The First Inexpensive, Simplified and Large Scale Synthesis of *p*-tert-butylcalix[7] and [9]arenes

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Abstract

The nuclear industry and the rare earth elements mining need methods in order to separate lanthanides and actinides. Large organic macrocycles have demonstrated their contribution to this domain. Due to the lack of an efficient and reproducible method of synthesis, the chemistry of large *p*-tert-butylcalix[n]arenes (with $6 < n < 10$) has been much less explored than the one of their inferior homologs. Excepted for the *p*-tert-butylcalix[8]arene which is obtained in good yields, the procedures described in the literature for the preparation of *p*-tert-butylcalix[7] and [9]arenes involve many steps of purification and lead to, in the very best case, a couple of grams of product, after one month of labor. In this work, a set of experiments with varying parameters has demonstrated the crucial role of the solvent and of the amount of catalyst in the macrocyclization reaction. Then, a scale-up study was done, the procedure being adapted and realized on a semi industrial scale reactor. Finally, an original purification pathway avoiding the numerous silica-gel chromatographies and recrystallizations was set up and optimized. This simplified procedure opens gateways for the preparation of a few dozen grams of pure *p*-tert-butylcalix[7] and [9]arenes and should lead to the preparation of new selective complexants.

Keywords: *p*-tert-butylcalix[7]arene; *p*-tert-butylcalix[9]arene; scale-up; synthesis.

1. Introduction

The fast development of new technologies and electronics in particular, has drastically increased the needs of rare earth elements as lanthanides, scandium and yttrium. As a consequence, mining of rare earth containing ores, such as monazite, has exploded over the last three years. Those ores not only include the valuable lanthanides but also radioactive actinides such as uranium and thorium. Unfortunately, the actual extraction processes fail to separate the lanthanides from actinides and produce a large amount of radioelement containing wastes ^[1].

In the nuclear industry, separation of actinides from lanthanides is also an important challenge. Spent nuclear fuel contains moderate amounts of longlived minor actinides (Np, Am, Cm) together with other fission products, amongst which lanthanides represent one of the major components^[2]. To reduce long-term radiological risks to the environment, the transmutation of actinides into short-lived radionuclides has been proposed for conditioning, which requires their separation from lanthanides^[2,3].

A relevant method for their separation consists in using organic macrocycles, acting as selective ligands toward those elements and possessing a tunable size^[4]. The *p*-tert-butylcalix[n]arenes macrocycles, cyclic

oligomers composed of *n* *p*-*tert*-butylphenol units linked together by methylene bridges (with *n* varying from 4 to 20, see **Fig. 1**), are good candidates for this purpose^[5].

Although they are more famous in the field of macrocyclic and supramolecular chemistry^[6,7,8] few groups around the world dedicate their efforts to involve *p*-*tert*-butylcalixarenes in separation of lanthanides and actinides^[9]. The best efficiency was usually observed with CMOP functionalized *p*-*tert*-butylcalix[4]arene, which display the best ability to extract and also good selectivity^[10]. Concerning the superior homologs, CMPO- and amide-substituted calix[6] and [8]arenes revealed to be efficient for the separation of An^{3+}/Ln^{3+} from radioactive wastes^[10].

Contrarily to their inferior homologs, *native* large *p*-*tert*-butylcalixarenes (i.e non-functionalized *p*-*tert*-butylcalix[*n*]arenes with $n \geq 6$) can act as polyaryloxy ligands toward rare earth elements. For example, the native *p*-*tert*-butylcalix[6], [7], [8] and [9]arenes have shown the ability to form stable complexes with europium and uranyl^[11]. Also, in presence of uranyl salts, the *p*-*tert*-butylcalix^[12]arene drove to crystals revealing an original tetranuclear complex^[12]. Despite the great potential they represent for radioactive wastes treatment, very few groups have explored the large *p*-*tert*-butylcalix[*n*]arenes ($n > 6$) in general, as this requires a lot of synthetic effort in organic chemistry. The Gutsche's synthesis of *p*-*tert*-butylcalix[*n*]arenes (with $7 < n < 20$) has allowed to isolate and characterize the entire family of *p*-*tert*-butylcalix[*n*]arenes^[13]. However, this procedure is not selective and involves fastidious isolation of each calixarene and also their separation from the linear oligomers. After at least one month of separation labor (dozen of columns and crystallizations), from several hundreds of milligrams to gram scale of each macrocycle can be obtainedⁱ.

Another procedure was reported for the synthesis of *p*-*tert*-butylcalix[9]arene by using a "6 + 3" cyclization reaction between linear phenolic hexamers and a triphenolic unit (2,6-bis(5-*tert*-butylsalicyl)-4-*tert*-butylphenol) under basic conditions^[14]. However, this method is not selective and produces all the possible sizes of the macrocycles. More recently, Bew and Sharma have reported a straightforward and selective synthesis of *p*-*tert*-butylcalix[9]arene displaying an approximate 30-35% conversion rate^[15]. However, our attempts to reproduce this synthesis have shown that after the reported purification treatment, the yield in pure product

drastically fellⁱⁱ. All these routes of synthesis don't allow the preparation of a significant amount of product. This is clearly a hindrance for the elaboration of selective chelatants based on large *p*-*tert*-butylcalix[*n*]arenes, such synthesis studies necessitating generally several grams of starting compounds. Consequently, working with large macrocycles is still considered as a challenge and up to now very few organic and physical chemistry have been reported for this class of molecules. A simplified large scale method of preparation of *p*-*tert*-butylcalix[7] and [9]arenes would certainly open perspectives for the conception of new host molecules^[16,17], new metallic ligands design^[18,19,20], development of original supramolecular assembly^[21], and also for the conception of new selective actinide/lanthanide chelatants^[22,23].

Here we describe an optimized and particularly simplified procedure for the synthesis of *p*-*tert*-butylcalix [7] and [9]arenes. The procedure was scaled-up, allowing the preparation of about 96 g *p*-*tert*-butylcalix[7]arene and 25 g of *p*-*tert*-butylcalix [9]arene after ten days of work. Due to the very low price of the starting materials, the cost of about those two macrocycles are respectively of 15 \$/g and 60 \$/g, making this approach attractive. For this, a scale-up study was done and in the second part, an original purification procedure was set up and optimized.

Fig. 1. Reaction of Macrocyclization involved in the *p*-*tert*-butylcalix[*n*]arenes synthesis.

2. Materials and Methods

2.1 General methods. The composition of the crude mixture was systematically determined by using an inverse phase HPLC. HPLC analyses were performed using a KONTRON instrument consisting of a series 2 pumps, an HPLC DETECTOR 430 UV/VIS detector set at 281 nm, and a 4.6 mm id (Internal Diameter), 25 cm, EC 250/4.6 NUCLEOSIL 100-5 C18 HPLC column packed with 5 μ m, non-end-capped, silica-based particles. The separation of *p*-*tert*-butylcalix[*n*]arenes

ⁱ excepted for the *p*-*tert*-butylcalix[8]arene which is obtained through a reproducible procedure in good yields (ca. 65 %)

ⁱⁱ Despite several attempts, the best yields that we have obtained were around 5%.

was accomplished with a mixture of two eluants A and B. Eluant A consisted of 99 % CH₃CN with 1 % AcOH (acetic acid). Eluant B consisted of 57 % CH₂Cl₂ and 43 % MTBE (methyltert-butylether) in a 12:9 ratio and 1 % AcOH. A and B set at a flow rate of 0.8 mL/min and a pressure of 45 Bars. A 80/20 mixture of A and B was run isocratically.

The reaction was realized in a semi-industrial scale unit^[24]. A dual envelop reactor of 30 litres capacity was used. The temperature was set up by using an automatic regulation controlled from a monitor using *Delta-V* software. On the reactor is attached a column with Rachig rings to control the reflux. On top of the column, a pipe allows to introduce solvent under vacuum. The reactor was heated through dual envelope with circulated warm oil. (see Supporting Information File for general protocols).

Concerning the X-Ray Diffraction Analysis, suitable crystals were mounted on a Nonius KappaCCD diffractometer using Mo K λ radiation ($\lambda = 0.71069$ Å). Intensities were collected at 150(1) K by means of the COLLECT software^[25]. Reflection indexing, Lorentz-polarization correction, peak integration, and background determination were carried out with DENZO. Frame scaling and unit-cell parameters refinement were made with SCALEPACK^[26]. A semi-empirical absorption correction was applied using the program DIFABS^[26]. The structures were solved by direct methods with SIR97^[27]. The remaining non-hydrogen atoms were located by successive difference Fourier map analyses. H-atoms were placed geometrically and included in the refinement using soft restraints on the bond lengths and angles to regularize their geometry (C-H in the range 0.93-0.98 Å and O-H = 0.82 Å) and isotropic atomic displacement parameters ($U(H)$ in the range 1.2-1.5 times U_{eq} of the adjacent atom). In the last cycles of the refinement, the hydrogen atoms were refined using a riding mode. The structure refinement was carried out with CRYSTALS^[28] (see Supporting Information for full crystallographic data).

2.2 Procedure for the synthesis of *p*-tert-butylcalix[7] and [9]arenes. Twenty-five liters of 1,2-dichloroethane were first introduced into the reactor. Then, 1000 g (1 éq.) of *p*-tert-butylphenol, 1300 g (1.13 éq.) of PTSA and finally 660 g (1.1 éq.) of s-trioxane²⁹ were introduced through the top of the reactor. The system was closed and

after 10 min of vigorous stirring, heating was started. After 2h the reaction mixture changed from a colourless clear solution to a colourless cloudy mixture. Every hour, an aliquot of reaction mixture was collected through the bottom of reactor and analyzed by HPLC. After 4 hours the reaction mixture became dark green and the HPLC analysis has shown that the reaction was complete (20 % in *p*-tert-butylcalix[7]arene and 10 % in *p*-tert-butylcalix[9]arene). Heating was stopped and the reactor was cooled to room temperature. When the temperature return at 30°C, the bottom valve was opened and all the mixture was collected in a 50 litres can. The crude was then transferred in a mixing decanter. Then, in order to quench the reaction, 5 litres of HCl (1M) were added. The two liquid layers were mixed together during 1 hour and were then separated. The organic layer was reloaded, and then washed again with 5 litres of HCl (1M). The two layers were separated and the aqueous layers were recombined and reloaded, then were washed with 5L of 1,2-dichloroethane in order to recover a maximum of organic layer. After separation, the organic layers were recombined, and finally washed twice with 5 litres of distilled water. Organic layer was separated, collected, and introduced into a *vacuum* evaporator. Heating was set up at 45°C, under a 20 mm Hg vacuum, allowing the 1,2-dichloroethane to be evaporated. After removal of all the solvent, the resulting dark solid was dried under *vacuum* in order to remove the traces of solvents. 900 g of crude dark solid were obtained. By portions of 50 g, the crude mixture was treated by following the procedure displayed on the **Fig. 2**. First, the crude was refluxed during four hours in hexane (60 g/L). Once the solution cold, a precipitate (P1) was separate by filtration from the mother liquors which were concentrated (Mixture **B**, 729 g). Starting from the evaporated mother liquors mixture **B**, a sequence of treatment/filtration in hot acetone (68 g/L), drive to 5 precipitates (P2a to P2e) and a final mother liquor mixture **C** (600 g). This mixture **C** was filtrated through silica gel (eluant 5/5 CH₂Cl₂/heptane) leading to a white solid.

A final recrystallization of this solid in acetone/ethanol drove to $5.33 \times 18 = 96$ g of the pure *p*-tert-butylcalix[7]arene **E** (purity > 98 %). Once they have been mixed together, the collected precipitates P2b-2c became the mixture **D** (37.6 g). A recrystallization of mixture **D** in chloroform/acetonitrile led to $1.39 \times 18 = 25$ g of the pure *p*-tert-butylcalix[9]arene **F** as a white crystalline solid (purity > 98 %).

Fig. 2. Procedure's Synoptic of purification of pure *p*-tert-butylcalix[7] and [9]arenes.

***p*-tert-butylcalix[7]arene E** (96 g) as white solid. mp > 238 °C dec; IR ν (cm⁻¹) 3132, 2956, 2868, 1484, 1203; ¹H NMR (300 MHz, CDCl₃) : δ (ppm) = 1.33 (s, 63H, C(CH₃)₃), 3.95 (br s, 14H, Ar-CH₂-Ar), 7.24 (s, 14H, Ar-H), 10.38 (br s, 7H, OH); ¹³C NMR (400 MHz, CDCl₃) : δ (ppm) = 31.7 (C(CH₃)₃), 33.1 (Ar-CH₂-Ar), 34.2 (C(CH₃)₃), 126.3 (Ar-H), 127.6 - 144.5 - 147.4 (Ar); LRMS (ES⁺) m/z 1135.7 ([M+H]⁺) and 1157.7 ([M+Na]⁺), HRMS (ES⁺) for (C₇₇H₉₉O₇ ([M+H]⁺)), calculated 1135.7385, found 1135.7404. Crystal data for ***p*-tert-butylcalix[7]arene**, C₈₁H₁₀₄N₂O₇, Mr = 1217.72, T 150(2) K, triclinic, space group P-1, a = 14.417(2), b = 14.542(2), c = 18.350(3) Å, α = 74.96(1)°, β = 84.96(1)°, γ = 82.424(9)°, V = 3677.1(10) Å³, density = 1.100 Mg/m³, m = 0.07 mm⁻¹, Z = 2, F(000) = 1320, Crystal size 0.38 x 0.37 x 0.30 mm³, Theta range for data collection 1.4 to 27.9°, Index ranges -18 ≤ h ≤ 18, -19 ≤ k ≤ 19, -24 ≤ l ≤ 24, reflections 8678 with I > 2.0σ(I), wR(F²) = 0.189. CCDC deposit number: 801715.

***p*-tert-butylcalix[9]arene F** (25 g) as white solid. mp > 293 °C dec; IR ν (cm⁻¹) 3255, 2954, 2869, 1485, 1202; ¹H NMR (300 MHz, CDCl₃) : δ (ppm) = 1.30 (s, 81H, C(CH₃)₃), 3.96 (br s, 18H, Ar-CH₂-Ar), 7.22 (s, 18H, Ar-H), 9.82 (br s, 9H, OH); ¹³C NMR (400 MHz, CDCl₃) : δ (ppm) = 29.9 (Ar-CH₂-Ar), 31.7 (C(CH₃)₃), 34.2

(C(CH₃)₃), 126.3 (Ar-H), 127.6, 144.5, 147.4 (Ar); LRMS (ES⁺) m/z 1481.8 ([M+Na]⁺), HRMS (ES⁺) for (C₉₉H₁₂₆O₉Na⁺ ([M+Na]⁺)), calculated 1481.9300, found 1481.9296. Crystal data for ***p*-tert-butylcalix[9]arene**, C₉₉H₁₂₆O₉.6(C₃H₆O), Mr = 1808.56, T 150(2) K, triclinic, space group P-1, a = 16.502(3), b = 18.406(3), c = 20.983(5) Å, α = 107.34(1)°, β = 109.77(2)°, γ = 98.95(2)°, V = 5487(2) Å³, density = 1.095 Mg/m³, m = 0.07 mm⁻¹, Z = 2, F(000) = 1968, Crystal size 0.42 x 0.37 x 0.36 mm³, Theta range for data collection 0.7 to 27.9°, Index ranges -21 ≤ h ≤ 21, -23 ≤ k ≤ 24, -27 ≤ l ≤ 27, reflections 11234 with I > 2.0σ(I), wR(F²) = 0.235. CCDC deposit number: 801716. (see Supporting Information File for full characterization data)

3. Results and Discussion

After checking the Standard Gutsche's experiment could be reproduced in our laboratory, a set of experiments with varying parameters was undertaken. Indeed, it was necessary to determine the respective influence of parameters such as temperature, solvent and amount of PTSA on the conversion rate in *p*-tert-butylcalix[7] and [9]arenes. Each reaction was realized on 0.15 g of

p-tert-butylphenol starting materials (entries 1 to 6, Table 1), the conversion rates were measured by HPLC.

3.1 Effect of the amount of PTSA. The amount of PTSA was varied from 0.03 (entry 1, Table 1) to 1 equivalent (entries 2, Table 1). These experiments have demonstrated that a stoichiometric presence of PTSA (versus 0.03 equivalent) allowed to reach four times faster the optimum conversion rate in *p*-tert-butylcalix[7] and [9]arenes without changing the distribution of the different calixarenes. Regarding the low price of the PTSA, these conditions (1 equiv.) were selected for a large scale synthesis.

3.2 Effect of solvent and temperature on the macrocyclic reaction. Since the experiments were realized under atmospheric pressure and under reflux, the reaction mixture temperature was directly dependent of the solvent boiling point. Moreover, in order to see the influence of solvent on conversion rates in *p*-tert-butylcalix[7] and [9]arenes, usual solvents with different polarity and organic nature were chosen. After checking that all the reactant were soluble under reflux conditions, toluene ($\mu = 0.36$ debye, Bp = 111 °C (1 Atm)), dichloromethane ($\mu = 1.54$ debye, Bp = 39 °C (1 Atm)), and acetonitrile ($\mu = 3.84$ debye, Bp = 82 °C (1 Atm)) were selected.

As previously observed in the literature^[17], it rapidly appeared that the reaction of macrocyclization didn't work at all in acetonitrile and occurred slowly in toluene (entries 4 and 5, Table 1). Then, comparing the dichloromethane to the chloroform (entry 3 and 2 respectively, Table 1) the distribution of different calixarenes was almost superimposable, presenting a conversion rate of about 20 % and 15 % in *p*-tert-butylcalix[7] and [9]arenes respectively. However, due to its lower boiling point under 1 Atm, 24 hours reaction duration in dichloromethane were necessary to obtain such a chromatogram compared to the 8 hours in chloroform. This demonstrates the crucial role of the temperature on the reaction kinetic. In the dichloromethane, when the reaction was heated longer in the time, the HPLC's display a significant increase of the conversion rate in *p*-tert-butylcalix[8]arene, which is more favorable macrocycle of this reaction, as it was demonstrated in previous studies⁸.

With the observation that the reaction occurs in halogenated solvent, experiments were realized in 1,2-di-

chloroethane which present a near polarity and a higher boiling point than dichloromethane and chloroform ($\mu = 1.19$ debye, Bp = 83.5°C (1 Atm)). The results are presented in the entry 6. Similar pattern of distribution in different calixarenes with conversion rates of ca 20 % in *p*-tert-butylcalix[7]arene and 10 % in *p*-tert-butylcalix[9]arene were obtained in only 4 hours. Here, the higher temperature of the experiment has drastically increased the Kinetic's reaction without almost affecting the distribution of the different produced calixarenes. However, a slightly decrease in conversion rate in *p*-tert-butylcalix[7] and [9]arenes has been observed. Finally, regarding the constraints we had to observe by using the semi industrial process (i.e. for security reasons, not more than eight hours of heating were allowed), 1,2-dichloroethane appears to be the most efficient solvent to realize the large scale synthesis.

3.3 Simplification of the procedure. With the idea to transfer the experiments on a half industrial scale, it was important to simplify the procedure. Indeed the addition of PTSA once the *p*-tert-butylphenol/formaldehyde chloroform solution is under reflux, was technically awkward to be realized in our half-industrial scale equipment. Trials were realized and have shown that the mixing of the three solids together, following by the solvent addition, before refluxing hasn't any influence on the composition of the crude mixture of calixarenes. Moreover, usually the water formed during the reaction is gradually extracted by a Dean-Stark condenser. Since our plant was not set up for such a water removal, we had to see what consequences to let the water in the reaction mixture had. Our experiments have demonstrated that the absence of a Dean-Stark condenser didn't change the results obtained before. We expect that result is probably due to the extremely poor solubility of water in 1,2-dichloroethane. Finally, the real scale up study had to show that the results observed at the milligram scale could be reproduced on a kilogram scale.

For this, trials with increasing amounts of starting *p*-tert-butylphenol (0.15, 10, 20, 40 and finally 1000 g) were realized (Fig. 3). As shown in the Table 1 (entries 6 to 10), conversion rates in *p*-tert-butylcalix[7] and [9]arenes are preserved: respectively 19 % and 10 % (0.15 g), 26 % and 10 % (10 g), 21 % and 9 % (20 g), 14 %³⁰ and 9 % (40 g), and 20 % and 10 % (1000 g). All these results allow us to propose the final procedure described in the *matériel and method* part.

Table 1. Conversion rates in *p*-tert-butylcalix[7] and [9]arenes in the tested conditions experiments. All the experiments were realized under reflux of the corresponding solvent.

Entries	Solvent	Amount of PTSA	Amount of <i>p</i> -tBuPhOH	Duration	Conv. Rate of [7]	Conv. Rate of [9]
1	CHCl ₃	0.033 eq.	0.15 g	8 h	15	7
2	CHCl ₃	1 eq.	0.15 g	8 h	20	12
3	CH ₂ Cl ₂	1 eq.	0.15 g	24 h	22	15
4	CH ₃ CN	1 eq.	0.15 g	48 h	0	0
5	Toluene	1 eq.	0.15 g	48 h	14	3
6	1,2-DCE	1 eq.	0.15 g	4 h	19	10
7	1,2-DCE	1 eq.	10 g	4 h	26	10
8	1,2-DCE	1 eq.	20 g	4 h	21	9
9	1,2-DCE	1 eq.	40 g	4 h	14	9
10	1,2-DCE	1 eq.	1000 g	4 h	20	10

Fig. 3. Conversion Rates in *p*-tert-butylcalix[7] and [9]arenes depending of the amount of the starting *p*-tert-butylphenol.

3.4 Improvement of the purification procedure. As mentioned in the introduction, the separation and purification sequences in Gutsche's procedure are laborious, necessitating numerous steps of crystallization and silica chromatographies to obtain pure *p*-tert-butylcalix[7] and [9]arenes. Moreover, this procedure is described on a scale leading to small amount of compounds. In order to prepare a very large quantity of these compounds, a simple and efficient purification procedure was necessary.

After allowing the reaction mixture to go back at room temperature, a classic workup of liquid-liquid extraction with an aqueous solution of HCl (1M) was realized in order to quench the reaction. Once the organic layers settled and recombined the solvent was removed under reduced pressure, leading to a 900 g crude mixture **A**

containing 20 % and 10 % respectively in *p*-tert-butylcalix[7] and [9]arenes (Spectrum **A**, **Fig. 4**).

For laboratory convenience, the crude mixture **A** was treated by 50 g portions. We undertook to separate the two calixarenes by using recrystallization and simple filtration through silica gel only, avoiding the fine chromatography separation steps. For this, we first checked the solubility table given in the literature¹⁵. Due to the relative insolubility of the *p*-tert-butylcalix[6] and [8]arenes in hexane, it seemed judicious to us to treat the crude mixture in boiling hexane. Several tests allow us to optimize the mass concentration of crude (60 g/L) as well as the duration of the treatment (4 hours reflux). Once the solution cold, a precipitate (P1) was separated by filtration from the mother liquors which was concentrated, leading to mixture **B**. The HPLC analysis of the precipitate and the mother liquors revealed that *p*-tert-butylcalix[6] and [8]arenes were removed from the crude mixture (Spectrum **B**, **Fig. 4**).

Starting from the evaporated mother liquor mixture **B**, a sequence of treatment in hot acetone (68 g/L), drive to 5 precipitates (P2a to P2e) and a mother liquor mixture **C** (spectrum **C**, **Fig. 4**). The final mother liquor (mixture **C**) displays about 30 % of the *p*-tert-butylcalix[7]arene. We have found that a straightforward filtration through silica gel (eluant 5/5 CH₂Cl₂/heptane) was the most efficient way to remove the linear oligomers of the mixture **C**. A 85 % purity in *p*-tert-butylcalix[7]arene fraction was collected. A final recrystallization of this solid acetone/ethanol led to 96 g of the pure *p*-tert-butylcalix[7]arene (purity > 98 %, spectrum **E**, **Fig. 4**). The HPLC analyses of each solids coming from acetone treatment, have

shown that most of the *p*-*tert*-butylcalix[9]arene was in the P2b and P2c fractions. Once mixed, the collected precipitates P2b-2c became the mixture **D**, containing about 85 % in *p*-*tert*-butylcalix[9]arene (spectrum **D**, Fig. 3). A final recrystallization of mixture **D** in chloroform/ acetonitrile led to 25 g of the pure *p*-*tert*-butylcalix[9] arene (purity > 98 %, spectrum **F**, Fig. 4). It should be noted that, for the first time, our large scale synthesis led, in a relatively

simple procedure, to 96 g of *p*-*tert*-butylcalix[7] arene and 25 g of *p*-*tert*-butylcalix[9]arene of isolated pure compounds.

The purity of the obtained products was confirmed by HPLC, ¹H and ¹³C NMR. Moreover, single crystals of each calixarene were grown and analyzed by XRD. Two original structures were obtained, confirming the structure of the obtained *p*-*tert*-butylcalix[7] and [9]arenes. The two X-ray structures are shown in the Fig. 5.

Fig. 4. HPLC chromatograms of the fractions A-F. *p*-*tert*-butylcalix[n]arenes are noted “[n]” on the spectra. M is a mixture of linear oligomers and *p*-*tert*-butylcalix[4]arene. Procedure’s Synoptic of purification to obtain pure *p*-*tert*-butylcalix[7] and [9]arenes.

Fig. 5. Crystal structures of *p*-*tert*-butylcalix[7]arene (left) and *p*-*tert*-butylcalix[9]arene (right). Solvent molecules are omitted for clarity.

5. Conclusion

In this paper, we have presented a straightforward procedure allowing for, the first time, the preparation of few dozen of grams of highly pure *p*-*tert*-butylcalix[7] and [9]arenes (purity > 98 %). After controlling the influence of the amount of catalyst, solvent nature and introduction procedure, we obtained a new protocol which is the simplest one compared to all the syntheses described in the literature. Indeed, we manage to reduce the steps necessary to obtain the both large calixarenes. For each calixarene, firstly, two treatments in hot solvent, following by an ultimate recrystallization for the *p*-*tert*-butylcalix[9]arene and a silicagel filtration, completed by a recrystallization for the *p*-*tert*-butylcalix[7]arene is sufficient to produce both the pure calixarenes in significant amounts. Finally, the low cost of the starting materials makes this approach definitely attractive. This simplified procedure will open new gates for the development of the *p*-*tert*-butylcalix[7] and [9]arenes in supramolecular chemistry in general, but also for the conception of a new range of selective lanthanides/actinides ligands.

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Associated content

Supporting Information. General protocols, Crystallographic data, ¹H NMR, ¹³C NMR, ¹³C-DEPT NMR, IR, Mass spectra, HPLC Chromatograms of *p*-*tert*-butylcalix[7 and 9]arenes.

References

- [1] Cotton, S. in “Lanthanide and Actinide Chemistry”, Eds. John Wiley & Sons (2006).
[doi:10.1002/0470010088](https://doi.org/10.1002/0470010088)
- [2] Mathur, J. N.; Murali, M. S.; Nash, K. L. *Solvent Extr. Ion Exch.* **2001**, 19, 357–390.
[doi:10.1081/SEI-100103276](https://doi.org/10.1081/SEI-100103276)
- [3] Madic, C.; Cordier, P. Y. GB Patent 2,313,471, **1997**; Chem. Abstr., 128, 209974.
- [4] Choppin, G. R.; Nash, K. L. *Radiochim. Acta* **1995**, 70–71, 225–236.
- [5] Dam, H. H.; Reinhoudt, D. N.; Verboom, W. *Chem. Soc. Rev.* **2007**, 36, 367–377.
[doi:10.1039/b603847f](https://doi.org/10.1039/b603847f)
- [6] Ludwig, R.; Lentz, D.; Nguyen, T. K. D. *Radiochim. Acta* **2000**, 88, 335–343.
[doi:10.1524/ract.2000.88.6.335](https://doi.org/10.1524/ract.2000.88.6.335)
- [7] Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., “Calixarenes 2001”; Eds.; Kluwer Academic Publishers: Dordrecht, Holland, (2001).
- [8] Gutsche, C. D., in “Calixarenes Revisited, Monographs in Supramolecular Chemistry”; J. F. Stoddart, Ed. The Royal Society of Chemistry: Cambridge, U.K., (1998).
- [9] Mandolini, R.; Ungaro, R., “Calixarenes in Action”; Imperial College. Press (2000).
[doi:10.1142/9781848160354](https://doi.org/10.1142/9781848160354)
- [10] Mokhtari, B.; Pourabdollah, K.; Dallali, N. J. *Radioanal. Nucl. Chem.* **2011**, 287, 921–934.
[doi:10.1007/s10967-010-0881-1](https://doi.org/10.1007/s10967-010-0881-1)
- [11] (a) Barbosa, S.; Carrera, A. G.; Matthews, S. E.; Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Rouquette, H.; Schwing-Weill, M. J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 719–723.
[doi:10.1039/a900210c](https://doi.org/10.1039/a900210c) (b) Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Jakobi, R. A.; Kraft, D.; Mauprivez, O.; Rouquette, H.; Schwing-Weill, M.-J.; Simon, N.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1175–1182.
[doi:10.1039/p29960001175](https://doi.org/10.1039/p29960001175) (c) Arduini, A.; Böhmer, V.; Delmau, L.; Desreux, J. F.; Dozol, J.-F.; Carrera, M. A. G.; Lambert, B.; Musigmann, C.; Pochini, A.; Shivanyuk, A.; Ugozzoli, F. *Chem.-Eur. J.* **2000**, 6, 2135–2144.
[doi:10.1002/1521-3765\(20000616\)6:12<2135::AID-CHEM2135>3.0.CO;2-A](https://doi.org/10.1002/1521-3765(20000616)6:12<2135::AID-CHEM2135>3.0.CO;2-A) (d) Delmau, L. H.; Simon, N.; Schwing-Weill, M.-J.; Arnaud-Neu, F.; Dozol, J.-F.; Eymard, S.; Tournois, B.; Böhmer, V.; Grüttner, C.; Musigmann, C.; Tunay, A. *Chem.*

- Commun. **1998**, 1627–1628. [doi:10.1039/a802555j](https://doi.org/10.1039/a802555j)
- [12] Sansone, F. ; Fontanella, M. ; Casnati, A. ; Ungaro, R. ; Böhmer, V. ; Saadioui, M. ; Liger, K. ; Dozol, J.-F. *Tetrahedron* **2006**, 62, 6749–6753. [doi:10.1016/j.tet.2006.05.009](https://doi.org/10.1016/j.tet.2006.05.009)
- [13] (a) Fleming, S.; Gutsche, C. D.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; Stewart, D. F.; White, A. H. *Dalton Trans.* **2003**, 3319–3327 [doi:10.1039/b305041f](https://doi.org/10.1039/b305041f) (b) Delaigue, X.; David, G. C.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; Stewart, D. F.; White, A. H. *Supramol. Chem.* **2004**, 16, 603–609. [doi:10.1080/10610270412331318827](https://doi.org/10.1080/10610270412331318827)
- [14] Leverd, P. C.; Dumazet-Bonnamour, I.; Lamartine, R.; Nierlich, M. *Chem. Commun.* **2000**, 493–494. [doi:10.1039/b000909l](https://doi.org/10.1039/b000909l)
- [15] Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, 121, 4136–4146. [doi:10.1021/ja983964n](https://doi.org/10.1021/ja983964n)
- [16] Dumazet, I.; Regnouf-De-Vains, J.-B.; Lamartine, R. *Synth. Commun.* **1997**, 27, 2547–2555. [doi:10.1080/00397919708004122](https://doi.org/10.1080/00397919708004122)
- [17] Bew, S. P.; Sharma, S. V. *Chem. Commun.* **2007**, 975–977. [doi:10.1039/b608482f](https://doi.org/10.1039/b608482f)
- [18] Clark, E. T.; Makha, M.; Sobolev, A. N.; Raston, C. L. *Dalton Trans.* **2008**, 4855–4859. [doi:10.1039/b807511e](https://doi.org/10.1039/b807511e)
- [19] Bavoux, C.; Baudry, R.; Dumazet-Bonnamour, I.; Lamartine, R.; Perrin, M. J. *Incl. Phenom. Macro.* **2001**, 40, 221–224. [doi:10.1023/A:1011881715379](https://doi.org/10.1023/A:1011881715379)
- [20] Fleming, S.; Gutsche, C. D.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; Stewart, D. F.; White, A. H. *Dalton Trans.* **2003**, 3319–3327. [doi:10.1039/b305041f](https://doi.org/10.1039/b305041f)
- [21] Leverd, P. C.; Dumazet-Bonnamour, I.; Lamartine, R.; Nierlich, M. *Chem. Commun.* **2000**, 493–494. [doi:10.1039/b000909l](https://doi.org/10.1039/b000909l)
- [22] Delaigue, X.; Gutsche, C. D.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; Stewart, D. F.; White, A. H. *Supramol. Chem.* **2004**, 16, 603–609. [doi:10.1080/10610270412331318827](https://doi.org/10.1080/10610270412331318827)
- [23] Bertino Ghera, B.; Wu, Q.; Leydier, A.; Coleman, A. W. J. *Incl. Phenom. Macro.* **2009**, 64, 367–370. [doi:10.1007/s10847-009-9561-6](https://doi.org/10.1007/s10847-009-9561-6)
- [24] Macerata, E.; Sansone, F.; Baldini, L.; Ugozzoli, F.; Brisach, F.; Haddaoui, J.; Hubscher-Bruder, V.; Arnaud-Neu, F.; Mariani, M.; Ungaro, R.; Casnati, A. *Eur. J. Org. Chem.* **2010**, 2675–2686.
- [25] Karavan, M.; Arnaud-Neu, F.; Hubscher-Bruder, V.; Smirnov, I.; Kalchenko, V. J. *Inclusion Phenom. Macrocyclic Chem.* **2010**, 66, 113–123. [doi:10.1007/s10847-009-9660-4](https://doi.org/10.1007/s10847-009-9660-4)
- [26] Reactor DN225, Grignard type, dual envelope, made by ESTRELLA AG, 4107 Ettingen, Suisse. A detailed technical scheme of the semi-industrial unit is provided in the supporting information.
- [27] Nonius, B. V. COLLECT; Nonius: Delft, The Netherlands, 1997–2001.
- [28] Otwinowski, Z.; Minor, W. “Methods in Enzymology”; Carter, C. W.; Jr., Sweet, R. M., Eds.; Academic Press: New York, **1997**, 276, 307–326.
- [29] Walker N. and Stuart D. *Acta Crystallogr.* **1983**, Sect A, 39, 158–166.
- [30] Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, 32, 115–119. [doi:10.1107/S0021889898007717](https://doi.org/10.1107/S0021889898007717)
- [31] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K. and Watkin, D. J., *J. Appl. Crystallogr.* **2003**, 36, 1487–1489. [doi:10.1107/S0021889803021800](https://doi.org/10.1107/S0021889803021800)
- [32] S-trioxane decomposes in three formaldehydes in the condition reaction.
- [33] The low conversion rate in p-tert-butylcalix [7]arene observed for this trial was probably due to an inefficient stirring.