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A Path To Industrial Production of Calix[8 & 4]arenes

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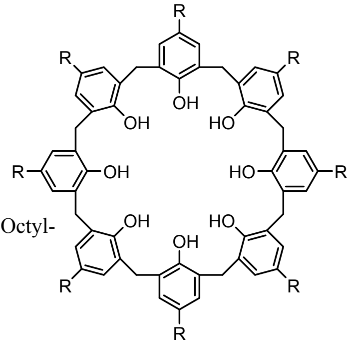
New Synthesis: 80% yield,
Highly Concentrated,
Highly Selective,
Work-up by Simple Filtration

R = *tert*.-Butyl-, *tert*.-Amyl, *tert*.-Octyl-



Abstract:

Highly selective and high yield synthesis for production of calix[8]arenes in concentrated reaction masses is described. Obtained purities are > 98% having yields > 80%, with isolation by simple filtration. The developed approach allows for subsequent 'in-situ' formation of calix[4]arenes. The syntheses are amenable to large scale manufacturing.

Kinetic observations during the formation of calix[4]arenes from calix[8]arenes are included. Furthermore, details related to 'soluble' calix[4]arene are described.

Introduction:

Calixarenes are cyclic condensation products of *para*-substituted alkylphenols with formaldehyde (s. e.g. Schemes 1 and 2). When considering such calixarenes, three procedures for the preparative synthesis of main calixarenes with four, six and eight aromatic ring units in *Organic Synthesis*[1 - 3] may be considered benchmark preparations and are exemplified for the historically most prominent three *tert.*-

butylcalixarene species [4]. The utilized catalysts are sodium hydroxide (for [8 & 4]) respectively, and potassium hydroxide (for [6]). When reviewing the strengths and weaknesses of the calix[8 & 4]arene syntheses, the following should be recognized: *tert*.-butylcalix[8]arene **2b** formation is worked with less than 18% (wght.) *para-tert*.-butylphenol **1b**. While the reaction occurs rapidly, it is not entirely selective and gives about 10% of a mix of [4] and [6]. For a pure **2b**, a recrystallization is desired, which may be a challenge due to its poor solubility with the overall yield being 64%[3]. While other *para*-substituted phenol derivatives are mentioned[4,5], the selectivities or yields are limited.

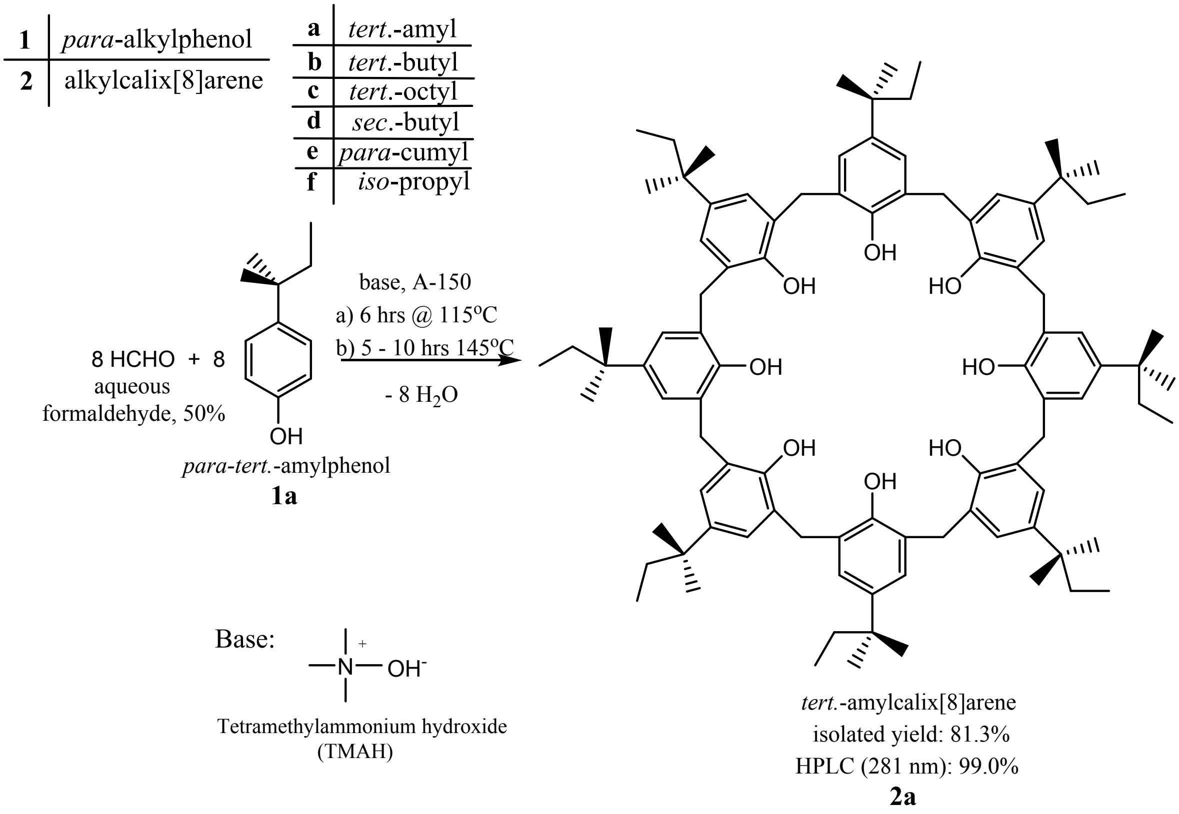
It is *tert*.-butylcalix[4]arene **3b**, which not only includes a detrimental dilution, but also creates a technical challenge for large scale production. When **1b** and aqueous 37% formaldehyde solution are heated without the presence of any solvent and above the boiling point of water, a thick slurry or frothing results which multiplies the loaded volume. Then it is diluted, heated to 260°C (with water still to be eliminated), and finally, the desired product is obtained in a poor space yield but with 61% theoretical yield, prior to re-crystallization. The re-crystallized yield is described at 49%[1].

Nevertheless, with all the technical difficulties which limit **2b** and **3b** production to pilot quantities, these compounds or substituted derivatives, have found their way into published technical applications, where they are added in small quantities. Their special features enhance performance and offer significant value for specific applications. Examples include polymerization accelerators in cyanoacrylate-based super glues[6], and charge control additives in toner resin[7]. A highly substituted calix[4]arene in its 1,3-alternate conformation even presents a solution for significant end-of-lifecycle issues of nuclear power fuels[8].

Results and Discussion:

This note presents a general approach which overcomes the described difficulties for production of calix[8 & 4]arenes. Outlined in Scheme 1 is a calix[8]arene synthesis, starting from *para-tert*.-amylphenol **1a**:

Scheme 1:



Under these reaction conditions, side reactions were minimized, and formaldehyde is given time to react with the alkyphenol. In Scheme 1, tetramethyl ammonium hydroxide (TMAH, 2 mol% in relation to alkylphenol) was found to catalyze the reaction with 50% aqueous formaldehyde, although other formaldehyde sources work as well. The reaction times are longer compared to benchmark cases. When working with aqueous formaldehyde, it is distinguished between a reflux and a distillation phase. The reflux phase can be between 6 to 12 hours and builds mostly linear precursors. It is then taken to 145°C for 5 to 10 hours to remove the water and cyclize to the calix[8]arene with high selectivity. Even following a lengthy reflux phase, free formaldehyde can be detected in the aqueous distillate from this distillation step. While industrial solvent aromatic-150® (A-150) is described in Scheme 1, other solvents work as well. It can be very concentrated as one only needs enough solvent to be able to stir the obtained suspension of the final calix[8]arene. The solvent amount is specific to the alkyl-substituent in the *para*-position for each calix[8]arene example. In the example of Scheme 1 (Example 1 of Table 1) one needed only 90 g A-150 for 123 g **1a**, which equals ~ 58% (wt.) solid content of alkylphenol in solvent. In this example, 115 mol % formaldehyde was used.

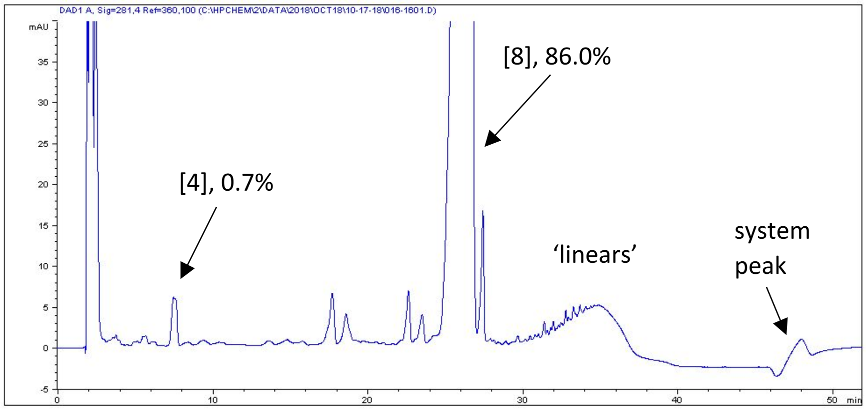
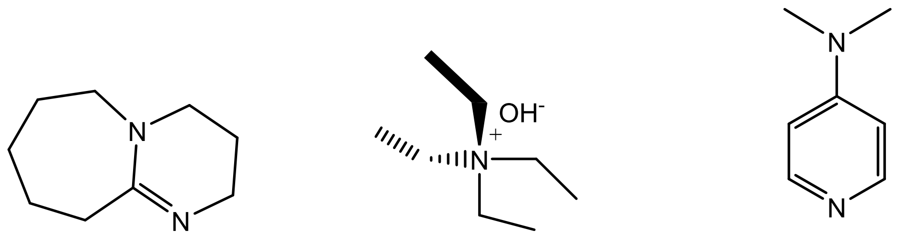


Figure 1: HPLC (281 nm) of Crude [8] Reaction Mass **2a** (Example 1, Table 1)

Figure 1 displays the HPLC (area % detected at 281 nm) of the final crude reaction mass of the reaction in Scheme 1, showing selectivity toward the calix[8]arene over other ring sizes. Work-up is a simple filtration with a subsequent wash with solvent to remove the 'linears', un-reacted alkylphenol and catalyst. By this wash, the unreacted alkylphenol can be brought below 0.1%, which is a critical level for impurity in an industrial context. It was dried and a light powdery product obtained. The yield in this example was above 81% of the theoretical yield, with an HPLC-purity of 99.0%. The HPLC method does not quantify the remaining solvent and unreacted monomer.

Chart 1:



Diazabicyclo[5.4.0]undec-7-ene (DBU)

Tetraethylammonium hydroxide (TEAH)

4-(Dimethylamino)-pyridine (DMAP)

Chart 1 provides additional well working catalyst examples for this synthesis but is not exhaustive. DBU is a cyclic amine and DMAP is an amino-substituted aromatic heterocycle, demonstrating that it must not be an ammonium hydroxide derivative which provides the solution. Different nitrogen-containing bases work to varying degrees and their comprehensive actions are not yet fully understood.

Table 1: Examples for calix[8]arene Syntheses

Example-#	*Phenolic starting compound*	*Aldehyde source / mol % HCHO*	*Solvent*	*Cata-lyst*	*Reflux phase time [hrs]*	*Distillation phase time [hrs]*	*Isolated yield [% of theory] / product*	*HPLC-purity [area% at 281 nm][a]*	*Free phenolic monomer in final product [% (wt.)]*	*Theoretical solid content[b]*	*[8]-compound previously referenced*
1	**1a**	aqueous HCHO, 50% / 114.1	A-150	TMAH	6 (at 115°C)	10	81.3 / **2a**	99.0	0.44	58.2	5a
2	**1a**	aqueous HCHO, 50% / 114.1	Diphenyl-ether / xylene[c]	TMAH	12	10	81.2 / **2a**	98.8	< 0.05	40.6 (including xylene)	
3	**1a**	aqueous HCHO, 50% / 113.9	A-150	DMAP	12	10	79.9 / **2a**	99.0	0.18	44.9	
4	**1b**	aqueous HCHO, 50% / 100.1	A-150	DBU	15.25	6.5	n.d.[d]	(~ 95.5% [8])[e]	-	56.6 (too viscous for filtration)	
5	**1b**	aqueous HCHO, 50% / 114.9	Diphenyl-ether / xylene[c]	TEAH	12.5	10	81.2 / **2b**	98.1	0.07	35.7 (without xylene as it was added for distillation step)	13
6	**1c**	aqueous HCHO, 50% / 114.9	Hexa-decane	TEAH	12	10	79.4 / **2c**	97.0	0.13	47.6	5a
7	**1d**	aqueous HCHO, 50% / 99.9	A-150	TMAH	12	10	66.3 / **2d**	99.2	< 0.05	36.1	
8	**1e**	aqueous HCHO, 37% / 115.5	A-150	TMAH	12	10	61.2 / **2e**	91.0	0.99	47.2	14
9	**1f**	aqueous HCHO, 50% / 115.1	A-150	TMAH	12	10	73.7 / **2f**	98.1	< 0.05	35.1	5a
10	**1a**	paraform, 95% / 105.8	A-150	TMAH	-	10[f]	79.5 / **2a**	98.5	0.18	60.0	

[a] HPLC method does not capture remaining solvent nor residual starting monomer, which are determined by GC

[b] 'Theoretical solid content' is defined as weight-% of starting substituted phenol mass in the mass of the applied solvent (approximately the amount of solvent needed to keep final obtained reaction mass in manageable slurry)

[c] Xylene added as an azeo-carrier for water in the distillation step

[d] Reaction mass too thick to be filtered; a preparative column chromatography showed ~ 80% (wt.) calixarenes in the solids

[e]In the calixarene fraction from preparative column chromatography the [8]arene made 95.5% (area-% HPLC at 281 nm) of all calixarene derivatives

[f]With paraform no 'reflux-phase'

The approach with these catalysts is universal. Table 1 illustrates examples with different *para*-substituted phenols, different solvents, different catalysts, and different sources of formaldehyde. The last five columns display the results. The isolated yields are shown in the eighth column, which are in the ~ 80% range for the major alkylphenols, *tert.*-butyl **1b**, *tert*.-amyl **1a** and *tert*.-octyl **1c**. The ninth column gives purity determined by HPLC analysis at 281 nm of the final, isolated product. The information in the eleventh column is the 'theoretical solid content', defined as the weight-% of starting monomer in the applied amount of solvent only, which still permitted an acceptable stirring of the obtained final product suspension. Therefore, the table shows that e.g. for **1b** (example 5) the obtained suspension of the final reaction mass reaches above ~ 38 weight % of starting monomer in the solvent, already a suspension that is difficult to stir, while e.g. **1c** (example 6) can be managed just below 50% (wt.).

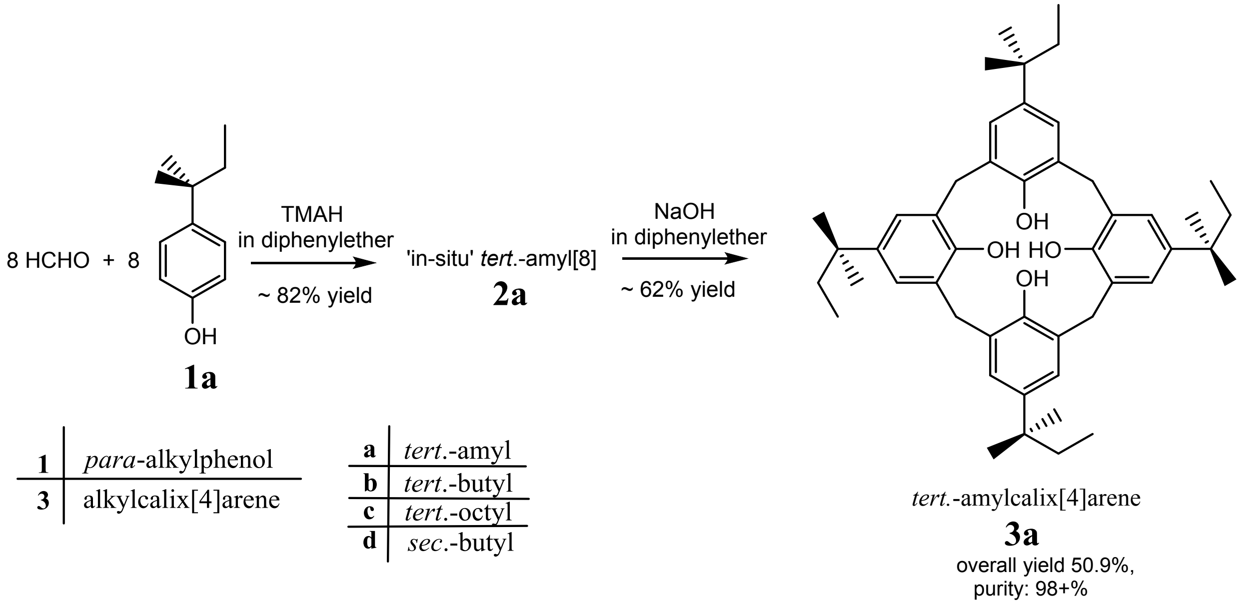
Due to the chiral carbon atom in **1d**, the product **2d** represents a mixture of diastereomers.

Various sources of formaldehyde can be used, for example paraform (Example 10, Table 1). Use of this source precludes a reflux phase.

While the purity of the calixarene products could be brought above 98% (HPLC, 281 nm), this was not true for the *para*-cumyl[8] **2e**, which remained at 91% even after several washes with double the amount of solvent volume. This was not caused by lack of selectivity toward the calix[8]arene, but rather by 'linear' impurities, which are potentially less prone to be removed by the washing solvent, due to the influence of the second aromatic group of the cumyl-phenol moiety. HPLC and ^{1}H-NMR of the isolated product of **2e**[14] are displayed in the supporting information.

Table 1 illustrates two solvents for the calix[8]arene synthesis with a boiling point above 250°C. If one has calix[8]arene in a high concentration, as it is in a thick reaction mass from the described [8]-synthesis, one can obtain calix[4]arene in meaningful space yields following David Gutsche's method, described in 'Pathways for the Reversion of *p-tert*.-Butylcalix[8]arene to *p-tert*.-Butylcalix[4]arene'[9]. One only needs to switch the catalyst and add some sodium hydroxide to the 'in-situ' [8]-reaction mass, and then heat to 250 - 260°C as indicated in Scheme 2.

Scheme 2:



Therefore, the first part of the reaction is the same as described for the production of calix[8]arenes. However, there is no work-up and it is continued 'in-situ' to the next step. It should be noted that at the time the NaOH catalyst is added, and prior to the increased heating to 250 - 260°C, all water from the condensation reactions has been removed, making for a safer heating step, compared to the benchmark approach[1].

Table 2: Examples of calix[4]arene Syntheses

Example-#	*Monomer, type of conversion*	*Solvent*	*Catalyst: 1 step toward 'in-situ' [8] / 2 step for [4]arene*	*Reflux phase, then distillation phase time [hrs]*	*Time at 250 – 260°C [hrs]*	*Isolated yield [% of theory] / product*	*HPLC-purity [area% at 281 nm][a]*	*Theore-tical solid content[b]*	*[4] Compound previously referenced*
1	**1a** -> 'in-situ' [4]	Diphenyl-ether	TMAH / NaOH (10.9 mol%)	Like example 2 table 1[c]	3	50.9 / **3a**	98.1% [4] (1.2% [8])	24.2%	5a
2	**1a** -> 'in-situ' [4]	Diethylene glycol dibutyl ether	TMAH / NaOH (32 mol%)	Like example 2 table 1 but with diethylene glycol dibutyl ether instead of diphenyl-ether[c]	2	45.0 / **3a**	96.0% [4] (3.3% [8])	44.9%	
3	**1b** -> 'in-situ' [4]	Diphenyl-ether	TMAH / NaOH (14.3 mol%)	Like example 5 table 1[c]	3	50.1 / **3b**	98.5% [4]	~ 25%	13
4	**2a** -> **3a**	Diethylene glycol dibutyl ether	NaOH (17 mol%)	not applicable	5	69.6 / **3a**	99.7% [4]	11.2%	
5	**1d** -> 'in-situ' [4]	Diphenyl-ether / xylene	TEAH / NaOH (32 mol%)	Like example 2 table 1 but with **1d** instead of **1a** and 30% more solvent	1	33.4 / **3d**	94.6% [4] (4.7% [8]) – 1. distillation, 2. acetone isolation due to solubility of *sec.*-bu[4] – not yet optimized	33.5%	11
6	**1c** -> [4] 'in-situ'	Hexa-decane	TEAH / NaOH (16 mol%)	as for example 6 in table 1	4	43.2 / **3c**	96.7%	50.7%	5a

[a]HPLC method does not capture remaining solvent nor residual starting monomer; they are determined by GC

[b]'Theoretical solid content' is defined as weight-% of starting monomer mass in the mass of the applied solvent together with the mass of the 'anti-solvent', where applicable

[c]For these early attempts, xylene was not yet added as an azeo-carrier for the water removal in the distillation step for the 'in-situ'-calix[8]arene formation

Table 2 gives an overview of selected examples for the [8] -> [4] ring contraction using 50% aqueous formaldehyde. The amount of sodium hydroxide catalyst ('mol-%') was calculated by assuming that all the starting alkylphenol would become calix[8]arene. The mass of added sodium hydroxide is considered in relation to such hypothetical amount of calix[8]arene, to result in the given mol-% numbers.

For these examples the published procedure from Prof. Gutsche was followed[9], except that it was more concentrated during the 260°C hot phase. Following this reflux phase, after cooling, an 'anti-solvent' (e.g. ethylacetate) was added to exhaustively precipitate the desired calix[4]arenes. The final product was then filtered through a Büchner funnel and washed with anti-solvent. The free phenolic monomer in the final product was below 0.05% (wt.) by GC.

Considering these examples, one can appreciate why it is preferable to work with the *tert*.-amyl variants. Their suspensions can be handled in more concentrated form than e.g. for *tert*.-butyl and one can therefore achieve better space-yields with *tert*.-amylcalix[8 & 4]arenes.

Examining the purity (HPLC, 281 nm) of the [4]arenes indicates that the main impurity is the unconverted calix[8]arene. This purity depends on completion of conversion of [8] but concentration from which [4] is precipitated out of the solution also plays a factor. The more dilute, the remaining calix[8]arene was kept in solution the better and the higher the [4]-purity.

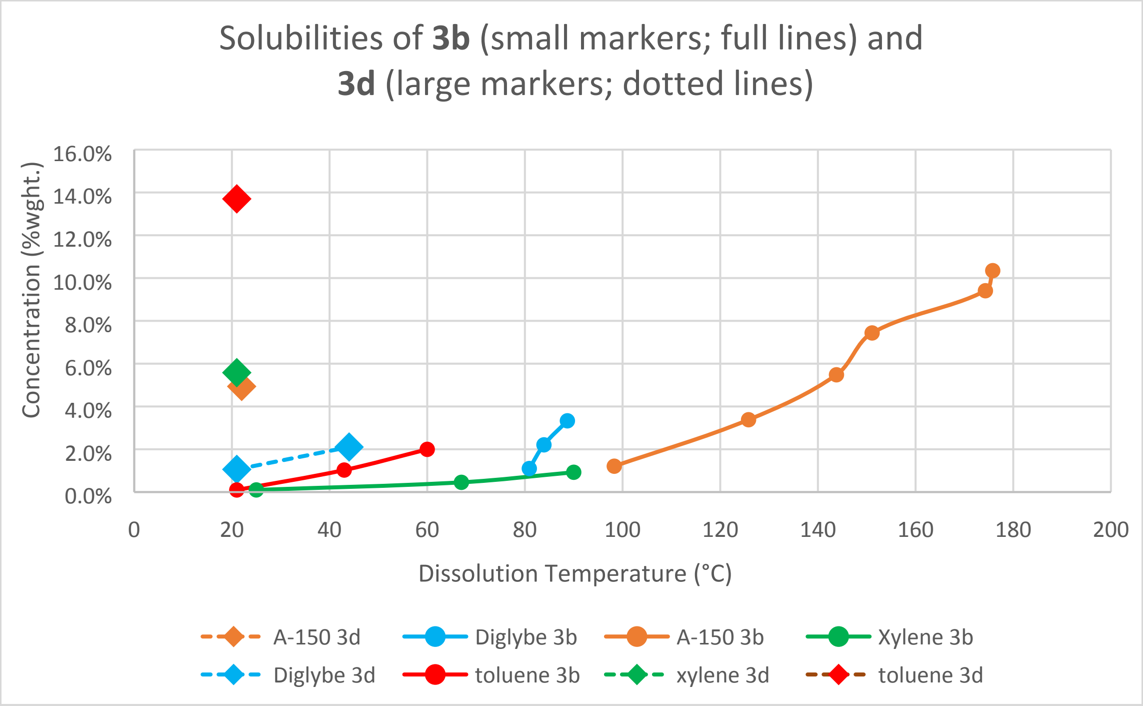
In diethylenglycol dibutyl ether (b.p. 256^{o}C) the isolated yield (Example 2, Table 2) is not as high, because lower amounts of 'in-situ' calix[8]arene are formed in the first reaction step. However, a higher 'space-yield' can be achieved, as no 'anti solvent' is needed to precipitate the calix[4]arene.

The same is true for hexadecane as solvent for 'in-situ' **2c** (Example 6, Table 2). The theoretical solid content in this example is above 50%. Such paraffinic solvents have already been suggested in EP 0447977A1[10].

The isolation of *p-sec*.-butylcalix[4]arene is considered in Example 5, Table 2. Conversion of the 'in-situ' formed **2d** was straightforward, but even with large amounts of 'anti-solvent' the in the HPLC clearly visible **3d** did not precipitate.

Such a compound had an unusual solubility for a butylcalix[4]arene and isolation required a different strategy. The employed solvent, diphenylether, was reduced via vacuum distillation and all by-products were dissolved in acetone from the obtained resin. Then, at room temperature, the remaining solid **3d** (and remaining **2d**) could be filtered off. The **2d** content in the obtained material was reduced by dissolving in hot acetone solution and filtering hot. A product with an HPLC-purity (281 nm) of 98+% quality was achieved (s. Supporting Information).

Graph 1:



Graph 1 illustrates the solubility characteristics of **3d** and compares it to **3b**. While the latter is insoluble at room temperature in toluene, **3d** is soluble with almost 14% (wt.). Some interesting applications of a soluble butylcalix[4]arene scaffold are to be expected. It is recognized that due to the chiral carbon atom in the side chain of the starting monomer, the obtained **3d** is a mixture of diastereomers (s. Supporting Information), which might explain the unusual solubility in contrast with the other calixarene species studied.

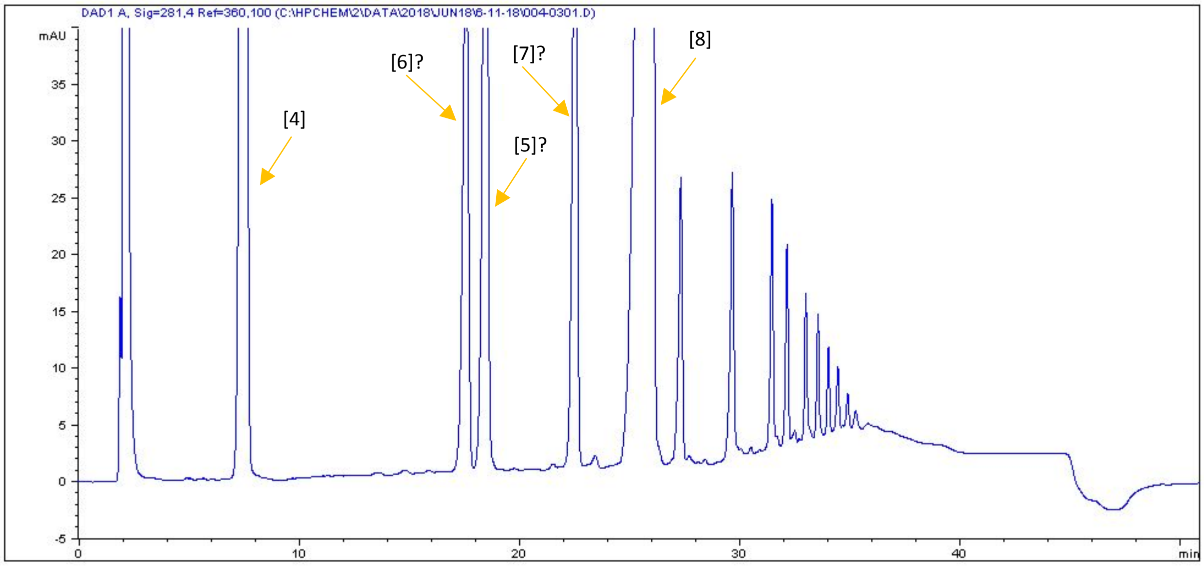


Figure 2: HPLC (at 281 nm) of Crude Reaction Mass for Synthesis of **3a** in DPE at 240°C

Referencing the publication ‘Pathways for the Reversion of *p*-*tert*.-Butylcalix[8]arene to *p*-*tert*.-Butylcalix[4]arene’[9] by David Gutsche, the author described the reaction of a mixture of regular and fully deuterated *p*-*tert*.-butylcalix[8]arene in a 1 : 1 ratio (by weight) and then considered the deuterium-substituted product distribution of the obtained [4]arenes. He wanted to check if ‘Molecular Mitosis’ would occur and split each [8]-molecule in half. It appears that the obtained species were not pure un-deuterated or fully deuterated, but were rather mixtures, indicating an un-symmetrical path to the reaction products.

Figure 2 supports Gutsche’s observation. It shows an HPLC-chromatogram of a *p*-*tert*.-amylcalix[8]arene reaction mass while being heated to 260°C. The figure is a snapshot of when 240°C was reached. In Figure 3, sharp individual signals can be seen. These signals represent different ring-sized calixarenes. Therefore, it appeared that initially all kinds of calixarenes were formed, including larger ones such as [9], [10] or potentially even larger. In the end of the 260°C phase, they fell mostly back to the thermodynamic [4] product.

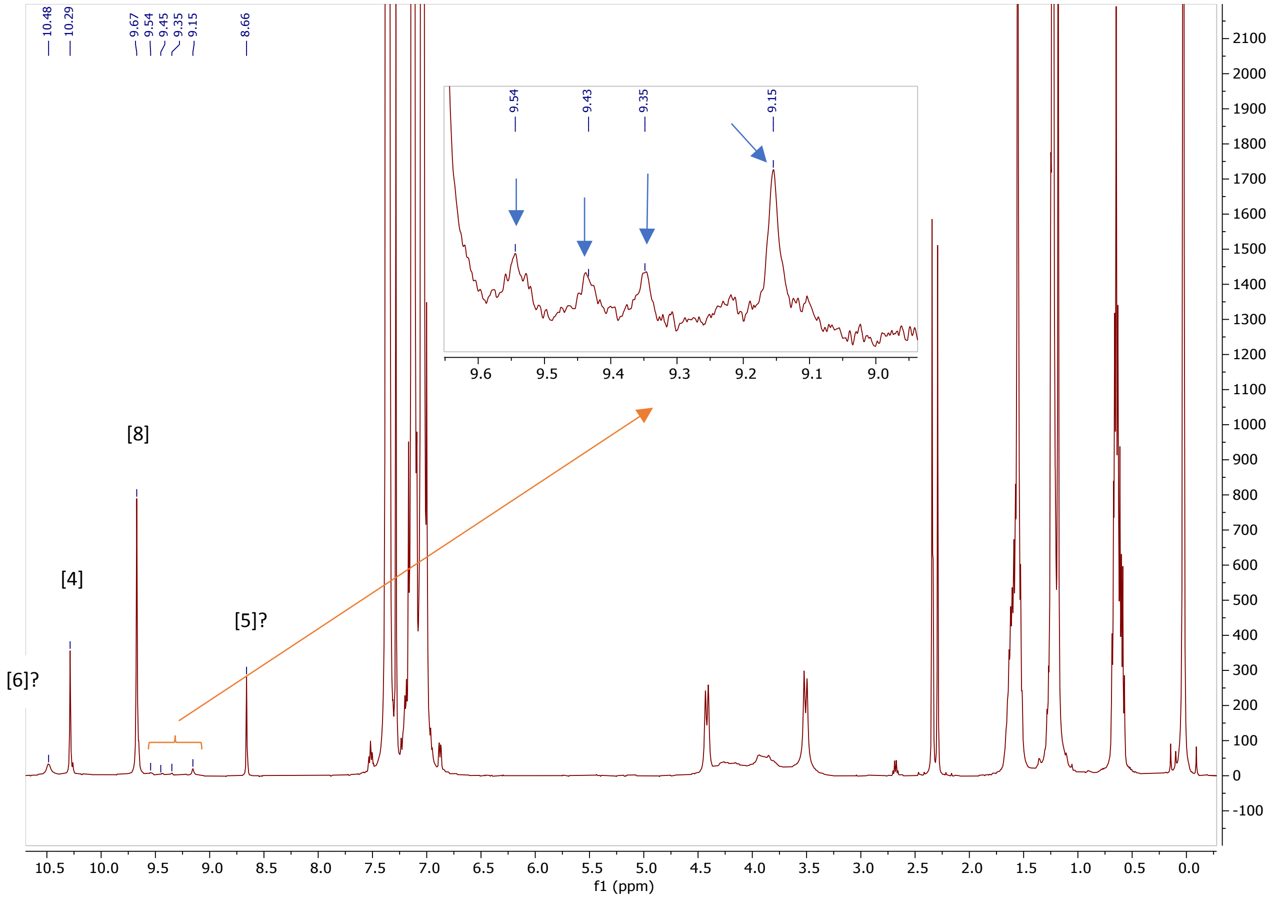


Figure 3: ^{1}H-NMR (500 MHz, CDCl$_3$) of Crude Reaction Mass of **3a** at 240^{o}C

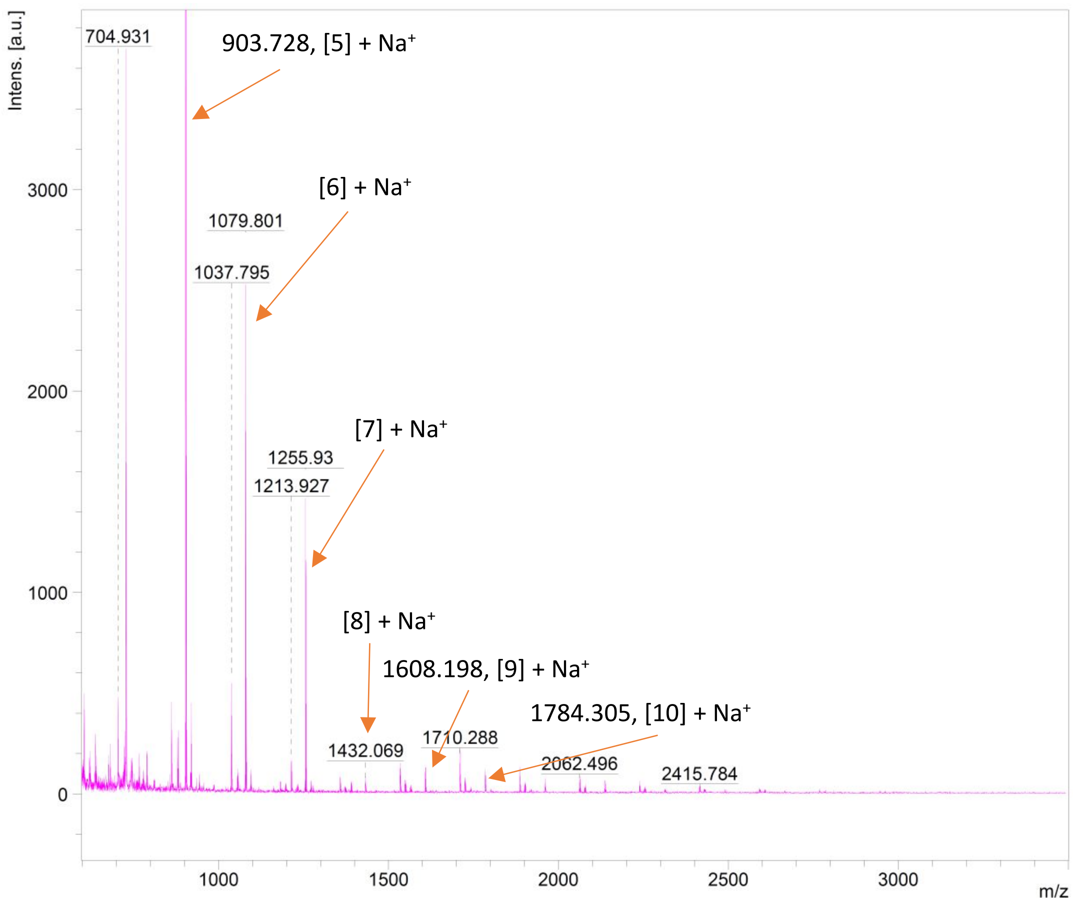


Figure 4: MALDI of Crude Reaction Mass of **3a** at 240ºC

Figure 3 shows the corresponding proton NMR spectrum (in $CDCl_3$) to this HPLC reaction mass, it shows tiny singlets on the right side of the phenolic proton of the *tert*.-amylcalix[8]arene (at 9.65 ppm). While this is the *tert*.-amyl-case, and not all members of the *tert*.-amylcalix[*n*]arene family are yet isolated and characterized, one may still draw an analogy to the *tert*.-butyl-case and compare to the proton-NMR (in $CDCl_3$) of the isolated different ring-sizes Stewart and Gutsche had published in their *JACS* paper from 1999[12]. The [9, 10, 11, …] show the phenolic protons at 20ºC at the locations where they are observed here for the amyl-case.

The MALDI spectrum in Figure 4 supports the assumptions. Since not all *tert*.-amylcalix[*n*]arenes are yet characterized, some assignments in Figures 2 and 3 are indicated with a question mark.

Conclusion:

Based on the presented technology, the production of the calix[8 & 4]-species can be simplified, and previous technical challenges, can be overcome. [8]-arenes can be made highly selective and in high concentrated reaction masses with isolation by simple filtration and no need for re-crystallization. Utilizing the ‘in-situ’ [8]-reaction masses, one can safely proceed to [4]-arene syntheses and obtain [4] in much higher space yields. Therefore, the synthesis of such materials does not need to be limited to pilot scale quantities anymore. Simplified manufacturing processes should also allow for greater availability of desired materials, and eventually the benefits of larger volume of production that provide to ultimate end-users in diverse industries.

Experimental Section:

All chemicals were reagent grade and were used without further purification. The reaction products in above examples were characterized by various methods, including ^{1}H- and ^{13}C{^{1}H}-NMR, GPC, HPLC, and MALDI. In all examples, heating was provided using electric heating mantles controlled by thermocouples and *J*-Kem boxes. Preparative column chromatography for Example 4, Table 1, was performed on silica gel (Aldrich, high purity grade, pore size 60 Ångström, 200 - 400 mesh particle size). Solvent system was plain chloroform for the calixarene fraction (appeared first) and a mixture of acetone : methanol : chloroform (1 : 1 : 1 by volume) to evaluate the linear components.

^{1}H NMR spectra were recorded on a Bruker Avance HD (500 MHz) spectrometer and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.27 ppm). Data are reported as: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br: broad, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a Bruker Avance HD (126 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm).

MALDI mass spectra were obtained on Bruker Autoflex speed MALDI ToF-ToF spectrometer using the thin layer method using 1 µL of a saturated α-Cyano-4-hydroxycinnamic acid (HCCA) acetone solution as the initial layer on a stainless-steel plate and placing 1 µL of a calixarene chloroform solution on top of the dried matrix. Mass spectra were calibrated externally using the peptide calibration standard mixture from Bruker (a mass range between ~1000 and 3500 Da).

GC analysis for calixarene solvent and remaining monomer analysis was done on an Agilent 5890 Series II gas chromatograph with a split injection and FID detection using a standard (5%-Phenyl)-methylpolysiloxane column. When a sample contained both **1a** and diphenyl ether, a DB-1701 column was needed for separation. An external standard method of calculation was used. The analysis was done using tetrahydrofuran solvent.

High-Performance Liquid Chromatography (HPLC) was done on a Hewlett Packard 1100 Series HPLC System using Agilent InfinityLab Poroshell 120 EC-C18 HPLC columns 3.0 x 150 mm, 2.7 µm (Agilent Technologies) and a UV detector set at 281 nm. HPLC grade solvents were used. Samples were dissolved in stabilized chloroform. To obtain a high peak resolution for calixarene compounds with varying ring sizes, particularly from ring size 4 to ring size 8, the following combinations of solvents, gradients, and flow rates were used:

Flow rate: 0.4 ml/minute

Gradient	Time (min)	% C	%D
	0	90	10
	5	90	10
	20	80	20
	30	40	60

35	20	80
40	20	80
42	90	10

C = 99/1 acetonitrile/glacial acetic acid; D=12:9:1 $MeCl_2$:MTBE (methyl *tert*.-butyl ether):glacial acetic acid

para-tert.-Amylcalix[8]arene **2a**:

Example 2 in Table 1:

A 500 ml round bottom flask with overhead stirrer, thermocouple, overhead addition tank, moisture trap (could be switched to allow reflux), and condenser was loaded with 123.2 g (0.25 mol) **1a** briquettes, 90.2 g diphenylether and 10.2 g xylene. A gentle nitrogen breathing was applied to go over the surface of the reaction mass and it was heated to ~ 90^{o}C. When all the **1a** and the DPE/xylene had formed a clear solution, 5.5 g (2.0 mol%) of a 25% solution of tetramethylammonium hydroxide in methanol was added dropwise. Within 25 minutes, a total of 52.2 g (0.855 mol, 114.0 mol%) of aqueous formaldehyde (49.2%) was added.

After the end of the formaldehyde addition, the reaction was kept at 90^{o}C for 1 hour and then heated to reflux (beginning at 96^{o}C) for a total of 12 hours. At the end the reaction, the mass had a temperature of about 100^{o}C. At this point, the reaction mass was diluted with 60.1 g more DPE and 20.1 g more xylene solvent. The purpose of the added xylene was to be able to consistently remove the formed water to avoid potential boil-over episodes, as it was now the goal to finish the polycondensation; and, therefore the reaction temperature slowly raised to 145^{o}C and the water trap switched to remove water. It was kept for 10 hours at 145^{o}C until a total of 34.5 g of lower layer were removed. This aqueous layer contained 6.4% (wght.) formaldehyde. A pot sample showed 1.02% (wt.) remaining **1a**. The reaction was interrupted at night.

It was cooled to 60^{o}C and the reaction mass filtered easily through a Büchner funnel. The filter cake was successively washed with portions of xylene (together 106.2 g) to result after drying in a vacuum oven at 130^{o}C in **2a** with < 0.05% (wt.) free **1a** and 2.78% (wt.) DPE and an HPLC purity of 98.8% (281 nm). The isolated yield was 110.0 g (81.2% of the theory on dry base).

Example 1 in Table 1 (more forceful reflux-phase and more concentrated in a different solvent):

A 500 ml round bottom flask equipped as in the previous example was loaded with 123.2 g (0.75 mol) **1a** briquettes and 88.6 g A-150. A very gentle nitrogen breathing was applied, heated and 5.5 g (2.0 mol%) of a 25% solution of tetramethylammonium hydroxide in methanol added dropwise. At 90^{o}C, within 7 minutes a total of 51.0 g (0.855 mol, 114.1 mol%) of the aqueous formaldehyde solution (50.4%) was added.

After the end of the formaldehyde addition, the reaction was kept at 90^{o}C for one hour. The reaction was set to reflux conditions and forcefully heated, while allowing the distillate to return into the reaction flask. With this strong heating (it took 17 minutes from room temperature to 100^{o}C), the pot temperature could be raised within 60 min from 100 - 108^{o}C. During the next 60 minutes it climbed to even 111^{o}C to reach after 4.5 hours after the start a pot temperature of 115^{o}C. It was then held at 115^{o}C for an additional 1.5 hours. A sample showed 0.52% free formaldehyde and 8.93% unreacted alkylphenol. It was switched to distillation and the reaction mass brought to 145^{o}C and held there for 10 hours, while the water and the excess formaldehyde were distilled out. The final reaction mass showed 86.0% (HPLC, area at 281 nm) **2a** and 1.98% (wt.) **1a**.

In the 38.5 g of aqueous distillate a total of 2.50 g of formaldehyde could be detected.

It was cooled to ~ 60^{o}C and easily filtered through a Büchner funnel. The filter cake was successively washed with A-150 to result after drying (vacuum oven at 130^{o}C) in 108.8 g of **2a** with 0.44% (wt.) free

1a and 1.17% (wt.) A-150 and an HPLC purity of 99.0% (281 nm). The isolated yield was 81.3% (of the theory on dry base).

Example 10 from Table 1 (with paraform as formaldehyde source):

A 500 ml round bottom flask equipped as in the previous example was loaded with 149.8 g (0.91 mol) **1a** briquettes, 99.9 g A-150 and 30.5 g (0.965 mol 'HCHO', 105.8 mol%) paraform (95%). It was slowly stirred and a very gentle nitrogen breathing applied and 6.74 g (2.0 mol%) of a 25% solution of tetramethylammonium hydroxide in methanol added dropwise.

It was warmed and at 83°C the reaction mass cleared up. The temperature was raised within 10 min to 91°C, in further 15 min to 102°C, and then subsequently in 60 more minutes gradually to 145°C. From 120°C, on condensate collected in the Dean-Stark-trap. As the batch got thicker the stirrer speed was increased up to 250 rpm. It was kept for a total of 10 hours at 145°C.

26.8 g of aqueous distillate were obtained. It was cooled to 80°C and the thick reaction mass was transferred with 55.6 g A-150 into a Büchner funnel and rinsed with 45.2 g A-150 to give after drying in a vacuum oven at 130°C 128.2 g **2a** with 98.5% HPLC-purity (281 nm), 0.25% A-150 (wt.) and 0.18% (wt.) **1a** in a yield of 79.5% (of the theory on dry base).

***para-sec*.-Butylcalix[8]arene 2d** (mixture of diastereomers):

2d was prepared as **2a** in Example 1 in Table 1. It was started with 112.7 g (0.75 mol) **1d**. Isolated yield was 80.7 g (66.3% yield) of a white powder of **2d** with < 0.05% (wt.) **1d** and < 0.05% (wt.) A-150. HPLC-purity was 99.2% (281 nm).

^{1}H-NMR (500 MHz, chloroform-*d*): δ = 9.58 (s, 1H), 6.98 (s, 2H), 4.39 (d, *J* = 13.5 Hz, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 2.50 (s, 1H), 1.86 – 1.30 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.77 (t, *J* = 7.3 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ = 146.9, 141.1, 129.0, 127.1, 40.9, 32.1, 31.6, 30.9, 22.4, 21.7, 12.2, 12.1.

MALDI in 'Supporting Information'.

para-tert.-Amylcalix[4]arene **3a**:

Example 1 in Table 2:

For the 'in-situ' **2a** formation it was worked as described as for Example 2 in Table 1 except that here no xylene was yet added. Loads were 122.9 g (0.75 mol) **1a** briquettes, 115.1 g diphenylether, 5.5 g (2.0 mol%) of a 25% solution of tetramethylammonium hydroxide in methanol and 50.8 g (0.846 mol, 113.1 mol%) of the formaldehyde (50%).

After the end of the reflux phase, 86.3 g more diphenylether solvent was added and within 2.5 hours heated to 145°C. Without xylene around, this up-heating had to be carefully monitored while adjusting the nitrogen stream to remove the released water. It took about 2.5 hours to reach 145°C in the pot. After 10 hours at this temperature, the reaction mass was cooled and 0.82 g (0.01 mol) of an aqueous NaOH solution (50%) added and gradually heated to a temperature of 250 - 260°C over the course of 3 hours. Stirring was monitored to avoid caking. The reaction mass became a clear dark liquid. Then it was kept for 3 hours at ~ 260°C and then cooled.

At room temperature, 184.1 g ethylacetate were added, which caused the product to precipitate. It was filtered through a Büchner funnel and washed in three portions with a total of 155.6 g ethylacetate. After extended suction, 69.4 g dry filter cake of **3a** with < 0.05% (wt.) free **1a**, 1.3% (wt.) ethylacetate and 2.1% (wt.) diphenylether in a theoretical yield of 50.9% (of the theory on dry base) was obtained. The HPLC purity (at 281 nm) was 98.0% with 1.2% **2a**.

Example 2 in Table 2 (no 'anti-solvent' necessary):

It was worked as in Example 1 in Table 2 except that the solvent was diethylene glycol dibutyl ether. Because no xylene was added as azeo-carrier, caution was observed when after the end of the reflux-phase, the temperature had to be increased to 145°C. The following amounts were used: initially 123.2 g (0.75 mol) **1a** briquettes in 100.1 g diethylene glycol dibutyl ether with 8.2 g (0.3 mol%) of a 25% solution of tetramethylammonium hydroxide in methanol and a total of 65.8 g (0.975 mol, 130.0 mol%) of the aqueous formaldehyde (44.5%).

Prior to the distillation phase, the reaction mass diluted with 51.2 g more diethylene glycol dibutyl ether. It took about 2.5 hours to go from 100°C to 145°C in the pot. After 10 hours at 145°C, 48.7 g lower layer were removed from the Dean-Stark trap. It contained 22.8% formaldehyde (11.1 g = 0.36975 mol = 37.9% of the starting load of formaldehyde). A reaction mass showed 1.92% (wt.)**1a**.

Then 2.4 g (0.03 mol) of an aqueous NaOH solution (50%) was added and gradually heated over 2 hours to a temperature of 250 - 260°C. Stirring was monitored to avoid caking. It was kept for 2 hours at ~ 250 - 260°C.

It was cooled down, and the obtained suspension was filtered through a Büchner funnel and washed with a total of 100.7 g ethylacetate. After drying under vacuum at 130°C, 59.7 g **3a** was obtained. It had < 0.05% (wt.) free **1a**, < 0.05% (wt.) ethylacetate and 0.31% (wt.) diethylene glycol dibutyl ether. The HPLC purity (at 281 nm) was 96.0% **3a** and 3.3% **2a**. The yield was 45.0% (of the theory on dry base).

Associated Content:

Supporting Information

HPLC, GC (remaining solvent), ^{1}H-, ^{13}C{^{1}H}-NMR and MALDI of compounds **2a** (example 2 in table 1), **3a** (example 1 in table 2), **2d**, **3d**, **2e** and **2f** as well as HPLC and GC (remaining solvent) of compounds **2a** (example 1 in table 1), **2b**, **3b**, **2c** and **3c**. Background for all MALDI in the supporting information.

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