[4]resorcinarenes have been investigated by many researchers.[3, 4] However, such a thermally induced conformation change has not been observed. This is due to the flexibility of methylene linkages and no hydrogen bonds between resorcinol units in the C-unalkylated calix[4]resorcinarene. Therefore, the property of C-unalkylated calix[4]resorcinarene will be different from that of other calix[4]resorcinarenes and a new application is expected.

In conclusion, a C-unalkylated calix[4]resorcinarene was formed by the HCl-catalyzed condensation of 1,3-dimethoxybenzene with paraformaldehyde and the conformation of the product was found to depend on the amount of conc.HCl. The chair-like stereoisomer was preferentially formed under the condition using larger amount of conc.HCl. The conformation changed from a chair-like isomer to a boat-like one by heating in the temperature range from 240 to 250 °C in bulk.

Experimentals

Materials

Commercially available 1,3-dimethoxybenzene, paraformaldehyde, conc.HCl, and anhydrous chloroform (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 20.7 g (0.15 mol) of 1,3-dimethoxybenzene and 9.00 g (0.30 mol as formaldehyde) of paraformaldehyde in 150 mL of 2-ethoxyethanol was charged in a three-necked flask equipped with a reflux condenser. A fixed volume of conc.HCl (3, 9 or 30 mL) was added and the mixture was heated at 100 °C for 9 h. After cooling to room temperature, the resulting precipitate was filtered off and dried in vacuum. The crude product was stirred in large amount of anhydrous chloroform under reflux for 5 h to separate stereoisomers. A chair-like isomer and few linear oligomers were obtained from the chloroform solution and a pure boat-like isomer was obtained from the precipitant. A pure chair-like isomer was obtained by recrystallization from concentrated chloroform solution. Total isolated yield : 18.4 g (81.9 %).
^{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, H_d), 3.61(s, 12, H_{c_h}); boat-like isomer: δ□6.41(s, 4, H_a), 6.19(s, 4, H_b), 3.78(s, 24, H_c), 3.69(s, 8, H_d).
IR (KBr) : 2900 cm^{-1}(-OCH_3)
mp (DSC): chair-like isomer : can not be determined due to conformation change to

boat-like isomer; boat-like isomer: 370 °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-10AD equipped with two TSKgel GMHXL columns and a TOSOH UV-8011 spectrophotometer (270 nm) as a detector, and THF as an eluent at 1.0 mL/min. The chromatograms were analyzed by a Shimadzu C-R7A plus data processor. ^1H NMR spectra were recorded on a JEOL JNM-EX270 FT-NMR spectrometer at 270 MHz. $CDCl_3$ was used as a solvent 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. Mass spectra were recorded on a JEOL JMS-SX102A.

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