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Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713649759>

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To cite this Article Vocanson, Francis and Lamartine, Roger(1996) 'Characterization of synthetic precursors of *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylcalix[8]arene. Mechanisms of formation of calix[4]arene and calix[8]arene', *Supramolecular Chemistry*, 7: 1, 19 – 25

To link to this Article: DOI: 10.1080/10610279608054991

URL: <http://dx.doi.org/10.1080/10610279608054991>

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Characterization of synthetic precursors of *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylcalix[8]arene. Mechanisms of formation of calix[4]arene and calix[8]arene.

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(Received June 15, 1994)

The immediate precursors of *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylcalix[8]arene have been determined by the characterization and the quantitative evaluation of molecules present during the reactions, as described in "Organic Synthesis". The calix[4]arene could have two origins: the cyclization of linear species named pseudocalixarenes and the transformation of calix[8]arene in calix[4]arene by "molecular mitosis". The calix[8]arene could be due to the cyclization of species called hemicalixarenes.

INTRODUCTION

The resulting products of the base induced condensation reaction between *p*-substituted phenol and formaldehyde are named "calixarenes". This chemistry¹ has developed since 1980, because these macrocycles exhibit a natural cavity for which the size increases with the number of phenolic units constituting the cycle. The mechanism of formation^{2,3} of the calix[4]arene and the calix[8]arene is actually unknown. However, Gutsche has proposed the existence¹ of "hemicalixarenes" and "pseudocalixarenes" to explain the formation of these macrocycles.

For *p*-*tert*-butylcalix[8]arene, Gutsche¹ has proposed a pathway which involves a pair of bis(hydroxymethyl) linear tetramers associating to form a dianionic hemicalixarene; by extrusion of water and formaldehyde from the hemicalix[8]arene then yields calix[8]arene.

For *p*-*tert*-butylcalix[4]arene, Gutsche¹ has proposed a pathway which involves a hemicalix[8]arene which yields calix[4]arene by "molecular mitosis". Another pathway involves the cyclization of a bis(hydroxymethyl) linear tetramer called a pseudocalix[4]arene.

In a previous work⁴, we have identified the precursors of *p*-*tert*-butylcalix[6]arene by the characterization and the quantitative determination of molecules present during the reaction. In this work, we have proceeded in the same manner for *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylcalix[8]arene, with respect to the conditions of "Organic Synthesis"; reaction diagrams are drawn and mechanisms are proposed.

EXPERIMENTAL

We have studied the synthesis of *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylcalix[8]arene described respectively by Gutsche and Iqbal⁵ in "Organic Synthesis" for the first macrocycle, and by Munch and Gutsche⁶ in "Organic Synthesis" for the second.

Preparation and study of formation of *p*-*tert*-butylcalix[4]arene versus time

There are two steps in this synthesis. In the first step, 20 g (0.133 mol) of *p*-*tert*-butylphenol, 0.24 g (0.006 mol) of sodium hydroxide pellets at 98% and 12.4 mL of 37%

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formalin solution (0.166 mol of HCHO) are placed in a 500 mL, three necked, round-bottomed flask. The open flask, placed in a heating mantle, is heated 2 hours at 110 °C. During this period, samples are taken every 15 minutes by a Pasteur pipette; they are weighed and stored at -20 °C. After the heating mantle is removed, the mixture is allowed to cool to room temperature. A yellow, viscous mass is formed.

In the second step, 200 mL of warm diphenyl ether is added to dissolve the residue. The three-necked flask is equipped with a condenser and a nitrogen inlet. The contents of the flask are heated with a heating mantle while a stream of nitrogen is blown rapidly over the reaction mixture to facilitate the removal of the water that is evolved. At reflux, samples are taken every 15 minutes. The samples are weighed and placed at -20 °C. The contents of the flask are refluxed for 1.5 hour. Then the heating mantle is removed, and the mixture is allowed to cool to room temperature and filtered.

Preparation and study of formation of *p*-*tert*-butylcalix[8]arene versus time

33.33 g (0.22 mol) of *p*-*tert*-butylphenol, 0.667 mL (0.00667 mol) of 10 N sodium hydroxide, 11.67 g (0.389 mol) of paraformaldehyde and 200 mL of xylene are placed in a 500 mL, three-necked, round-bottomed flask equipped with a Dean-Stark trap, a condenser, a mechanical stirrer and a nitrogen inlet. The air in the flask is replaced with nitrogen and the stirred contents of the flask are heated to reflux by means of a heating mantle. After 1 hour a white precipitate begins to form and the mixture is refluxed for 4 hours. Then the heating mantle is removed, the mixture is allowed to cool to room temperature, and filtered. At reflux, samples are taken by a Pasteur pipette every 10 minutes during the first hour, every 15 minutes during the second hour and then every 30 minutes. They are weighed and stored at -20 °C.

Chromatographic analysis

The analytical conditions are the same that these have been used in the previous work⁴ describing the mechanism of formation of *p*-*tert*-butylcalix[6]arene.

Thin Layer Chromatography (T.L.C.)

Separation is achieved on Silica Gel 60 precoated plates of Merck.

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.

Liquid Chromatography (L.C.)

L.C. 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/min is used for this work.

Physical measurements

Proton NMR spectra are obtained on a Bruker AC 200 instrument at 200 MHz at 20 °C in deuterated DMSO using Me₄Si as internal standard.

¹³C NMR spectra are recorded with a Bruker AC 200 instrument at 50 MHz at 20 °C in deuterated DMSO using Me₄Si as internal standard.

Mass spectra are recorded on a VG ZAB2-SEQ.

RESULTS AND DISCUSSION

Synthesis of *p*-*tert*-butylcalix[4]arene

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

G.C. allows 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 versus time. Between 0 and 120 minutes, the *p*-*tert*-butylphenol, written (1), decreases but it remains 20% (in moles equivalent of the phenol) at t = 120 minutes. We can also observe the formation of hydroxymethyl *p*-*tert*-butylphenol, written (1'), and bis(hydroxymethyl) *p*-*tert*-butylphenol, written (1''). The amount of (1') reaches its maximum at 15 minutes (32%) then decreases. The amount of (1'') reaches its maximum at 60 minutes and like (1') it decreases. At t = 120 minutes, 17.5% of (1') et 18.5% of (1'') are detected. Between 30 and 120 minutes, only traces of dimer (2), hydroxymethyldimer (2'), bis(hydroxymethyl)dimer (2''), trimer (3), hydroxymethyltrimer (3') and bis(hydroxymethyl)trimer (3'') can be observed. Between 0 and 30 minutes, 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., such as linear tetramers.

In order to identify such products, we use other analytical methods for the samples taken between 45 and 120 minutes. By T.L.C., we have detected the bis(hydroxymethyl)tetramer, written (4'). L. C. analysis has shown there are no calixarenes in the samples during this

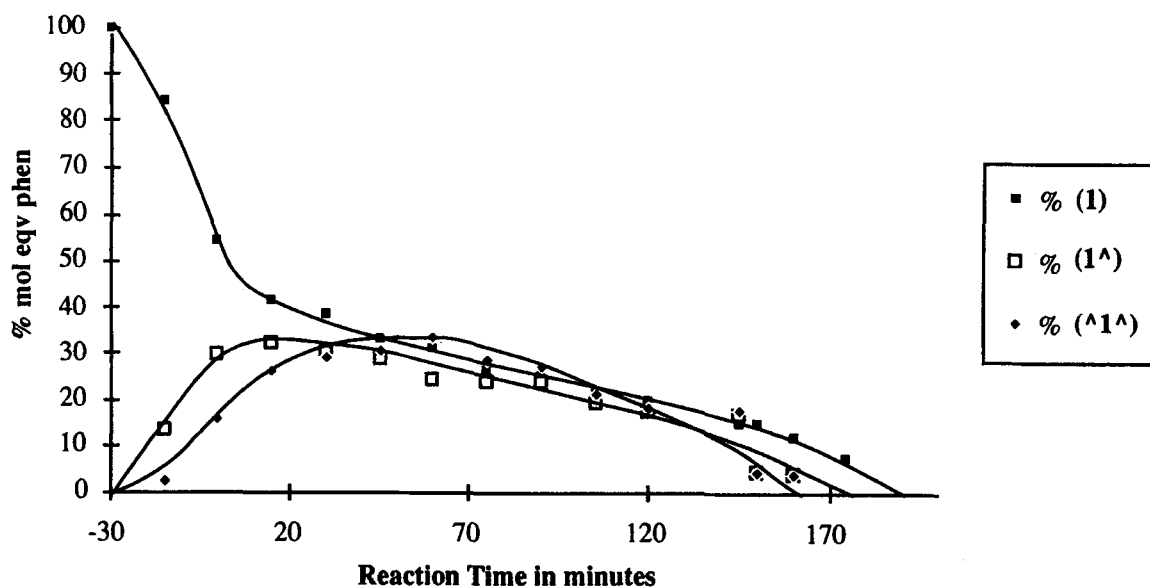


Figure 1 Reaction diagram: kinetics of formation of linear oligomers (first step) in the synthesis of *p-tert-butylcalix[4]arene*.

time. The ^1H NMR and ^{13}C NMR spectra of these samples have shown that they consist of a mixture of phenolic linear oligomers. The mass spectra, Figure 2, have confirmed the results of T.L.C.: a peak at m/z 703.8 can be noted which corresponds to $(^4^4)$ (MLi^+). $(^1^1)$, (2^2) , (3^3) and (4^4) are also detected but not pentamer, hexamer, heptamer and octamer linear oligomers. Nevertheless, it seems that tetramers are major products because only they are detected by T.L.C.

Determination and measurement of amounts of species present in the second step

Samples have been analysed by different techniques. T.L.C. has shown the presence of (1), (1^1) and $(^1^1)$ in the three first samples of this second step, but $(^4^4)$ and the bis(hydroxymethyl)hexamer, written $(^6^6)$, are detected from the second sample to the last. G.C. has confirmed the results of T.L.C.: (1), (1^1) and $(^1^1)$ are also detected in the three first samples of this second step.

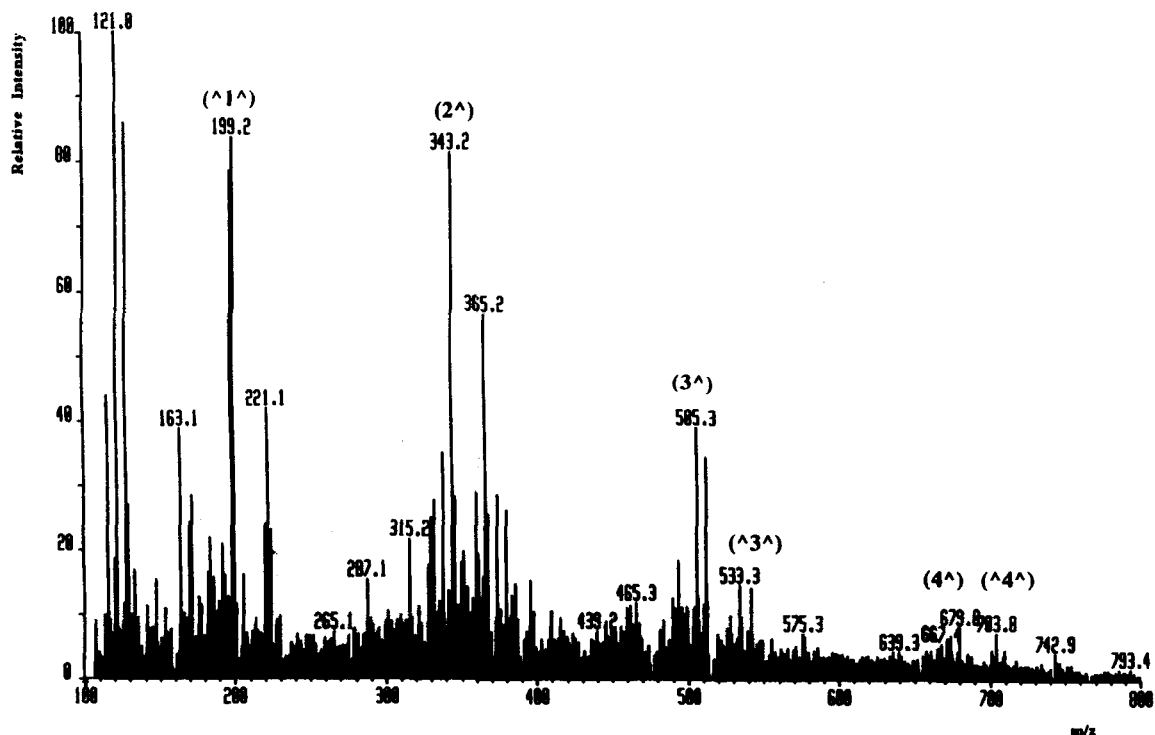


Figure 2 Mass spectrum of the last sample of the first step in the synthesis of *p-tert-butylcalix[4]arene*.

L.C. has been used for the determination and the measuring out of calixarenes. The first sample of this second step does not contain macrocycles. Then *p*-*tert*-butylcalix[6]arene and *p*-*tert*-butylcalix[8]arene are detected. Also a reaction diagram, Figure 3, has been traced showing the evolution of calixarenes versus time. The calix[4]arene forms during the 90 minutes of reflux and reaches 49% at the end of the manipulation. The calix[6]arene reaches its maximum (18.8%) at the beginning and then disappears progressively to represent 9.5% at the end of the experiment. The calix[7]arene appears at the beginning of reflux and its amount, which reaches 4.2% at the end, does not change during reflux. The calix[8]arene, like the calix[6]arene, disappears progressively with time until it reaches 3.3% at the end of the manipulation. Also in the final mixture there are 66% calixarenes and 34% linear oligomers.

Conclusions

We have identified the molecules present during the *p*-*tert*-butylcalix[4]arene synthesis as described in "Organic Synthesis". It has been shown that during the first step the species formed are (1), (1'), (1''), (4') and (4''). In the second step, four types of calixarene are formed when the reaction mixture is refluxing. The amounts of different macrocycles evolve versus time but the cyclic tetramer is the major product. The *p*-*tert*-butylcalix[4]arene is issued by the cyclization of linear tetramers upon refluxing with the loss of one formaldehyde molecule and one water molecule. Another origin of *p*-*tert*-butylcalix[4]arene could be the transformation of calix[8]arene in calix[4]arene by the "molecular mitosis" phenomenon.

In these conditions of synthesis, it seems that the *p*-*tert*-butylcalix[4]arene is primarily formed following

the "pseudocalixarenes" pathway, the linear tetramers being the identified pseudocalixarene.

Synthesis of *p*-*tert*-butylcalix[8]arene

Determination and measurement of amounts of species present during the reaction

By T.L.C., we have studied the ten first samples and we have detected the presence of (1), (1'), (1''), (2''), (3'') and (4').

By G.C., we have studied the same samples. In this way, we have been able to trace a reaction diagram, Figure 4, showing the evolution of species versus time. Between 0 and 25 minutes, all the species present in the reaction mixture can be measured. (1) decreases but it remains its 9.5% at $t = 25$ minutes. (1') appears, reaches its maximum, 22.3% at $t = 15$ min and disappears. (1'') reaches its maximum, 57.45% at $t = 25$ minutes. We can also observe the presence of (2''), (3) and (3''). Between 35 and 110 minutes, certain products can no longer be detected. During this period, (1'), (1''), (2''), (3) and (3'') disappear. Only (1) is detected at $t = 110$ minutes.

In order to identify the other products, we have used other analytical methods for the samples taken during the reaction.

L.C. has shown that calixarenes, Figure 5, appear at $t = 35$ minutes and then grow until the end of the reaction. *p*-*tert*-butylcalix[4]arene, *p*-*tert*-butyldihomooxalix[4]arene, *p*-*tert*-butylcalix[6]arene, *p*-*tert*-butylcalix[7]arene and *p*-*tert*-butylcalix[8]arene have been detected. The calix[4]arene progressively grows and reaches 7% (in mole equivalent of the phenol) at the end of the experiment. The oxacalixarene reaches its maximum, 36%, at $t = 65$ minutes and then decreases until 2.5% at $t = 265$ minutes. The calix[6]arene, like calix[4]arene

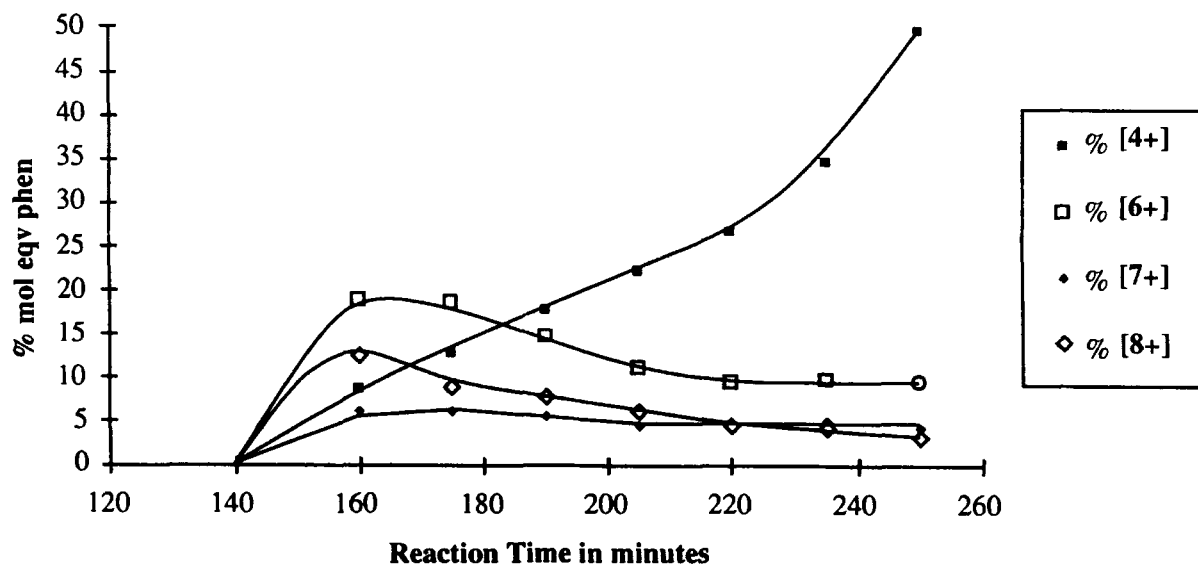


Figure 3 Reaction diagram: kinetic of formation of calixarenes (second step) in the synthesis of *p*-*tert*-butylcalix[4]arene.

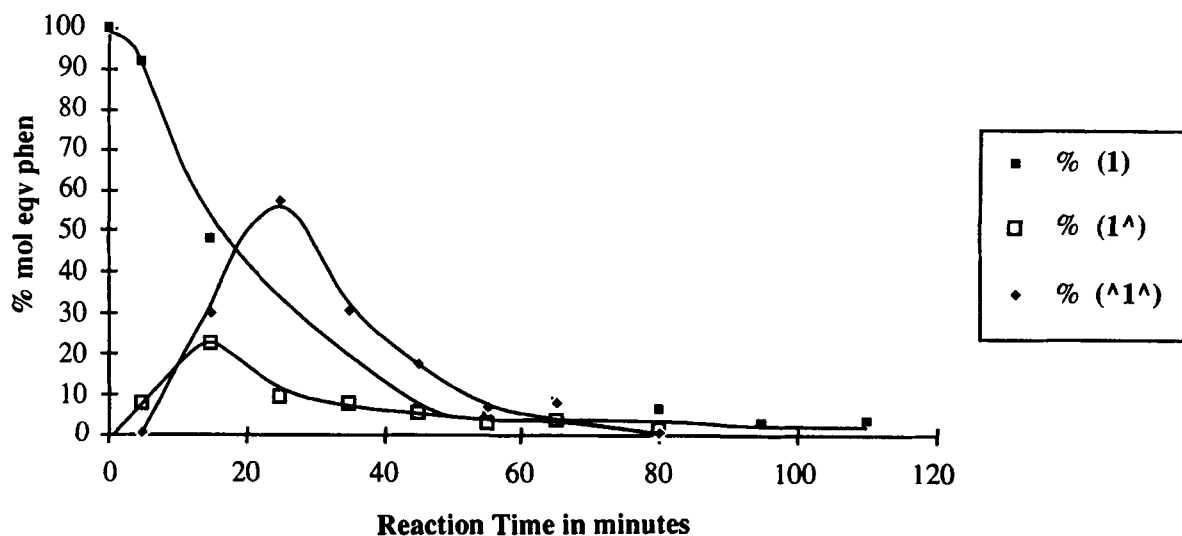


Figure 4 Reaction diagram: kinetic of formation of linear oligomers in the synthesis of *p-tert*-butylcalix[8]arene.

reaches its maximum, 11.5%, at the end of the reaction. The calix[7]arene and the calix[8]arene have the same evolution and reach, respectively, 7.2% and 61% at the end of the experiment. Nevertheless, one type of calixarene has not been identified. The mass spectra, Figure 6, obtained from the samples taken at $t = 45$ minutes and at $t = 55$ minutes, show the presence of (1^1), (2), (2^1), (2^2), (3), (4), (4^1), (4^2), (5), (5^1) and (6^1), but not heptamer and octamer. The *p-tert*-butylcalix[4]arene, *p-tert*-calix[6]arene, *p-tert*-butylcalix[7]arene and *p-tert*-butylcalix[8]arene are also detected. The unknown calixarene is probably the *p-tert*-butylcalix[5]arene. In the final mixture there are 89.2% of calixarenes and 10.8% of calix[5]arene and linear oligomers.

Conclusions

We have identified the molecules present during the *p-tert*-butylcalix[8]arene synthesis as described in "Organic Synthesis". It has been shown that the linear species formed are (4^1) detected by T.L.C. and S.M., and (4), (4^2), (5^1) and (6^1) not detected by T.L.C. but by S.M. Also it seems that the linear tetramers are really the precursors of calix[8]arene. No linear octamer has been detected. In these conditions it seems that the *p-tert*-butylcalix[8]arene is formed following the "hemicalixarenes" pathway. But an important part of the calix[8]arene synthesis seems to be due to the disproportion of *p-tert*-butyldihomooxalix[4]arene. Indeed, we have shown in other experiments that the oxalixarene under

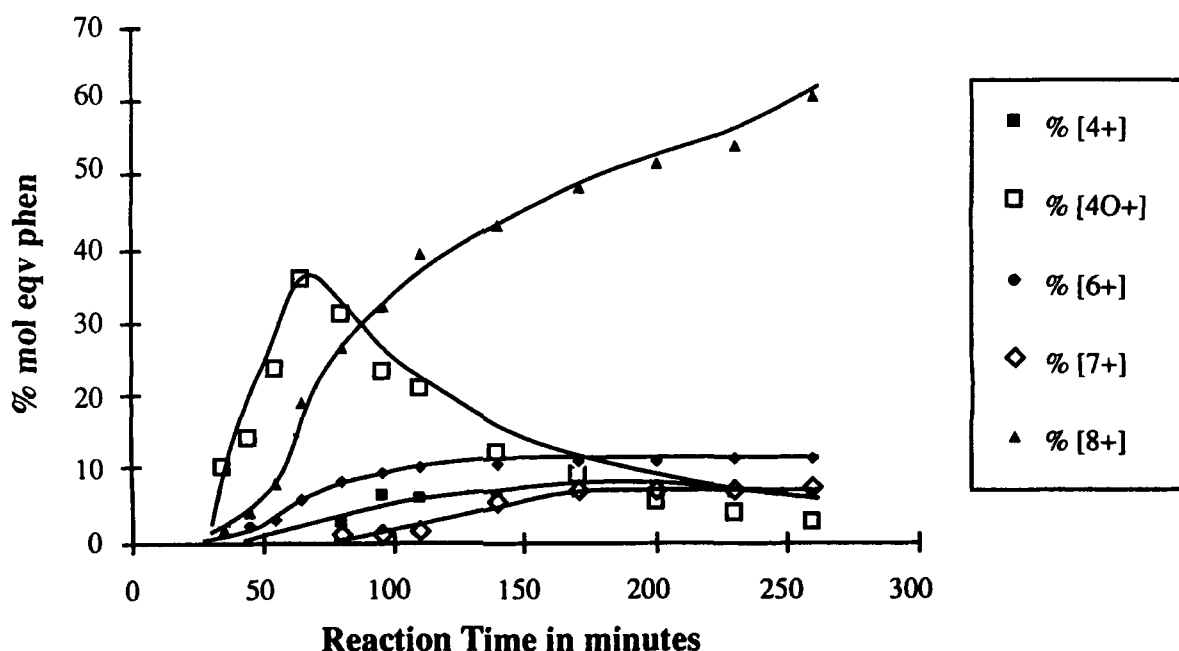


Figure 5 Reaction diagram: kinetic of formation of calixarenes in the synthesis of *p-tert*-butylcalix[8]arene.

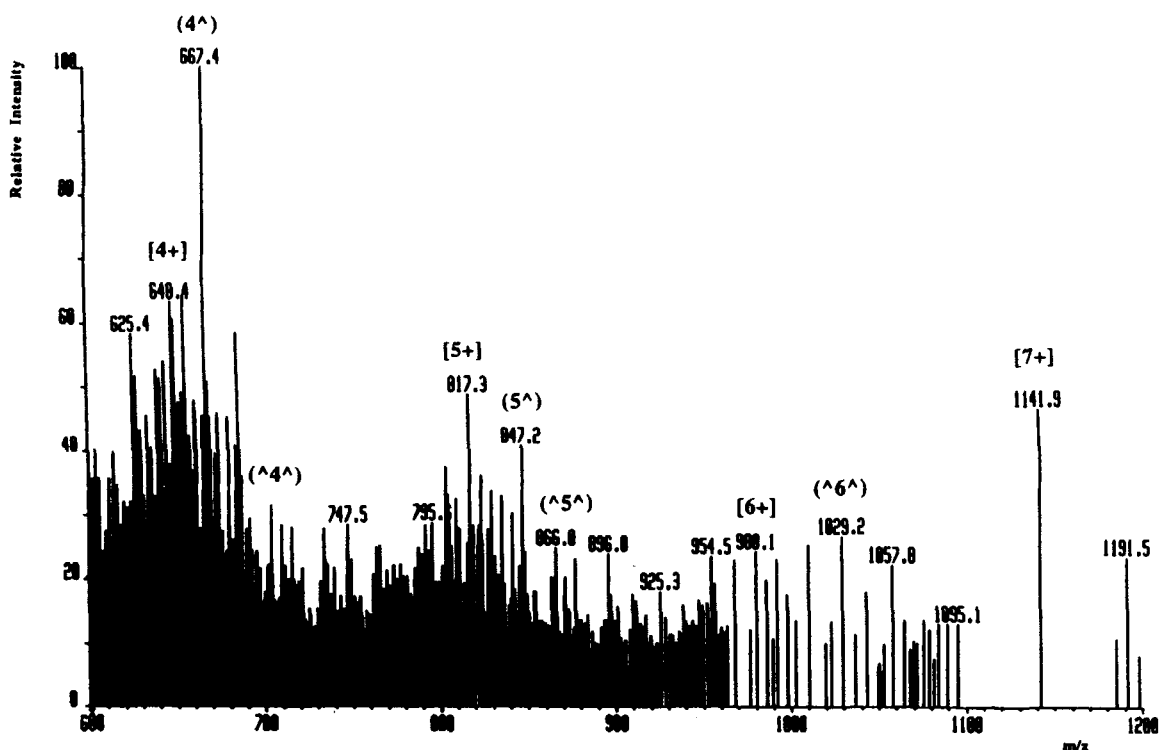
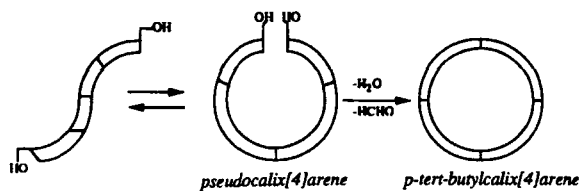


Figure 6 Mass spectrum of the sample taken at $t = 45$ minutes in the synthesis of *p*-*tert*-butylcalix[8]arene.

the same conditions is broken and transformed in calix[8]arene in 90% yield. The disproportion of the oxacalixarene during the reaction can be explained in this manner. In this way and according to the reaction diagram, we can consider that 17% of calix[8]arene would be formed by opening of the oxacalix[4]arene and by building up of hemicalex[8]arene.



CONCLUSIONS

For the *p*-*tert*-butylcalix[6]arene synthesis, it has been proposed⁴, Figure 7, that calix[6]arene is formed following the "pseudocalixarenes" pathway and is the product of a template effect.

For the *p*-*tert*-butylcalix[4]arene synthesis, it seems that the major pathway is the "pseudocalixarenes" pathway, Figure 7. On the other hand, the cyclic tetramer is the product of thermodynamic control because calix[8]arene is transformed in calix[4]arene with temperature and if the mixture is carried out at 145 °C instead of 250 °C, calix[8]arene is formed.

For the *p*-*tert*-butylcalix[8]arene synthesis, there is one origin for the cyclic octamer: the cyclization of "hemicalex[8]arenes" constituted of linear tetramers, Figure 7. This calix[8]arene is the product of kinetic control.

On the other hand, the reaction diagrams⁷ permit the development of other ways to synthesize different calixarenes such as *p*-*tert*-butyldihomooxalix[4]arene.

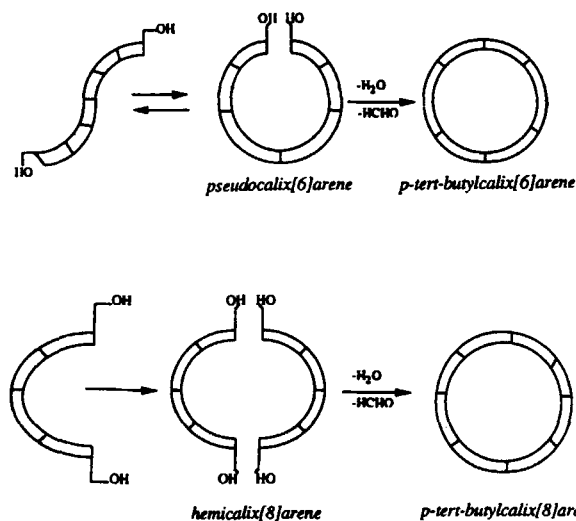


Figure 7 Mechanism of formation of *p*-*tert*-butylcalix[4]arene, *p*-*tert*-butylcalix[6]arene and *p*-*tert*-butylcalix[8]arene.

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