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Characterization of precursors of *p-tert*-butylcalix[6]arene synthesis. Mechanism of formation of *p-tert*-butylcalix[6]arene

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Gutsche has proposed the existence of "hemicalixarenes" and "pseudocalixarenes" to explain the formation of calixarenes. The characterization and the quantitative determination of molecules present during the reaction, described in "Organic Synthesis", have permitted us to determine the immediate precursors of p-tert-butylcalix[6]arene. The calix[6]arene could be due to cyclization of linear species named "pseudocalixarenes" and not due to duplication of molecules named "hemicalixarenes".

INTRODUCTION

In 1942 Zinke and Ziegler[1,2] used *p*-substituted phenols in the base-induced condensation reactions with formaldehyde, and the products they obtained were organic solvent-insoluble materials having high melting points. But the recent works of Gutsche[3,4] have shown that the resulting products of these reactions are cyclic oligomers that he has named calixarenes.

Calixarene chemistry has developed since 1980 because calixarenes exhibit a natural cavity. In a recent article, Shinkai[5] has said: "Calixarenes undoubtedly possess the potential to be classified as the third supramolecule" and he has pointed out the attractive properties of these macrocycles. But until now only a few species have been obtained by one-step syntheses[6–8], because these reactions are governed by several factors such as the nature and the amount of catalyst (base), the temperature of the reaction and the rate of removal of the water formed in the condensation reaction.

The mechanism[9,10] of the calixarene-forming reaction is actually unknown, and Gutsche[11] says: "The mechanism of formation of the calixarenes poses an interesting and incompletely solved problem". Synthesis conditions are now well defined for preparing calixarenes with 4,6 or 8 *p-tert*-butylphenol units with yields up to 90%; odd numbered calixarenes exist but are formed only in small amounts. Gutsche[4] has stated that "the preponderance of the even numbered calixarenes may indicate that cyclodimerization rather than cyclization is a major pathway, but more data are necessary before this can be supported or refuted", and he has proposed the existence[12] of "hemicalixarenes" and "pseudocalixarenes" to explain the formation of calixarenes. For *p-tert*-butylcalix[6]arene, Gutsche has proposed a possible pathway[9] which could involve a pair of bis-(hydroxymethyl)linear trimer anions associating to form a dianionic hemicalixarene; another pathway[12] could involve the cyclization of a bis(hydroxymethyl)linear hexamer called a pseudocalixarene. It has been assumed[9,12] that the *p-tert*-butylcalix[8]arene is the product of kinetic control, the *p-tert*-butylcalix[4]arene is the product of thermodynamic control and the *p-tert*-butylcalix[6]arene the product of a template effect.

In this work, we have identified the molecules present during the different steps of synthesis of *p-tert*-butylcalix[6]arene with respect to the conditions of "Organic Synthesis". The characterization and the quantitative determinations of molecules present during the reaction have permitted the drawing of reaction diagrams and the proposing of a mechanism.

EXPERIMENTAL

We have studied the synthesis of *p-tert*-butylcalix[6]arene described by Gutsche[7], Dhawan, Leonis and Stewart in "Organic Synthesis". Under these

*We are indebted to Professor Robert Perrin who died in April 1993.

conditions, *p-tert*-butylcalix[6]arene is obtained with a yield of 90%.

1. Preparation and study of formation of *p-tert* butylcalix[6]arene versus time

There are two steps in this synthesis. In the first step, 20 g (0.133 mol) of *p-tert*-butylphenol, 3 g (0.045 mol) of potassium hydroxyde pellets at 84%, and 27 mL of 37% formalin solution (0.36 mol of HCHO) are placed in a 500 mL, three necked, round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, a Dean-Stark trap and condenser. The flask is placed in a heating mantle. The reaction mixture is heated until a golden yellow dry mass is formed. During this period, samples are taken every five minutes, by a Pasteur pipette; they are weighed and stored at -20°C. This step is about 45 min length.

In the second step, 200 mL of *o*-xylene are added to the flask to dissolve the solid mass and give a solution. At reflux, samples are taken every ten minutes during the first hour and then every 15 minutes. The samples are weighed and placed at -20°C. Refluxing is continued 3 hours and then the heating mantle is removed, the mixture is allowed to cool to room temperature; finally the mixture is filtered.

2. Chromatographic analysis

Thin Layer Chromatography (T.L.C.)

Separation is achieved on Silica Gel 60 precoated plates of Merck using $(C_2H_5)_2O$-n Heptane (7/3) as eluent.

Gas Chromatography (G.C.)

G.C. was performed using an Intersmat IGC 120 DFL and a Shimadzu CR6-A recorder. We have separated mono, di and trinuclear methylolphenols using "Gaz ChromQ" +1% OV-17.01 and a glass column.

The sample is placed at 20°C and 50 mg are weighed. 2 drops of *o*-chlorophenol are weighed and added; then 50 mg of CH_3OH and CH_3COCH_3 are added. When the mixture is a solution, it is transformed by silylation employing 1 ml of bis(tri-methylsilyl)-trifluoroacetamide (BSTFA.) After separation we compare the peaks of the sample with peaks of the reference species using *o*-chlorophenol as internal reference. Response factors are 1.32 for the *p-tert*-butylphenol, 1.32 for the hydroxymethyl monomer, 1 for the bis(hydroxymethyl) monomer and 1 for the others. We have used Analysis-grade solvents from Aldrich.

Liquid Chromatography (L.C.)

The instrument consists of a Kontron "322 system" pump, Kontron injector, Kontron model 430 wavelength UV detector and Kontron "Data System" 450 integrator. The samples are separated at 20°C on a 25 cm × 4.6 mm Touzart and Matignon C18 ODS1 5 μ and monitored at 287 nm. A mobile phase of acetonitrile and *tert*-butyl methyl ether with a flow rate of 0.8 ml/mn is used for this work.

Standard solutions of *p-tert*-butylcalix-[4,4O,6,7,8]arenes are prepared at various concentrations and are injected separately at 20°C. Then, for each calixarene, the calibration curve is determined by a regression calculation.

All the samples are placed at 20°C and then 10 mg are taken if the sample is solid and 50 mg are taken if the sample is liquid. These quantities are placed in a 5 ml volumetric flask. The volume is completed with $CHCl_3$. Then, 20 μl aliquots of these solutions are injected. At integration, the calculated peak areas are converted to amount values with the aid of the stored calibration curve. We use HPLC-grade solvents from Aldrich.

3. Physical measurements

Proton NMR spectra are obtained on a Brucker AC 200 instrument at 200 MHz at 20°C in deuterated DMSO using Me_4Si as internal standard.

^{13}C NMR spectra are recorded with a Brucker AC 200 instrument at 50 MHz at 20°C in deuterated DMSO using Me_4Si as internal standard.

Mass spectra are recorded on a VG ZAB2-SEQ. These analyses were carried out by the Laboratory of Mass Spectrometry of the CNRS, Solaize, France.

RESULTS AND DISCUSSION

1. Determination and measurement of amounts of species present in the first reaction step

Precursors are mainly analysed by G.C. Hydroxymethylphenols are polar molecules with high melting points; they are silylated before being injected to prevent them from being destroyed in the column. In this manner, we are able to measure out oligomers constituted of 1 to 3 phenolic units. We study the samples taken during the first step and the three first samples of the second step. In this way, we are able to trace a reaction diagram (Figure 1) showing the evolution of species in time. Between 0 and 20 min, the disappearance of *p-tert*-butylphenol can be observed. During the same period, the hydroxymethyl monomer develops and then decreases, while the amount of bis(hydroxymethyl)monomer (written (**^1^**)) reaches it maximum at 20 min (78% in moles equivalent of the phenol). Between 20 and 30 min, the decrease of (**^1^**) and the increase of species with 2 and 3 bis(hydroxymethyl)phenol units (written (**^2^**) and (**^3^**)) can be observed. At 30 min, the bis-(hydroxymethyl)dimer reaches its maximum. Furthermore,

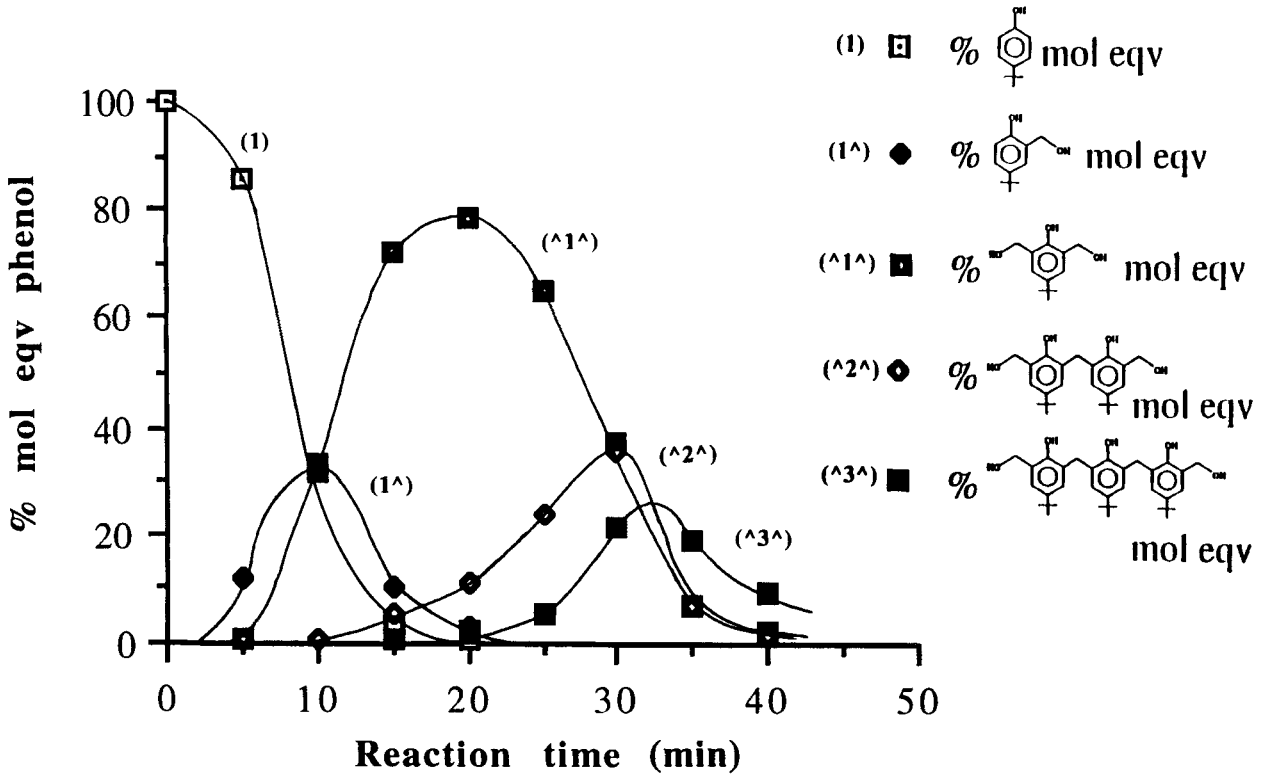

Figure 1 Reaction diagram : kinetic of formation of linear oligomers (first step).

all the species present in the reaction mixture can be measured out. After this time, certain products can no longer be detected, by G.C., like linear tetramers, linear pentamers, etc.

After 30 min, a rapid decrease of (**^2^**) and (**^1^**) can be observed, while the bis(hydroxymethyl)trimer (written (**^3^**)) reaches its maximum before disappearing progressively. At 40 min, only traces of (**^1^**) and (**^2^**) and 10% of (**^3^**) can be detected. Certain products are lacking in the reaction mixture. The bis(hydroxymethyl) tetramer (written (**^4^**)) cannot be measured out by G.C. so we have used T.L.C. and we have detected it, at 35 and 40 min but in small amounts. At 45 min, no product can be detected by G.C. and a new one is detected by T.L.C.

In order to identify such products, we use other analytical methods for the last sample of the first step; we are able to recognize the differents peaks[13] (Table 1) in the (^{1}H NMR spectrum and the integration of these peaks allows us to propose a structure of a molecule that could be the bis(hydroxymethyl)linear hexamer (written (**^6^**)).

The structure has been confirmed by using the (^{13}C NMR and the DEPT method[14,15] (Table 2). But we observe the presence of small peaks corresponding to hemiformals and a molecule with an ether bridge, which leads us to think that the final reaction mixture of the first step could be constituted of (**^6^**) with small quantities of (**^6^**) with one ether bridge and of the hydroxymethyl linear hexamer with one hemiformal group on one ortho position.

The mass spectrum (Figure 2) confirms these conclusions: an important peak at m/z 1028 can be noted which corresponds to (**^6^**) (MLi^+) and a small peak at m/z

Table 1 ^{1}HNMR data

Chemical shift	*Assignments*
-1.17 -1.22 ppm	H. $C(CH_3)_3$
-2.5 ppm	H. DMSO
-3.6 -3.9 ppm	H. Ar-CH_2-Ar
-6.9 -7.3 ppm	H. Ar-*H*
-4.4 -4.6 ppm	H. Ar-CH_2-OH
-4.6 -4.9 ppm	H. Ar-CH_2-O-CH_2-Ar
	H. Ar-$(CH_2O)_2H$

Table 2 ^{13}CNMR data

Chemical shift	*Assignments*
-31.4 – 31.6 ppm	C. $C(CH_3)_3$
-33.2 ppm	C. $C(CH_3)_3$
-34.3 ppm	C. Ar-CH_2-Ar (*o-o*)
-59.2 – 59.7 ppm	C. Ar-CH_2-OH
-121 – 125 ppm	C. Ar (-*m*)
-127.6 – 130 ppm	C. Ar (-*o*)
-140 ppm	C. Ar (-*p*)
-150 – 160 ppm	C. Ar-OH
-65 and 66 ppm	C. Ar-CH_2-O-CH_2-Ar
-87 and 93 ppm	C. Ar-CH_2-O-CH_2-OH

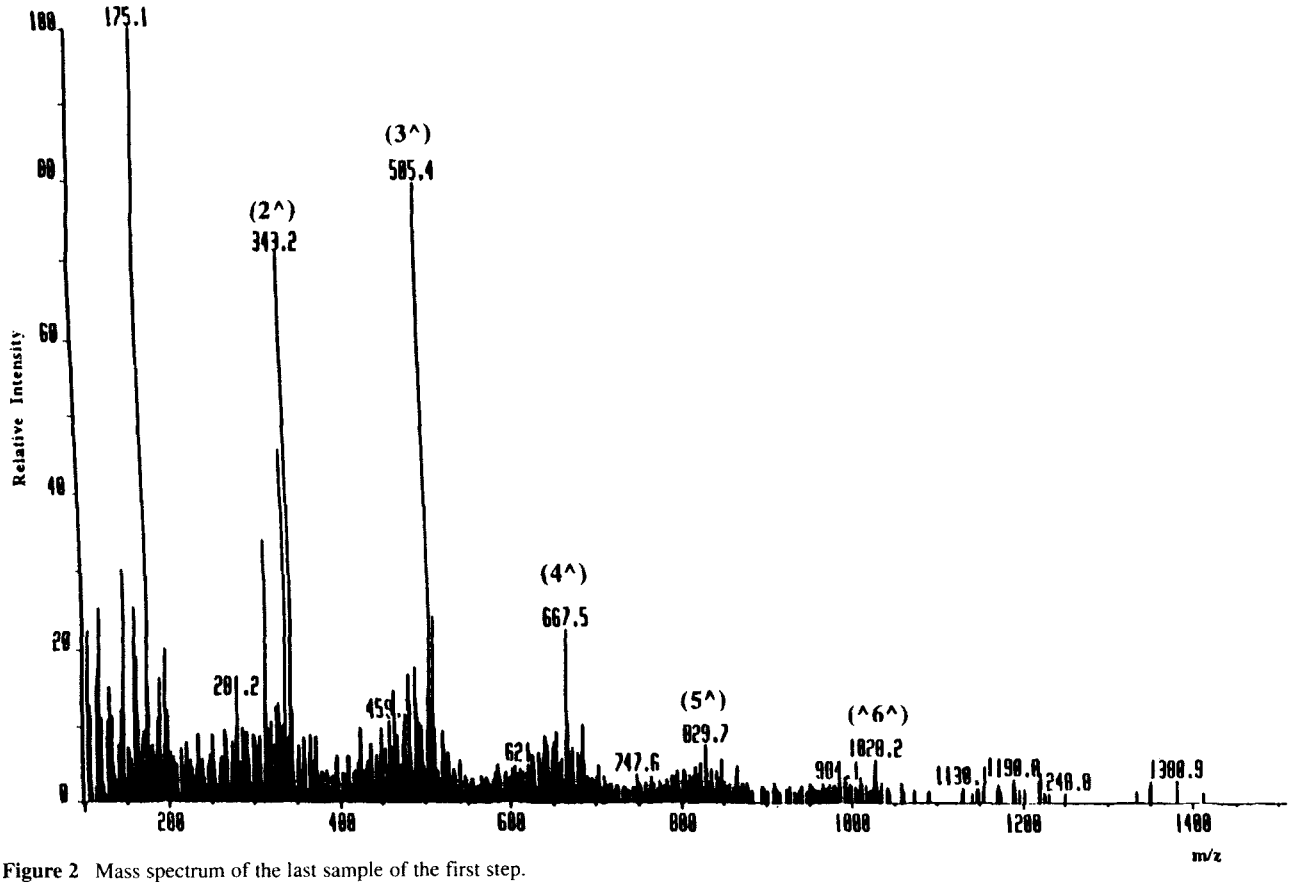

Figure 2 Mass spectrum of the last sample of the first step.

1058 which corresponds to (^6^) with one ether bridge (MLi^+) and hydroxymethyl linear hexamer with one hemiformal function. The presence of (^1), (^2), (^3) and (^4) detected on the mass spctrum is not confirmed in G.C. and T.L.C., so the molecules consisting of 1, 2, 3 or 4 phenol units must result from the degradation of (^6^) during the analysis.

These different methods associated with L.C., which shows that there are no calixarenes in the yellow mass, have allowed us to propose the bis(hydroxymethyl)linear hexamer structure (Figure 3) that is a molecule formed during the first step of the reaction.[16]

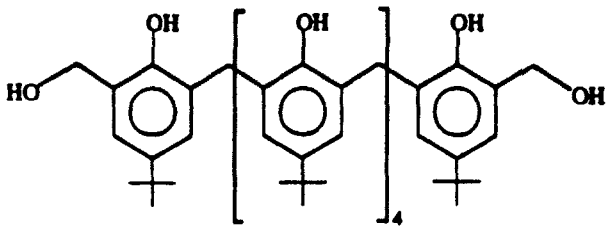

Figure 3 bis(hydroxymethyl)linear hexamer.

2. Determination and measurements of amounts of species present in the second step

In the second step, we use L.C. for the determination and the measuring out of calixarenes. The reaction diagram (Figure 4) shows the evolution of calixarenes in time.

The last sample of the yellow mass does not contain calixarenes. But these macrocycles appear when the yellow mass has been dissolved in xylene; however, even after 10 min at reflux, only small amounts of calixarenes can be detected. The calix[6]arene forms mainly during the first 80 minutes of refluxing. The calix[4]arene reaches its maximum after 1 hour of refluxing. When the reaction is finished, an analysis shows that we have 90% yield of calix[6]arene as in "Organic Synthesis".

CONCLUSIONS

We have identified the molecules present during the *p-tert*-butylcalix[6]arene synthesis as described in "Organic Synthesis[7]". It has been proposed that during the first step the main species formed could be the bis(hydroxymethyl)linear hexamer.

In the second step, this linear hexamer has been cyclized by refluxing with the loss of one water molecule and one formaldehyde molecule. The calix[6]arene is

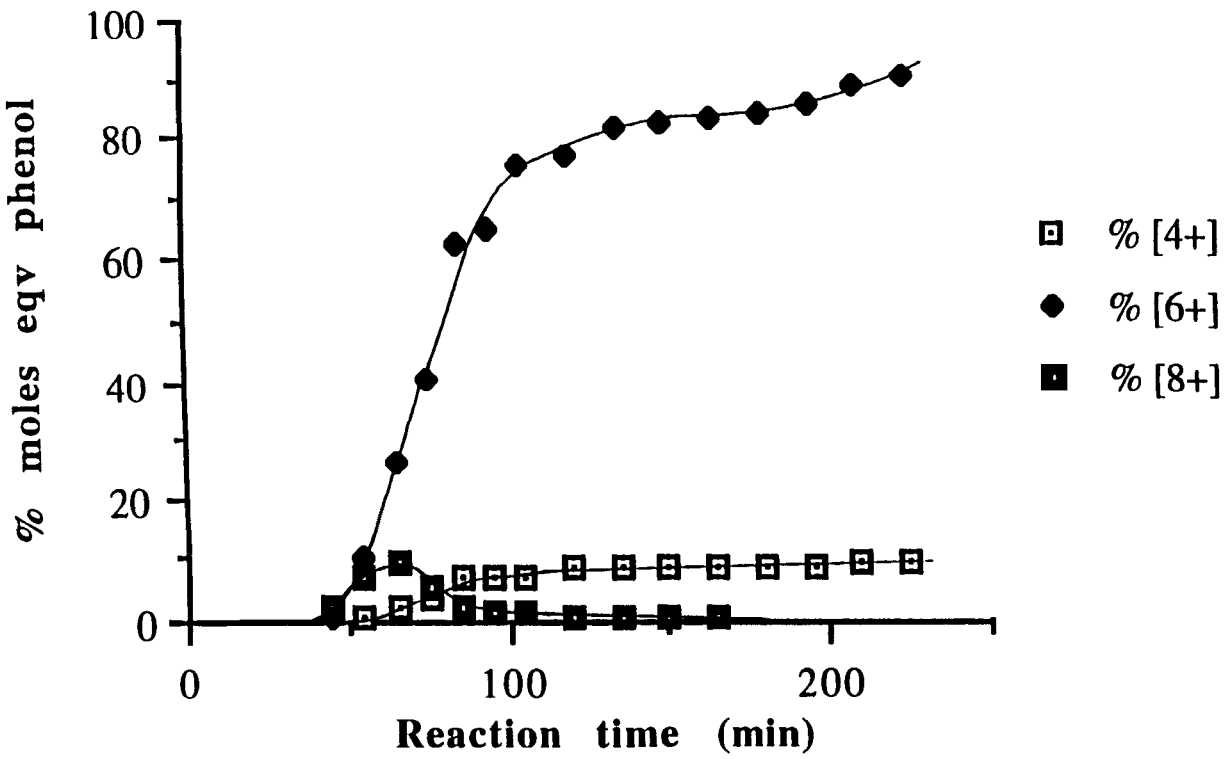

Figure 4 Reaction diagram : kinetic of formation of calixarenes (cyclization step).

formed when the solvent is added and heated to reflux. Therefore, the solvent effect seems to play an important role and allows the cyclization.

In this conditions of synthesis, it seems that the *p-tert*-butylcalix[6]arene is formed following the "pseudocalixarenes" pathway, the bis(hydroxymethyl)linear hexamer being the identified pseudocalixarene.

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16 In the last sample of the first step, we have not isolated a pure linear hexamer. To keep the conditions of the reaction mixture, the last sample of the first step has not been purified but directly analysed. So the material, on which the analysis were carried out, is probably not a single entity; indeed the main product detected corresponds to the bis(hydroxymethyl)linear hexamer, with traces of bis(hydroxymethyl)linear hexamer with one ether bridge and hydroxymethyl linear hexamer with one hemiformal group.