Petra HOFSTADLER, BSc

Conjugable *p*-Sulfonatocalix[4]arene Derivatives

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„Wissen bringt neues Unwissen hervor."

(Terry Pratchett)

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Abstract

This work deals with the preparation of an immobilizable *p*-sulfonatocalix[4]arene derivative. Starting from *p-tert*-butylcalix[4]arene, an *ipso*-substitution in sulfuric acid gave *p*-sulfonatocalix[4]arene which was further treated with 11-bromo-1-undecene to etherify the phenolic oxygen atoms. Hence an amphiphilic molecule was obtained which was used as co-surfactant for stabilizing dicylclopentadiene based emulsions. The immobilization of the *p*-sulfonatocalix[4]arene derivative on the surface of the emulsion templated, macroporous thermosetting material was achieved through curing of the emulsion.

The originally intended reaction for the etherification, an oxa-Michael addition of divinyl sulfone and the phenolic hydroxyl groups, could not be realized. Model studies of this reaction were performed employing divinyl sulfone and phenol. Good conversions were achieved using *tert*-butanol as solvent and 10 mol% potassium-*tert*-butoxide as base. Furthermore, it was shown that more acidic and sterically hindered phenol derivatives gave hardly any conversions in afore mentioned reaction under these reaction conditions.

Kurzfassung

Die vorliegende Arbeit beschäftigt sich mit der Herstellung eines immobilisierbaren *p*-Sulfocalix[4]arenderivates. Ausgehend von *p-tert*-Butylcalix[4]aren wurde durch eine *ipso*-Substitution in Schwefelsäure *p*-Sulfocalix[4]aren erhalten. In weiterer Folge wurden die phenolischen Sauerstoffe mit 11-Bromundec-1-en verethert. Somit wurde ein amphiphiles Molekül geschaffen, das als Co-Tensid zur Stabilisierung von Dizyklopentadien-Emulsionen eingesetzt wurde. Durch Aushärten dieser Emulsionen konnte eine Immobilisierung des *p*-Sulfocalix[4]arenderivates an der Oberfläche des emulsionsabgeformten, makroporösen duroplastischen Werkstoffes erreicht werden.

Die ursprünglich zur Veretherung geplante Reaktion, eine oxa-Michael Addition von Divinylsulfon an die phenolischen Hydroxylgruppen, konnte nicht realisiert werden. Modellstudien dieser Reaktion mit Divinylsulfon und Phenol zeigten, dass diese Reaktion in *tert*-Butanol als Lösungsmittel unter Zusatz von 10 mol% Kalium-*tert*-Butanolat als Base gute Umsätze liefert. Weiters konnte gezeigt werden, dass acide und sterisch gehinderte Phenolderivate unter diesen Reaktionsbedingungen nicht oder nur sehr unzureichend mit Divinylsulfon reagieren.

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1 Introduction

"Supramolecular chemistry is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by association of two or more chemical species."[1]

Supramolecular chemistry is settled at the interface between chemistry, physics and biology and has become a continuously growing scientific field. It plays an important role in life science as well as in material science and is linked with the term "self-assembly".[2] The concept of molecular self-assembling describes the spontaneous organization of molecules into structures or patterns through non-covalent forces. These non-covalent forces encompass hydrogen bonds, π-π interactions, electrostatic forces and van der Waals forces.[2] Quite a lot of self-assembly examples are omnipresent in nature and display sophisticated functions and structures. In 1987 the Nobel Prize was awarded to Donald James Cram, Jean-Marie Lehn and Charles John Pederson "for their development and use of molecules with structure-specific interactions of high selectivity".[3] Since this distinction was established, supramolecular chemistry has gained attention.

Many partitions of science take advantage of supramolecular effects. Interactions between molecules concerning recognition and sensing, *viz.* host-guest-interactions are of high importance. The development of efficient artificial receptors for molecular recognition and sensing enjoys great interest among biological, medical, environmental and chemical scientists.[4] Obviously, artificial receptors provide the possibility to obtain an insight in biological structures and processes and can pave the way for understanding them in detail.[5]

Calixarenes[6] are entitled as the third generation of supramolecules after cyclodextrins and crown ethers.[7] These basket-shaped compounds[8] represent versatile building blocks in

[1] Lehn, J. M.; *Angewandte Chemie International Edition,* **1988**, *27*, 89-112.
[2] Whitesides, G. M.; Grzybowski, B.; *Science*, **2002**, *295*, 2418-2421.
[3] http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/; 03.05.2016.
[4] a) Yilmaz, M.; Erdemir, S.; *Turkish Journal of Chemistry*; **2013**, *23*, 558-585. b) Lo, P. K.; Wong, M. S.; *Sensors*, **2008**, *8*, 5313-5335.
[5] Daze, K. D.; Hof, F.; *Accounts of Chemical Research*, **2013**, *46*, 937-945.
[6] Gutsche, C. D.; *Calixarenes: An Introduction*, The Royal Society of Chemistry, Cambridge, **2008**.
[7] Shinkai, S.; *Tetrahedron*, **1993**, *49*, 8933-8968.
[8] Gutsche, C. D.; Lin, L.-G.; *Tetrahedron*, **1986**, *42*, 1633-1640.

supramolecular chemistry and are outstanding due to their readily modifications.[7] Especially their ability to act as host molecules for a variety of neutral and ionic guest species, even in an efficient and selective way is remarkable.[6,22] The capacity of calixarenes to complex a specific guest species is determined by various structural factors, primarily the type of donor groups and the shape of the cavity.[6,22]

2 General Aspects

2.1 Calixarenes

Calix[n]arenes are macrocyclic oligomers consisting of phenol units linked by methylene bridges. These compounds are assigned to the class of [1_n]metacyclophanes, where *n* is the number of benzene rings.[9] The relevant structures are presented in Figure 1 and Figure 2. The name "Calixarene" was introduced by Gutsche.[10] The most common calixarenes are calix[4]arene, calix[6]arene and calix[8]arene, but a number of phenolic units up to 20 is known.[11]

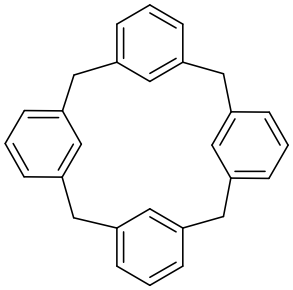

Figure 1. [1_4]Metacyclophane

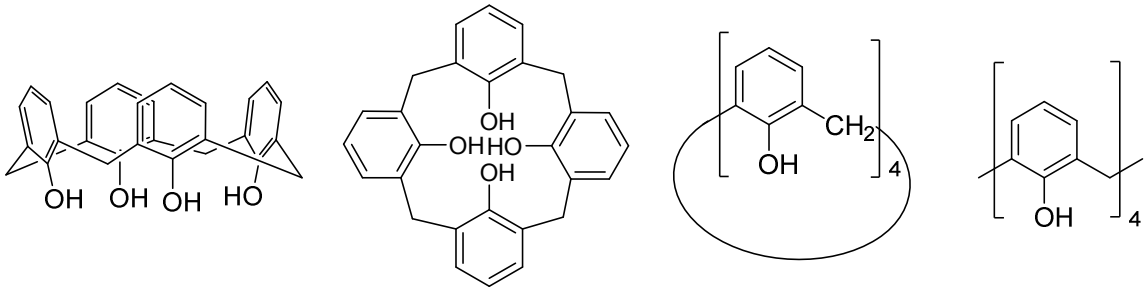

Figure 2. Various presentations of calix[4]arene

2.1.1 Historical Review

The historical origin of calixarenes is dated on the 19th century. Johann Friedrich Wilhelm Adolf von Baeyer pioneered the calixarene chemistry. Following Baeyer´s publications, 1872 can be considered as the first step towards these compounds. He observed the formation of a "kittartige Substanz" due to the mixture of formaldehyde and phenols in the presence of a

[9] Cram, D. J.; Steinberg, H.*; Journal of the American Chemical Society*, **1951**, *73*, 5691-5704.
[10] Gutsche, C. D.; Muthukrisnan, R.; *Journal of Organic Chemistry*, **1978**, *43*, 4905-4906.
[11] Steward, D. R.; Gutsche, C. D.; *Journal of the American Chemical Society*, **1999**, *121*, 4136-4146.

strong acid.[12] However, he did not succeed in the isolation of pure reaction products and therefore could not propose any possible structures. Nevertheless, the birth of phenol-formaldehyde chemistry was due to him.[6]

In 1894, Eugen Leo Lederer and Otto David Manasse studied the base-induced reaction of formaldehyde with phenol independently from each other. They achieved success in the isolation of *o*-(hydroxymethyl)phenol and *p*-(hydroxymethyl)phenol as well-defined crystalline solids.[13,14] Leo Hendrik Baekeland had laid the foundation for modern synthetic plastics. Under controlled conditions and a defined base load a phenoplast known as "Bakelit" was obtained. 1907 he filed for a patent on this process.[15]

In 1942, Alois Zinke and Erich Ziegler utilized *p*-substituted phenols in a condensation reaction with formaldehyde. This consideration was notable since only two reactive *ortho*-positions were remaining and thereby a reduction of cross-linking possibilities was ensured. As a result, they obtained glistening white crystals for which a cyclic tetrameric structure was postulated.[16]

By the 1950s John Warcup Cornforth and his coworkers picked up Zinke´s reaction and carried out studies on the formation as well as the conformation of the reaction products. The crystallographic studies subsequently indicated that the compounds produced by Zinke were clearly cyclic ones.[17,18] B.T Hayes and R.F. Hunter presented the proof of a cyclic tetramer according to a stepwise synthesis employing *p*-cresol and protecting groups chemistry.[19]

The next meaningful ward in calixarene chemistry was accomplished by the so called "Petrolite Procedure". The first one-pot synthesis of cyclic phenol-formaldehyde oligomers was managed and consequently the Petrolite group filed for patents in 1976 – 1977.[20]

The next milestone was placed in 1978 by Carl David Gutsche with the adoption of the name "Calixarene".[10]

In the following year, 1979, Giovanni Andreetti, Rocco Ungaro and Andrea Pochini resolved the first single crystal X-ray diffraction structure of *p-tert*-butylcalix[4]arene, serving as a host for toluene.[21]

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[12] a)Baeyer, A.*; Chemische Berichte*, **1872**, *5*, 25-26. b) Baeyer, A.; *Chemische Berichte*, **1872**, *5*, 280-282. c) Baeyer, A.; *Chemische Berichte*, **1872**, *5*, 1094-1100.
[13] Lederer, L.; *Journal für praktische Chemie*,**1894**, *50*, 223-226.
[14] Manasse, O.; *Chemische Berichte*, **1894**, *27*, 2409-2413.
[15] Baekeland, L. H.; *US Patent (942,699)*, **1908**.
[16] a) Zinke, A.; Ziegler, E.; *Chemische Berichte*, **1941**, *74*, 1729-1736. b) Zinke, A.; Ziegler, E.; *Chemische Berichte*, **1944**, *77,* 264-272.
[17] Cornforth, J. et al.; *British Journal of Pharmacology and Chemotherapy*, **1955**, *10*, 73-86.
[18] Cornforth, J. et al.; *Tetrahedron*, **1973**, *29*, 1659-1667.
[19] Hayes, B. T.; Hunter, R. F.; *Journal of Applied Chemistry*, **158**, *8*, 743-748.
[20] a) Burks, R. S.; Fauke, A. R., Munch, J. H.; *US Patent (4,032,514)*; filed **1976**, issued **1977**. b) Burks, R. S.; Fauke, A. R., Munch, J. H.; *US Patent (4,098,717)*; filed **1977**, issued **1978**. c) Burks, R. S.; Fauke, A. R., Munch, J. H.; *US Patent (4,259,464)*; filed **1976**, issued **1981**.
[21] Andreetti, G. D.; Ungaro, R.; Pochini, A.; *Journal of Chemical Society, Chemical Communications*, **1979**, *22*, 1005-1007.

A new chapter was opened in 1992 as Gutsche developed selective syntheses for calixarenes with a ring size of 4, 6 and 8.[22]

2.1.2 Nomenclature of Calixarenes

Calixarenes are designated to a discrete nomenclature since the IUPAC nomenclature is followed by very complicated names. The word "calixarene" is derived from the Greek word *calix* (chalice, cup) due to molecule´s resemblance with a vase and *arene* refers to the aromatic building block. To accommodate the number of aryl units, a bracketed number is inserted between "calix" and "arene". This gives "calix[*n*]arene", where *n* indicates the number of aryl units. The macrocycle is numbered according to IUPAC and substituents are stated with prefixes according to their position. Figure 3 shows the numbering of the macrocycle presented by the example of calix[4]arene (R = H).[6]

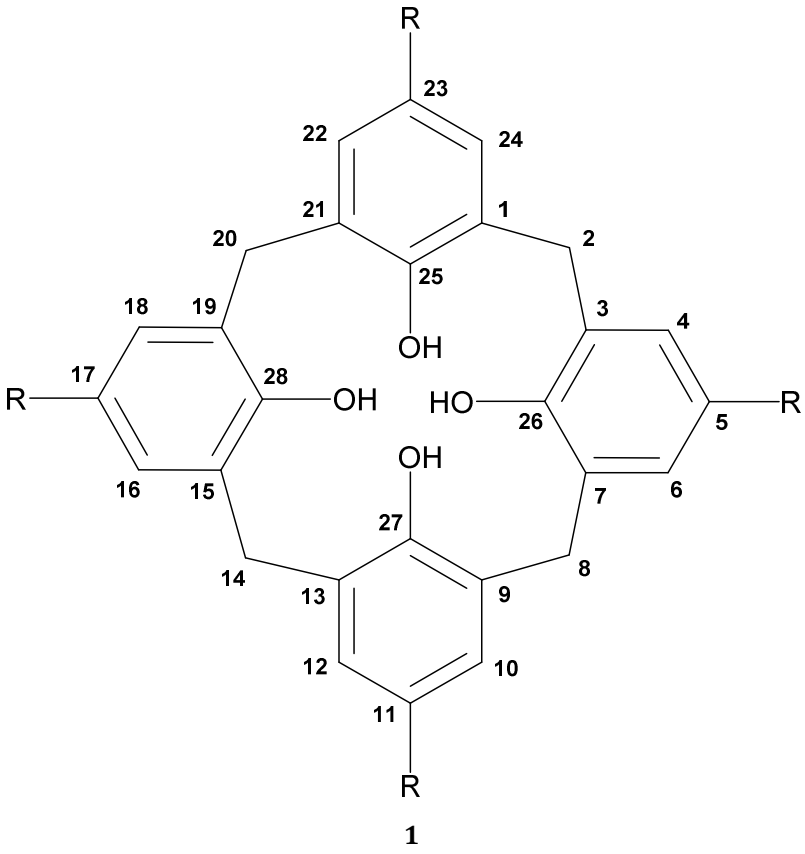


Figure 3. Numbering of calix[4]arene according to IUPAC nomenclature

Serving as an example, compound **1** (with R = *t*-butyl) is denoted as 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene. According to IUPAC nomenclature **1**, becomes 5,11,17,23-tetrakis(1,1-dimethylethyl)-pentacyclo[19.3.1.1^{3,7},1^{9,13},1^{15,19}]-octacosa-

[22] Gutsche, C. D.; *Calixarenes Revisited*, The Royal Society of Chemistry, Cambridge, **1998**.

1,(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol. Frequently, unsubstituted hydroxyl groups and the numbers of the *para*-positions are not explicitly mentioned. Therefore *p-tert*-butylcalix[4]arene is a common simplification for **1**.

Furthermore, the conformation of the calixarene is also taken into account.[6] They are composed of three parts, a wide upper rim, a narrow lower rim and a central annulus (Figure 4).

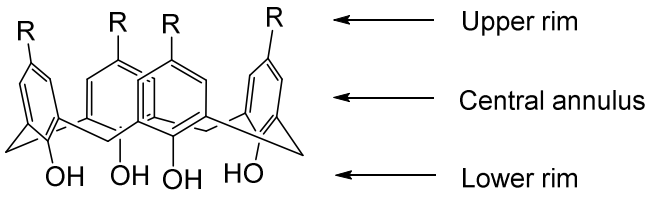


Figure 4. Assignment of the ring parts of calix[4]arene

2.1.3 Conformation of Calix[4]arenes

Calixarenes, which are built up by phenol and methylene units, are conformationally flexible compounds.[23] Cornforth assumed that calix[4]arenes are likely to have four conformations.[17] Depending on the orientation of each aryl group, which can project upwards or downwards relative to an average plane defined by the methyl bridges, the calixarene appears different. Later on, Gutsche designated these conformations as “cone”, “partial cone”, “1,2-alternate” and “1,3-alternate” (Figure 5).[6,23]

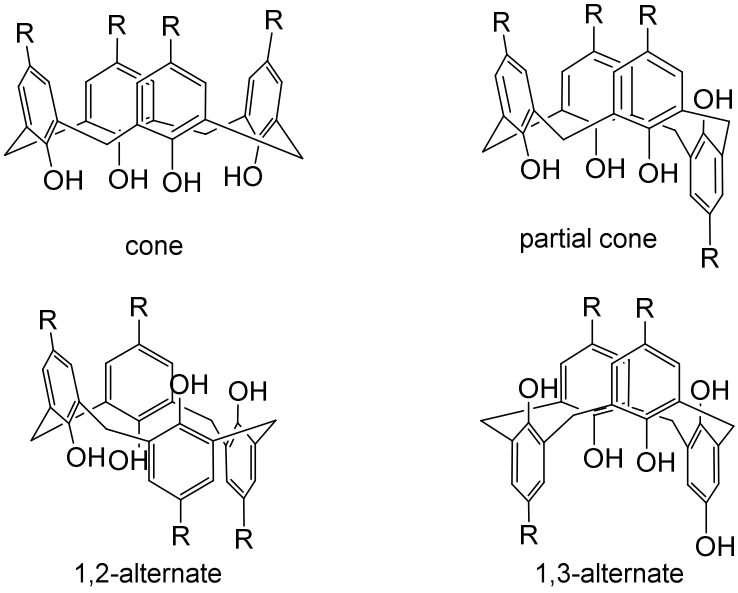


Figure 5. Conformations of calix[4]arenes

[23] Gutsche, C. D. et al.; *Tetrahedron*, **1983**, *39*, 409-426.

These conformations arise from two possible rotational modes of the phenol units: oxygen-through-the-annulus rotation and *para*-substituent-through-the-annulus rotation (Figure 6). The size of the substituent on the lower rim has a significant influence on the conformation.[23]

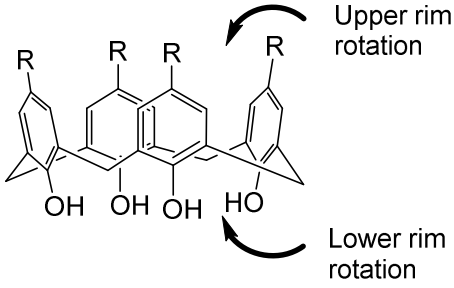


Figure 6. Rotational modes of calix[4]arene

The different conformations can be deduced by means of NMR-spectroscopy. This explanation is based on the consideration of the methylene bridge. The splitting pattern of the methylene protons is obtained by ^{1}H-NMR spectroscopy[23] and the chemical shift of the methylene carbons received by ^{13}C-NMR spectroscopy provides the conformational information.[24] Table 1 summarizes these findings.

Table 1. Conformations of calix[4]arenes, ^{1}H-NMR multiplicity and ^{13}C-NMR shifts of Ar-CH_2-Ar

Conformation	**^{1}H-NMR multiplicity**	**^{13}C-NMR shifts**
Cone	One pair of doublets (J = 12 Hz)	One signal, δ ~ 31 ppm
Partial cone	Two pairs of doublets (J = 12 Hz) (ratio 1 : 1) or one pair of doublets (J = 12 Hz) and one singlet (ratio 1 : 1)	Two signals, δ ~ 31 ppm and δ ~ 37 ppm
1,2-Alternate	One singlet and two doublets (J = 12 Hz) (ratio 1 : 1)	Two signals, δ ~ 31 ppm and δ ~ 37 ppm
1,3-Alternate	One singlet	One signal, δ ~ 37 ppm

It should be noted that, since intramolecular hydrogen bridges of phenolic hydroxyl groups are formed, *cone*-conformation in solution is encouraged. Even in the solid state, calix[4]arenes exist in the *cone*-conformation.

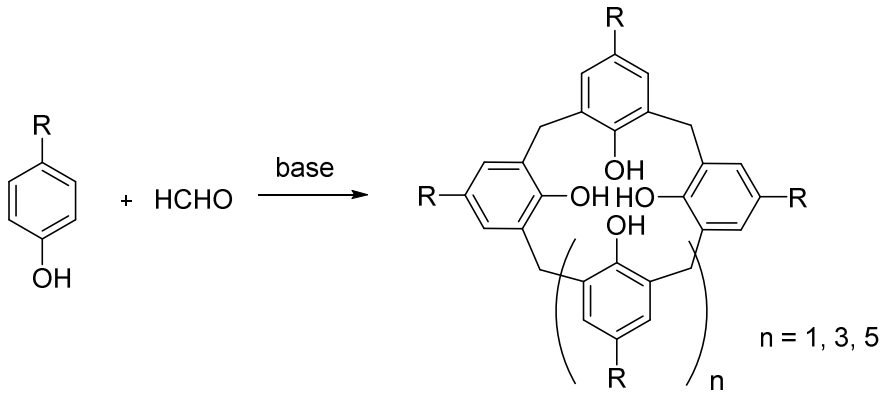
[24] Jaime, C. et al.; *Journal of Organic Chemistry*, **1991**, *56*, 3372-3376.

2.1.4 Synthesis of Calixarenes

Basically, calixarenes are synthesized via two established methods: one-step, base-induced synthesis or multi-step syntheses. The multi-step procedure itself can be further classified into a non-convergent and a convergent stepwise synthesis and represents the method of choice for synthesizing different *para*-substituted calixarenes and larger rings.

2.1.4.1 One-step, Base-Induced Synthesis

Based on Zinke´s and Cornforth´s work as well as Gutsche´s modifications,[25] this procedure offers an appropriate and efficient way for the preparing of "Major Calixarenes" (Scheme 1), even in large scale.[6] Calix[4]arenes, calix[6]arenes and calix[8]arenes can be isolated in 50, 85 and 63 % yields.[26] The yields obtained are influenced by the type and amount of base as well as the temperature applied. However, there are limitations concerning the substituents in *para*-position. Bulky alkyl groups such as *tert*-butyl, *tert*-pentyl and *tert*-octyl are the most appropriate.[6] The "Minor Calixarenes", namely calix[5]arenes and calix[7]arenes, can only be prepared in lower yields.[6] The major drawback of this procedure is that all calixarenes bear the same substituents at the *para*-position.



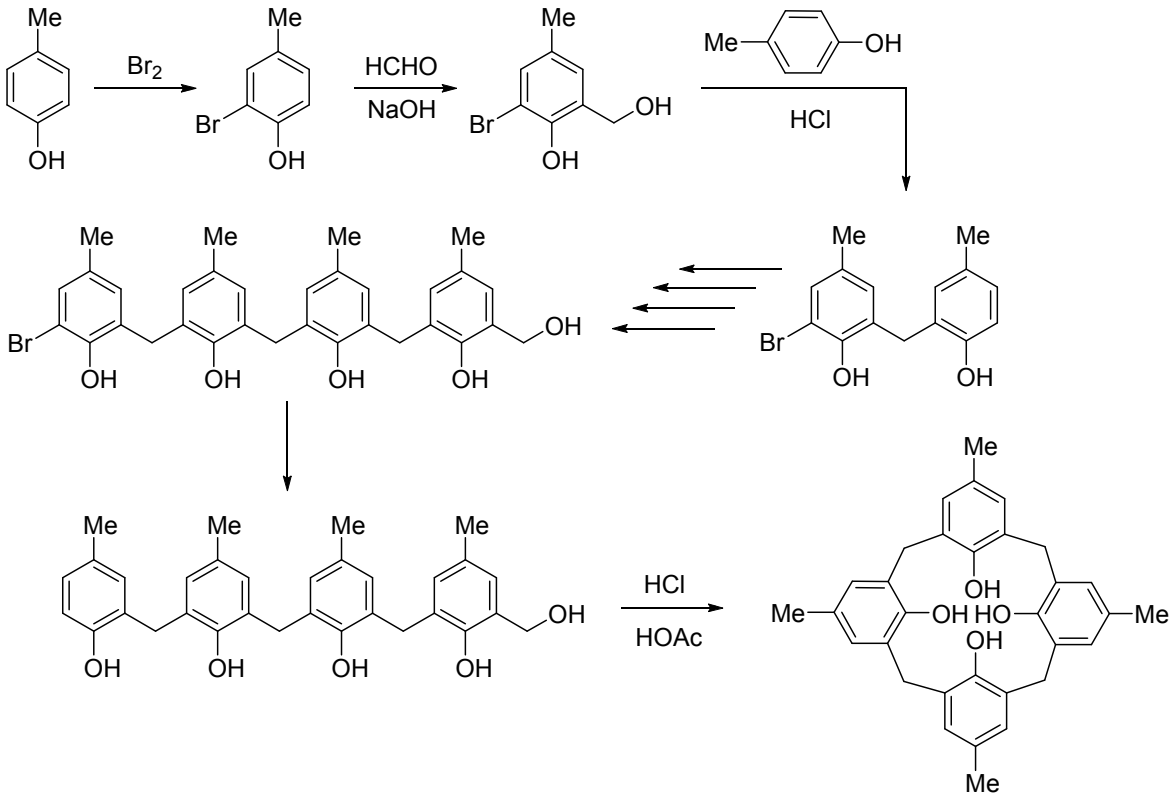
Scheme 1. One-pot, base-induced condensation of *para*-substituted phenol with formaldehyde

On the other hand, the acid-catalyzed condensation reaction leads to linear oligomers as main products.[27]

[25] Gutsche, C. D.; Iqbal, M., Stewart, D.; *Journal of Organic*, **1986**, *51*, 742-745.
[26] a) Gutsche, C. D.; Iqbal, M.; *Organic Syntheses*, **1990**, *68*, 234. b) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D.; *Organic Syntheses*, **1990**, *68*, 238. c) Munsch, J. H., Gutsche, C. D.; *Organic Syntheses*, **1990**, *68*, 243.
[27] Ludwig, L. B., Sr.; Bailie, A. G., Jr.; *Analytical Chemistry*, **1986**, *58*, 2069-2072.

2.1.4.2 Non-Convergent Multi-Step Synthesis

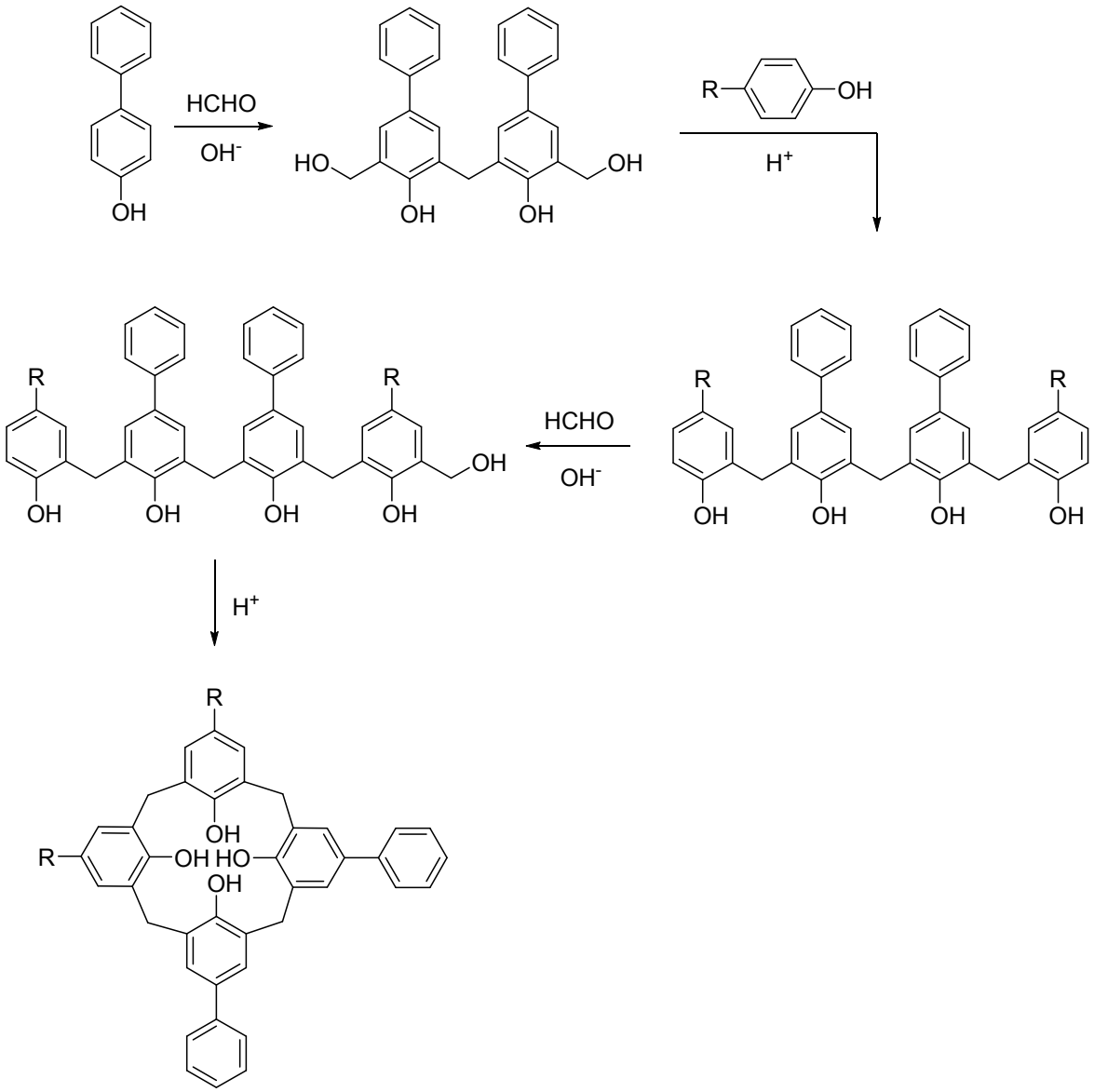
A non-convergent approach is characterized by the synthesis of a linear precursor at first and finally its ring closure reaction to form the product. Hayes and Hunter did the first non-convergent step-wise synthesis. *p*-Methylcalix[4]arene was prepared via a ten-step procedure (Scheme 2).[19] The advantage of the flexibility of this synthesis strategy is offset by low yields and great effort.



Scheme 2. Non-convergent multi-step synthesis of calix[4]arene (Hayes and Hunter methode)

No and Gutsche investigated a four-step synthesis which provides the possibility to obtain calixarenes in moderate yields (Scheme 3).[28]

[28] No, K., H.; Gutsche, C.D.; *Journal of Organic Chemistry*, **1982**, *47*, 2713-2719.



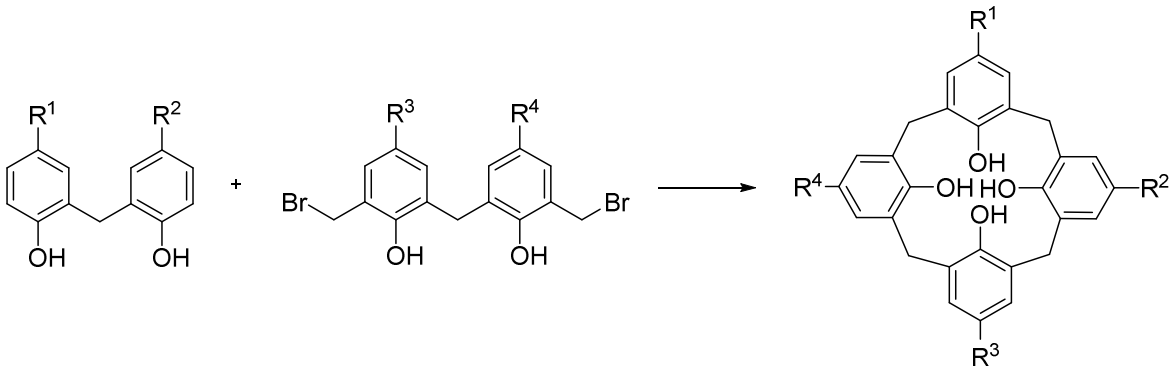
Scheme 3. Convergent multi-step synthesis of calix[4]arene (Gutsche and No methode)

2.1.4.3 Convergent Multi-Step Synthesis

The convergent synthetic route is also referred to as fragment condensation reaction. As the name suggests, appropriate fragments react with one another in a condensation reaction to form the product. Böhmer and coworkers recognized the deficiencies of the non-convergent method, *i.e.* long, tedious synthesis and low overall yields, and developed a convergent pathway with fewer reaction steps. The method is classified as "3+1",[29] "2+2" (Scheme 4),[30]

[29] a) Böhmer, V.; Chhim, Ph.; Kämmerer, H.; *Makromolekulare Chemie*, **1979**, *180*, 2503-2506. b) Böhmer, V.; Marschollek, F.; Zetta, L.; *Journal of Organic Chemistry*, **1987**, *52*, 3200-3205.
[30] Böhmer, V.; Merkel, L.; Kunz, U.; *Journal of the Chemical Society, Chemical Communications,* **1987**, 896-897.

"2+1+1"[31] and "1+1+1+1"[6] condensation. Depending on the precursors for the cyclization reaction, yields from 2 to 32 % can be achieved.[6]



Scheme 4. "2 + 2" convergent stepwise synthesis of calix[4]arene

2.1.5 Modification of Calix[4]arenes

Basically, the calixarene basket can be modified at three locations: at the upper rim, the lower rim and the methylene bridges.[6] By the introduction of functional groups, new macrocycles with improved and extended properties are accessible for new applications. Additionally, the conformational behavior can be controlled through modifications at the rims. While this kind of derivatization leads to an extenstion along the main axis, derivatization of the methylene bridges is followed by horizontal expansion. The latter is mentioned here for the sake of completeness but will not be discussed further.

2.1.5.1 Functionalization at the Lower Rim

Due to the present hydroxyl groups, calixarenes are already functionalized. This offers the possibility to attach other moieties by replacing the proton or even the entire hydroxyl group. Esterification and etherification reactions of the hydroxyl groups are most popular and well-studied. By the appropriate choice of reaction conditions, partially (mono-, 1,2-di and 1,3-di-) or completely (tetra-) substituted products and their conformers can be obtained. There are many factors determining the actual outcome of a specific reaction. More precisely, base, solvent, temperature and *para*-substituents have a significant influence. In combination with subsequent reactions of the incorporated groups, further modifications can be achieved.[6] Even calixarenes bearing different substituents at the lower rim can be prepared. However,

[31] a) Böhmer, V.; Goldmann, H.; Vogt, W.; *Journal of the Chemical Society, Chemical Communications,* **1985**, 667-668. b) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V.; *Journal of the American Chemical Society*, **1988**, *110*, 6811-6817.

this demands the combination of different synthetic strategies including protection group chemistry.

2.1.5.2 Functionalization at the Upper Rim

Although the multi-step synthesis is well adapted to modify the upper rim, it is not suited for large-scale productions.[6] Since *p-tert*-butylcalix[4]arene is easily available via a one-step procedure even in large scale, it is used as starting material for the upper rim derivatization. The *para*-substituent can be easily removed by a reverse Friedel-Crafts reaction and leaves the *para*-position available for attaching new functional groups. Subsequently, numerous modifications become possible such as halogenation,[32] nitration,[33,34,38a] sulfonation,[34] chloromethylation,[35] acylation[36] and formylation.[37] In some cases, the two separate steps can be accomplished in one and the derivatization occurs as an *ispo*-substitution.[38] Interestingly, the selective functionalization at the upper rim is more difficult to perform, but benefits from the more easily implemented selective functionalization at the lower rim.[39]

2.1.6 Amphiphilic Calixarenes

By the introduction of hydrophilic groups at one rim and hydrophobic groups at the other rim, calixarene-based surfactants are easily accessible.[45] Among the various calixarene derivatives, the water-soluble ones occupy an important position. The pioneer work concerning the synthesis of amphiphilic calixarenes was done by Shinkai *et al*. The first example of a water-soluble calixarene was reported in 1984[40] and shortly after, the synthesis of *p*-sulfonatocalix[6]arenes bearing alkyl chains.[41] These compounds were obtained by sulfonation of the parent calix[6]arene with concentrated sulfuric acid, followed by a neutralization step and final alkylation with an alkyl halide in basic media. The synthetic route is outlined in Scheme 5.[42]

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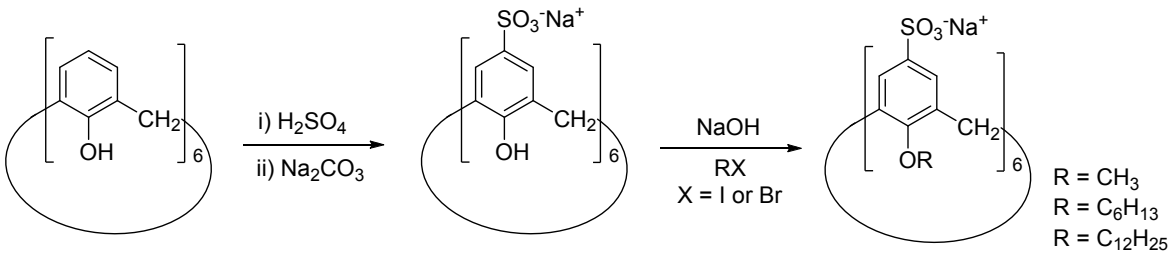
[32] Gutsche, C. D.; Pagoria, P. F.; *Journal of Organic Chemistry*, **1985**, *50*, 5795-5802.
[33] Shinkai, S. et al.; *Tetrahedron Letters*, **1985**, 3343-3344.
[34] Shinkai, S. et al.; *Journal of the Chemical Society, Perkin Transactions 1*, **1987**, 2297-2299.
[35] Almi, M. et al.; *Tetrahedron*, **1989**, *45*, 2177-2182.
[36] Shinkai, S. et al.; *Bulletin of the Chemical Society of Japan*, **1991**, *64*, 381-386.
[37] Ardurini, A. et al.; *Journal of the Chemical Society, Chemical Communications*, **1191**, 936-937.
[38] a) Verboom, W. et al.; *Journal of Organic Chemistry*, **1992**, *57*, 1313-1316. b) Mogck, O. et al.; *Tetrahedron*, **1998**, *54*, 10053-10068 c) Kumar, S.; Chawla, H. M.; Varadarajan, R.; *Indian Journal of Chemistry*, **2003**, *42B*, 2863-2865.
[39] Huang, Z.-T.; Wang, G.-Q.; *Journal of the Chemical Society, Perkin Transactions 1*, **1993**, 167-168.
[40] Shinkai, S. et al.; *Tetrahedron Letters*, **1984**, *25*, 5315-5318.
[41] Shinkai, S. et al.; *Journal of the American Chemical Society*, **1986**, *108*, 2409-2416.
[42] Basilio, N.; Francisco, V.; Garcia-Rio, L.; *International Journal of Molecular Sciences*, **2013**, *14*, 3140-3157.



Scheme 5. Synthesis of alkylated *p*-sulfonatocalix[6]arenes

The aggregation properties are significantly affected by the size of the macrocycle and the length of the alkyl chains. A correlation between the structure and aggregation behavior was recognized and an according classification proposed.[43] Amphiphilic calix[4]arenes exist in the fixed *cone* conformation, whereas the calix[6]arene and calix[8]arene derivatives are conformationally flexible due to rotation through the annulus. The measured critical micelle concentrations provide the basis for the classification into three categories: (i) nonmicellar calixarenes: calixarenes without long alkyl chains (e.g. methyl) do not form micelles; (ii) micelle-forming calixarenes: calixarenes bearing moderate alkyl chain lengths (e.g. hexyl) show self-aggregation into micelles; (iii) unimolecular micelle calixarenes: calixarenes bearing long alkyl chains (e.g. dodecyl) form unimolecular micelles.

Among these surfactants, *p*-sulfonatocalixarenes with attached hydrophobic alkyl chains are defined as "surfactants with a host-guest-type recognition site".[41] By reason of their water-solubility and ability to form inclusion complexes, they are of particular interest for the use as host receptors in supramolecular chemistry.[42] Also biological, pharmaceutical, analytical and crystal-engineering applications are promising due to pre-organized structures and the special binding behaviour.[44]

2.1.7 Applications of Calixarenes

Taking advantage of the easy availability and functionalization possibilites, calixarene derivatives are used in a wide range of applications. The field of implementation depends on the molecule´s properties which are given by the functional groups introduced.[45] Based on this versatility, they gained importance as receptors for biomolecules and in molecular recognition,[46] self-assembly and surfactants[47] just to mention some. At this point, host-guest

[43] Shinkai, S. et al.; *Journal of the Chemical Society, Perkin Transactions 1*, **1989**, 2039-2045.
[44] Guo, D.-S.; Wang, K.; Liu, Y.; *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, **2008**, *62*, 1-21.
[45] Basilio, N.; Garcia-Rio, L.; Martin-Pastor, M.; *Langmuir*, **2012**, *28*, 2404-2414.
[46] Nimse, S. B.; Kim, T.; *Chemical Society Reviews*, **2013**, *42*, 366-386.
[47] Helttunen, K.; Shahgaldian, P.; *New Journal of Chemistry*, **2010**, *34*, 2704-2714.

chemistry, i.e. high affinity and selectivity for the inclusion of neutral, cationic and anionic guests,[45] must be named. Selected examples for the industrial use[48] of calixarenes encompass the recovery of cesium and uranium, lanthanide sequestration, molecular separation and the use as phase transfer agents, catalyst or ion scavengers. Other noteworthy applications deal with the preparation of calixarene-based ionic liquids, the formation of metal nanoparticles as well as the utilization in biological and pharmaceutical fields.[49]

2.2 Michael Addition

1887 could be seen as the year of birth of the Michael addition reaction. Arthur Michael investigated the reaction of stabilized anions with *α,β*-unsaturated moieties systematically and lent his name to this type of reaction.[50] Nowadays, the Michael addition reaction is one of the most versatile and most important synthetic route for C–C bond formation.[51,52] The reaction is characterized by the addition of nucleophiles (Michael donors) to activated *α,β*-unsaturated olefins (Michael acceptors) in the presence of a catalyst.[52] Two ways of activation are possible:[56] (i) using bases for the deprotonation of alcohols to improve their nucleophilicity or the (ii) application of acids to activate the conjugated acceptor.

From a mechanistic point of view, a negatively charged intermediate is the outcome of a nucleophilic attack on the *β*-carbon of the acceptor which finally gives the Michael adduct via protonation.[53] The suitability of an olefin as Michael acceptor is dependent on its *π*-bond polarization. This bond activation is accomplished by adjacent electron-withdrawing substituents.[54]

The efficient coupling of electron deficient olefins with a large spectrum of nucleophiles reflects the reaction´s versatility. Heteroatomic donors involving oxygen, nitrogen, phosphorous and sulfur beside the carbon-based nucleophiles, allow a facile generation of C–O, C–N, C–P, C–S, and other C–X bonds.[55]

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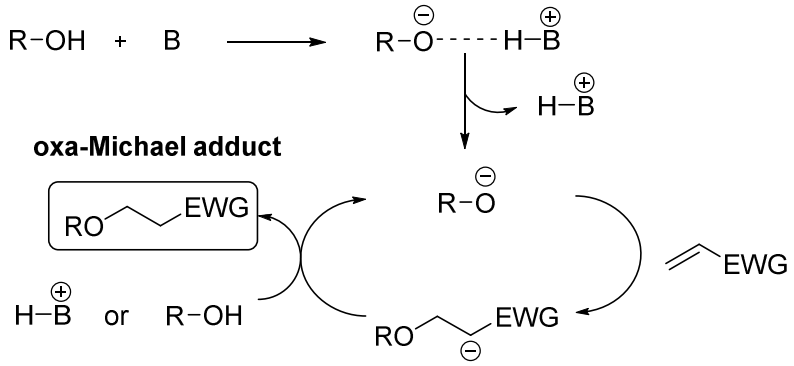
[48] Perrin, R.; Lamartine, R.; Perrin, M.; *Pure and Applied Chemistry*, **1993**, *65*, 1549-1559.
[49] a) Deska, M.; Dondela, B.; Sliwa, W.; *Archive of Organic Chemistry*, **2015**, 393-416. b) Sliwa, W.; Deska, M.; *Archive of Organic Chemistry*, **2011**, 496-551.
[50] Kürti, L.; Czako´, B.; *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, **2005**.
[51] Nising, C. F.; Bräse, S.; *Chemical Society Reviews*, **2012**, *41*, 988-999.
[52] Mather, B. D. et al.; *Progress in Polymer Sience*, **2006**, *31*, 487-531.
[53] Nair, D. P. et al.; *Chemistry of Materials*, **2014**, *26*, 724-744.
[54] Schultz, T. W. et al.; *Chemical Research in Toxicology*, **2007**, *20*, 1359-1363.
[55] Nair, D. et al.*; Chemistry of Materials*, **2014**, *26*, 724-744.

2.2.1 Oxa-Michael Addition

The oxa-Michael addition[51,56] represents the addition of oxygen nucleophiles to conjugated systems, usually base-catalyzed (Scheme 6). This type of reaction provides a series of valuable intermediates, especially for the synthesis of natural products. Despite the high synthetic potential, the oxa-Michael addition has gained less attention in the last years due to a series of drawbacks. The lack of selectivity and reactivity as well as reversibility issues must be listed as detrimental factors. The first example of an oxa-Michael addition was published in 1878 by F. Loydl.[57] He reported the base-catalyzed addition of water to malic acid yielding fumaric acid.



Scheme 6. Base-catalyzed oxa-Michael addition pathway[53,56]

2.2.2 Vinyl Sulfones as Michael Acceptors

Vinyl sulfones[58] (*α,β*-unsaturated sulfones) are common intermediates in organic synthesis. These compounds readily undergo diverse cycloaddition reactions and conjugate additions (Michael addition) and are well suited Michael acceptors due to their electron deficient double bond.

In the particular case, the homobifunctional reagent divinyl sulfone[59] was used as Michael acceptor. Both vinyl groups can participate in the addition reaction to nucleophiles. This feature provides the possibility to form diadducts with the same nucleophile. On the other hand, divinyl sulfone can be employed as linking agent, enabling the crosslinking[60] of polymeric chains for instance.

[56] Nising, C. F.; Bräse, S.; *Chemical Society Reviews*, **2008**, *37*, 1218-1228.
[57] Loydl, F.*; Justus Liebigs Annalen der Chemie*, **1878**, *192*, 80-89.
[58] Lopez-Jaramillo, F. J.; Hernandez-Mateo, F.; Santoyo-Gonzales, F.; *Integrative Proteomics*, **2012**, 301-326.
[59] Sereikaite, J. et al.; *Russian Journal of Bioorganic Chemistry*, **2003**, *29*, 254-257.
[60] Abend, Th.; Stamm, A. O.; Zollinger, Hch.; *Helvetia Chimica Acta*, **1996**, 1391-1400.

2.3 PolyHIPEs

Emulsions are heterogenic systems consisting at least of two immiscible liquids. This means that drops of one liquid (internal or dispersed phase) are dispersed in the continuous (external) phase. The maximum volume fraction of the internal phase for gaining monodisperse, spherical drops is given by the following equation:

$$\frac{\pi}{3 \cdot \sqrt{2}} = 0.7404804 \ldots.$$

74.05 % refers to the hexagonal close-packing arrangement and was first stated by Johann Kepler.[61] Since most emulsions are thermodynamically instable they are stabilized by an emulsifier, usually a surfactant.[62] The liquid with the higher solubility for the surfactant represents the continuous phase and is known as Bancroft´s rule.[63] Brancroft´s rule leaves the question open, which properties of a surfactant dictates its affinity for a particular phase. With the introduction of the hydrophobic-lipophilic balance concept (HLB) by Griffin, surfactants can be quantified according to their hydrophobic and lipophilic degree with a value on a scale from 0 to 20.[64]
Since the majority of emulsions are not formed spontaneously on contact of the phases, these have to be created by other means. Thus, the immiscible liquids are mixed together and are agitated or shaken, mostly with the aid of surfactants. Surfactants facilitate the emulsification or act against the breaking of an emulsion through the formation of a protective film.[62]

High internal phase emulsions (HIPEs) are highly viscous, paste-like emulsions characterized by an internal volume fraction greater than 74.05 %. Thus, the droplets of the internal phase are polydisperse and deformed (polyhedral shape), separated from each other only by a thin film of the external phase. The utilization of surfactants allows a reduction of the interfacial energy and therefore a stabilization of the system.[65]

PolyHIPEs are formed by from the polymerization of the continuous phase of HIPEs. Consequently, polyHIPEs are emulsion-templated polymers, providing an open, highly interconnected porous morphology. The polymerization of the continuous phase around the droplets of the internal phase is followed by solidification of the continuous phase. Then, removal of the internal phase results in a porous replica of the emulsion. The preparation of polyHIPEs can be easily implemented. Therefore, monomer(s) and surfactant are mixed and

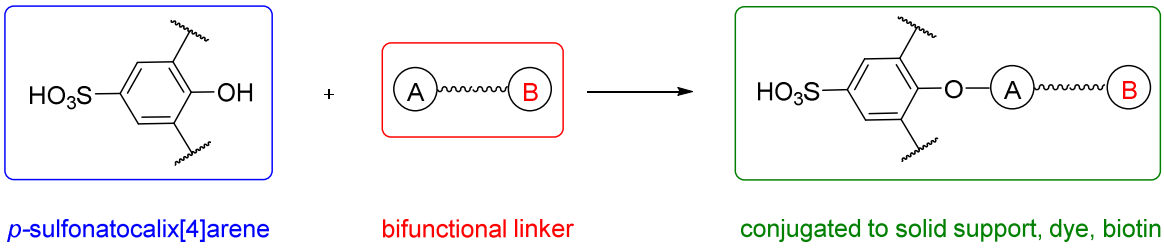
[61] Kepleri, J.; *Strena seu de nive sexangula*, **1611**.
[62] Schramm, L. L.; *Emulsion, foams and suspensions: Fundamentals and applications.* Weinheim, Wiley-VCH, **2005**.
[63] Bancroft, W.D., *Journal of Physical Chemistry*, **1912**, *16*, 177-233.
[64] a) Griffin, W. C.; *Journal of the Society of Cosmetic Chemists*, **1949**, *1*, 311-326. b) Griffin, W. C.; *Journal of the Society of Cosmetic Chemists*, **1954**, *5*, 249-256.
[65] Kovačič, S.; *Acta Chimica Slovenica*, **2013**, *60*, 448-454.

represent the continuous phase. Then the dispersed phase is added slowly and dropwise under constant agitation to the continuous phase. Subsequently, the polymerization of the continuous phase is started by adding the initiator. Usually, the obtained monolith is subjected to Soxhlet extraction for the complete removal of the internal phase. PolyHIPEs are used in several applications encompassing separation media, templates for tissue engineering, electrochemical sensors and solid phase peptide synthesis just to mention some.[66]

2.4 Objective of the Thesis

The main objective of this research work can be defined as the conjunction of *p*-sulfonatocalix[4]arenes with a bifunctional linker (Scheme 7). The special aspect of the linker was to provide the possibility for further conjugation after connection to the *p*-sulfonatocalix[4]arene. More precisely, a reactive terminal site is required to facilitate the further connection to a solid support, dye or biotin.

In particular, it was intended to functionalize calix[4]arenes at the lower rim via oxa-Michael addition. Divinyl sulfone was chosen as Michael acceptor and should serve as linker between the calix[4]arene and an additional functional entity.



Scheme 7. Objective of the thesis

The scope was not only based on the functionalization of calix[4]arenes, but also on the investigation of the base-catalyzed oxa-Michael addition with the aid of a model reaction.

[66] Feuerabendt, F.; Nithitanakul, M.; Pakeyangkoon, P.; *International Journal of Engineering Research and Reviews*, **2014**, *2*, 23-31.

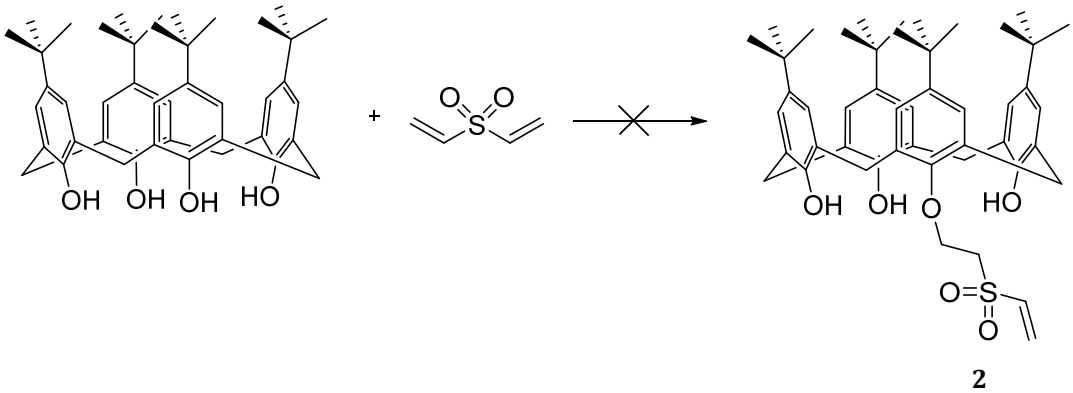
3 Results and Discussion

The amphiphilic calix[4]arenes to be synthesized bear sulfonate groups at the upper rim while the lower rim is modified via *O*-alkylation. The alkyl chains provide an additional reactive group at the terminal end which is available for further conjugation. Subsequently these molecules are incorporated into polyHIPEs via ring opening metathesis polymerization (ROMP).

3.1 Oxa-Michael Addition Attempts with Divinyl Sulfone

The intention was to functionalize calix[4]arenes at the lower rim via oxa-Michael addition. Divinyl sulfone was chosen as Michael acceptor and should serve as linker between the calix[4]arene and additional functional entity. Therefore experiments have been conducted to examine a possible conversion of divinyl sulfone with *p-tert*-butylcalix[4]arene.

Three approaches were pursued, starting with a suspension of *p-tert*-butylcalix[4]arene and divinyl sulfone (DVS) in *tert*-butanol via a base-catalyzed pathway. Differences result from the divinyl sulfone and base load as well as the kind of base used (Table 2). A common finding of these experiments is that the conversion towards the desired Michael adduct **2** does not take place (Scheme 8).



Scheme 8. Unsuccessful oxa-Michael addition of divinyl sulfone to *p-tert*-butylcalix[4]arene

Table 2. DVS and base quantities for the oxa-Michael addition of *p-tert*-butylcalix[4]arene and DVS

Entry	DVS (eq.[a])	Base	Base (total eq.[a])
1	1.44	Cs_2CO_3	2.55
2	7.40	Cs_2CO_3	2.64
3	4.37	Et_3N + Cs_2CO_3	2.07 + 1.01

[a] Equivalents with respect to *p-tert*-butylcalix[4]arene.

In the first experiment (entry 1, Table 2), the first portion of Cs_2CO_3 (1.55 eq.) was added at room temperature to a suspension of *p-tert*-butylcalix[4]arene and divinyl sulfone in *tert*-butanol. The conversion was continuously monitored via TLC. After 60 h reaction time the mixture was heated up to 60 °C and a change of colour from white to beige was observed. A further portion of Cs_2CO_3 (1.09 eq.) was added and the heating was removed after 63 h. Although divinyl sulfone was consumed during the reaction time, no conversion of *p-tert*-butylcalix[4]arene was detected. The reaction mixture was worked up and further investigated via TLC and ^{1}H-NMR spectroscopy. Instead of the desired product **2**, educt *p-tert*-butylcalix[4]arene and divinyl sulfone adducts with water were detected.

Based on these results, a second experiment (entry 2, Table 2) was carried out using higher amounts of divinyl sulfone and base under the same reaction conditions. Unfortunately, the same result as in experiment 1 was obtained. Thus, it can be assumed that the first hydroxyl group of *p-tert*-butylcalix[4]arene is far too acidic for the Cs_2CO_3 mediated oxa-Michael addition of divinyl sulfone.

Consequently, a base combination of triethylamine and cesium carbonate was used for experiment 3 (entry 3, Table 2). The desired interaction of triethylamine with the one hydroxyl group should enable Cs_2CO_3 attacking the second (less acidic) hydroxyl group resulting in an addition to divinyl sulfone. The reaction was carried out at room temperature for 69 h. A mixture of the starting materials, but no conversion was detected via TLC and ^{1}H-NMR spectroscopy after work up.

It is a well-known fact that calixarenes are stronger acids than their monomeric phenolic counterparts. However, an exact measurement of the pK_a values was stated to be difficult. Roughly summarized from literature, the values increase from pK_1 ~ 2, pK_2 ~ 10, pK_3 ~ 12 to pK_4 > 14. Consequently the first dissociation takes place quite easily. The reason for this is given by the stabilization of the monoanion relative to the parent species (dashed lines in Figure 7).[6]

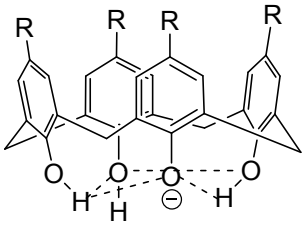
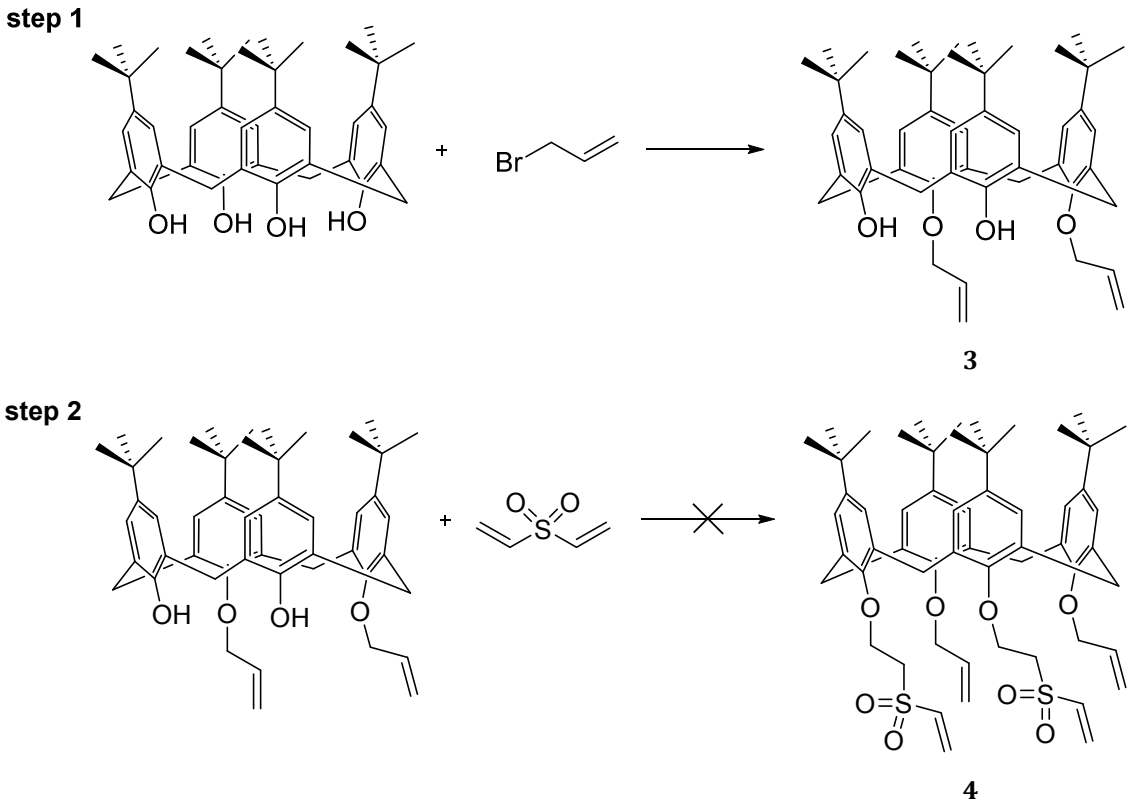


Figure 7. Stabilization of the calix[4]arene anion

In consideration of the previous results, a further approach encompassing two synthetic steps was pursued. The first step was needed for the *O*-alkylation of two *p-tert*-butylcalix[4]arene hydroxyl groups, yielding to residual hydroxyl groups with higher pK_a values suitable for the oxa-Michael addition of divinyl sulfone in the second step (Scheme 9).



Scheme 9. *O*-Alkylation of *p-tert*-butylcalix[4]arene followed by attempted oxa-Michael addition of divinyl sulfone

O-Alkylation was carried out based on the conditions described by Yang,[67] but with some changes according to the task. The synthesis of the dialkylated *p-tert*-butylcalix[4]arene **3** was performed satisfactorily and the desired product was detected via ^{1}H-NMR spectroscopy. For the second step, a suspension of **3** and divinyl sulfone in *tert*-butanol was mixed with

[67] Yang, Y.; Swager, T. M.; *Macromolecules*, **2007**, *40*, 7437-7440.

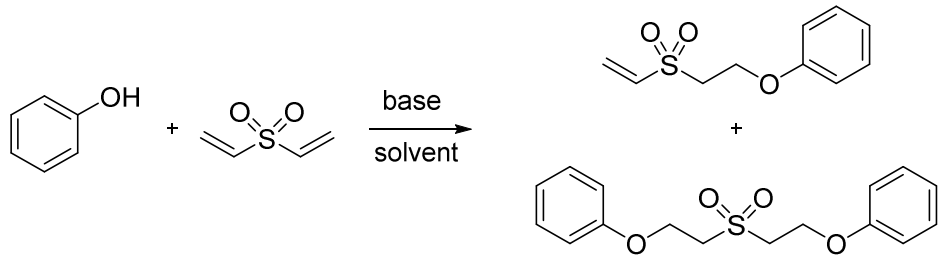
Cs_2CO_3. The resulting suspension was heated up to 30 °C in order to avoid solidification and the conversion was monitored via TLC over 75 h. A mixture of potential divinyl sulfone by-products, but no desired product **4** was detected via TLC and ^{1}H-NMR spectroscopy.

In conclusion, it can be stated that neither variations in divinyl sulfone load, base load and the kind of base, nor increasing the reaction temperature showed an apparently positive impact on the oxa-Michael addition of *p-tert*-butylcalix[4]arene. The previous alkylation exerted no significant influence as well.

As a consequence of these findings, further investigations have been made dealing with a model reaction (section 3.2).

3.2 Model Reaction

As already stated in section 3.1, the targeted oxa-Michael addition of divinyl sulfone and *p-tert*-butylcalix[4]arene was not feasible. Therefore the conversion of phenol with divinyl sulfone was chosen as model reaction, generally depicted in Scheme 10. This set up should help finding appropriate reaction conditions and improve the understanding of the reaction behavior. The reaction was carried out in various solvents, catalyzed by different bases and different loadings. With optimized reaction conditions in hand, the scope was extended to other substrates.



Scheme 10. Oxa-Michael addition of phenol to divinyl sulfone in the presence of a base, yielding mono- and diaddition products

The reactions were performed at room temperature with a divinyl sulfone concentration of 0.55 mol·L^{-1} and 3 eq. phenol (with respect to divinyl sulfone), if not stated otherwise. After defined periods of time, an aliquot part of the reaction mixture was taken, worked up and investigated via ^{1}H-NMR spectroscopy. Quantitative evaluation of the obtained spectra gave the ratio of residual divinyl sulfone, mono- and diadduct and the estimated amount of formed

by-product. An exemplary ^{1}H-NMR spectrum is shown in Figure 8, where the essential regions for divinyl sulfone, mono- and diadduct as well as by-products are highlighted.

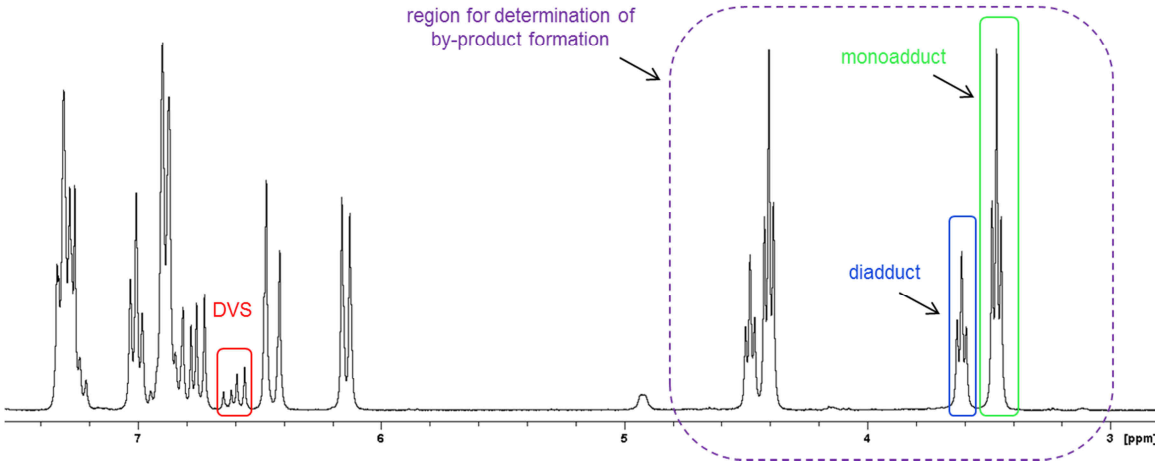


Figure 8. Exemplary ^{1}H-NMR spectrum of the raw product of an oxa-Michael addition of phenol to divinyl sulfone

The ratio was calculated from the integrals of CH and CH_2 groups next to the sulfone. The amount of formed by-product formation was estimated by considering the signals in the range of 3 – 4.8 ppm and setting their integral ratio to (mono+di)adduct.

3.2.1 Establishment of Optimized Reaction Conditions

3.2.1.1 Solvent Effect on the Addition of Phenol to Divinyl Sulfone

At the beginning, the solvent effect on the oxa-Michael addition was evaluated. The detailed results are summarized in Table 12. This series of experiments was carried out using 1 eq. base (with respect to DVS). Figure 9 illustrates the distribution of divinyl sulfone, monoadduct and diadduct after 24 h reaction time in the different solvents.

The best result concerning the conversion towards the diaddition product was obtained using *tert*-butanol (entry 1, Table 12). 83 % diadduct and < 0.1 % residual divinyl sulfone were observed after 24 h, whereas tetrahydrofuran (entry 3, Table 12) gave only 26.5 % diadduct. Using methanol (entry 4, Table 12), no quantitative statement regarding the formation of the phenol-adduct was possible. Instead, the formation of a mixed methanol-phenol-adduct was assumed. Interestingly, despite the 19-fold excess of methanol, phenol reacts faster. If both alcohols would show an equal reaction behavior, the distribution of the phenol or methanol

diadduct respectively, would correlate to 1/19. Actually, after 2 h a ratio of roughly 1/2 and after 24 h, of 1/3.5 was determined.

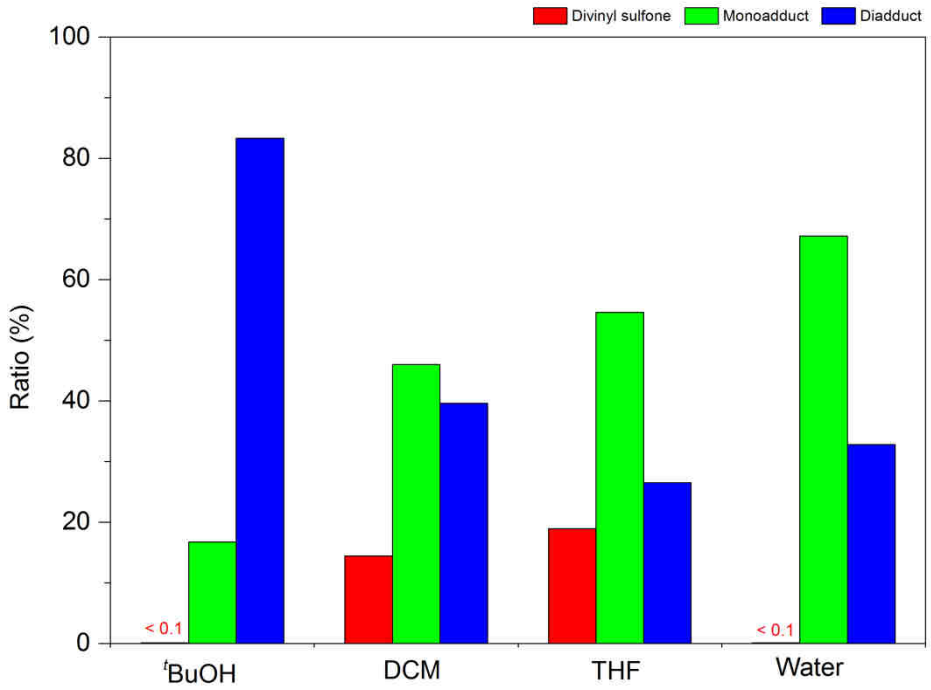


Figure 9. Ratio of divinyl sulfone, monoadduct and diadduct after 24 h in different solvents

3.2.1.2 Infrared Experiments

In order to get a deeper insight why *tert*-butanol is a suitable solvent for the model reaction, infrared experiments were carried out. Ying *et al.* found that the stretching frequency of the carbonyl absorption in acrylamide is shifted to lower wave numbers in case of an acrylamide-ionic liquid mixture as a result of hydrogen bond formation.[68] Based on these findings, a set of divinyl sulfone - solvent mixtures was examined spectroscopically. Table 3 provides the corresponding measured wave numbers of the ATR-IR experiments.

[68] Ying, A. *et al.*; *Journal of Organic Chemistry*, **2014**, *79*, 6510-6516.

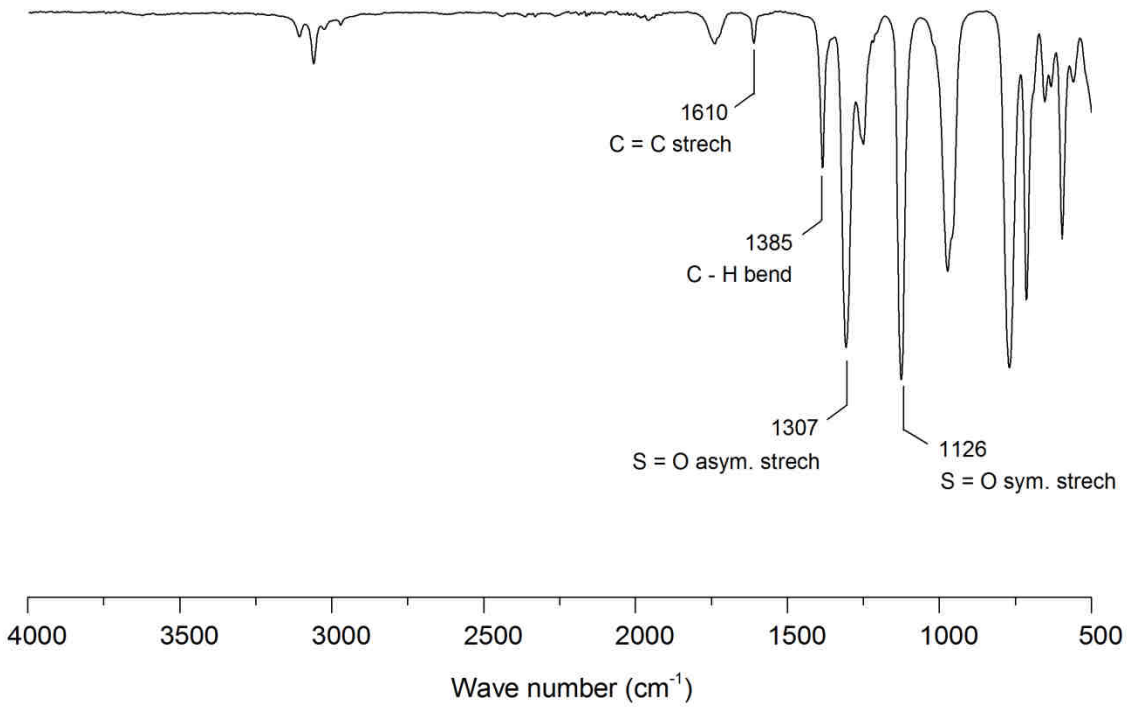


Figure 10. Infrared spectrum of divinyl sulfone and assigned bands

The sulfonyl stretching vibrations (Figure 10) are of particular interest due to considered hydrogen bonds coming from the solvent. Hence, a weakening of sulfonyl stretching vibrations and thus a shift towards lower wave numbers was expected. It is assumed that, weakening of mentioned vibrations contribute to the activation of the molecule for oxa-Michael addition.

It is found that water, methanol and *tert*-butanol affect the infrared absorption of sulfonyl group. These alterations could only be detected in mixtures with a 10-fold molar excess of solvent (entry 3, 7 and 9, Table 3). Contrary to the expectations, shifts to higher wave number are observed. However, there is evidence of a trend towards increasing molecule size (water < methanol < *tert*-butanol) and increasing impact on vibrational shift. A comparison of divinyl sulfone and divinyl sulfone – *tert*-butanol mixture is shown in Figure 11.

Phenol and tetrahydrofuran give no shifts concerning sulfonyl vibrations, even not in excess (entry 9 and 11, Table 3).

Table 3. Wave numbers of sulfone strechting vibrations in DVS – solvent mixtures

Entry	Solvent	Mixture (n/n)	Stretch asym. (cm^{-1})	Stretch sym. (cm^{-1})
1	DVS	pure	1307	1126
2	H_2O	1 : 1	1305	1125
3		1 : 10	1305	1125
4	MeOH	1 : 1	1307	1127
5		1 : 10	1314	1131
6	^{t}BuOH	1 : 1	1307	1126
7		1 : 10	1317	1134
8	Phenol	1 : 1	1306	1123
9		1 : 3	1305	1123
10	THF	1 : 1	1308	1126
11		1 : 10	1310	1128

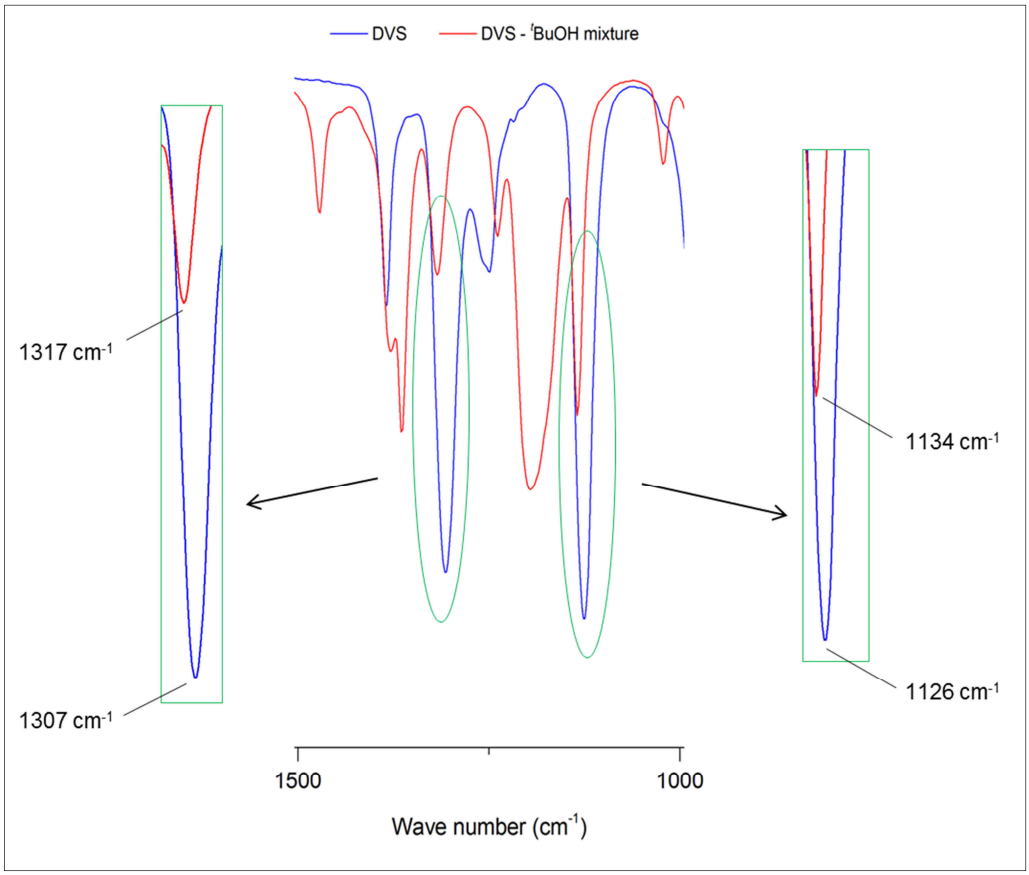


Figure 11. Comparison of infrared spectra (DVS and DVS – ^{t}BuOH mixture)

3.2.1.3 Base Effect on the Addition of Phenol to Divinyl Sulfone

The next step was to investigate the catalytic activity of different bases, when using 1 eq. base (with respect to DVS). The detailed results are summarized in Table 13 and the diadduct formation over time is presented in Figure 12.

All examined bases lead to good results (> 83 % diadduct) after 24 h reaction time. The best performance concerning the conversion to the diaddition product is observed using potassium carbonate (entry 2, Table 13) giving 96.5 %. Potassium carbonate leads to a slow conversion but almost no by-product formation was observed. Cesium carbonate (entry 1, Table 13) enables a fast conversion (85.1 % diadduct even after 2 h) and also less by-product formation. Interestingly, the amount of diadduct reached a maximum after 2 h and tends to decline thereafter at the expense of monoadduct formation. A fast and constant diadduct formation is achieved using potassium-*tert*-butoxide (entry 3, Table 13). However, the by-product ratio is higher.

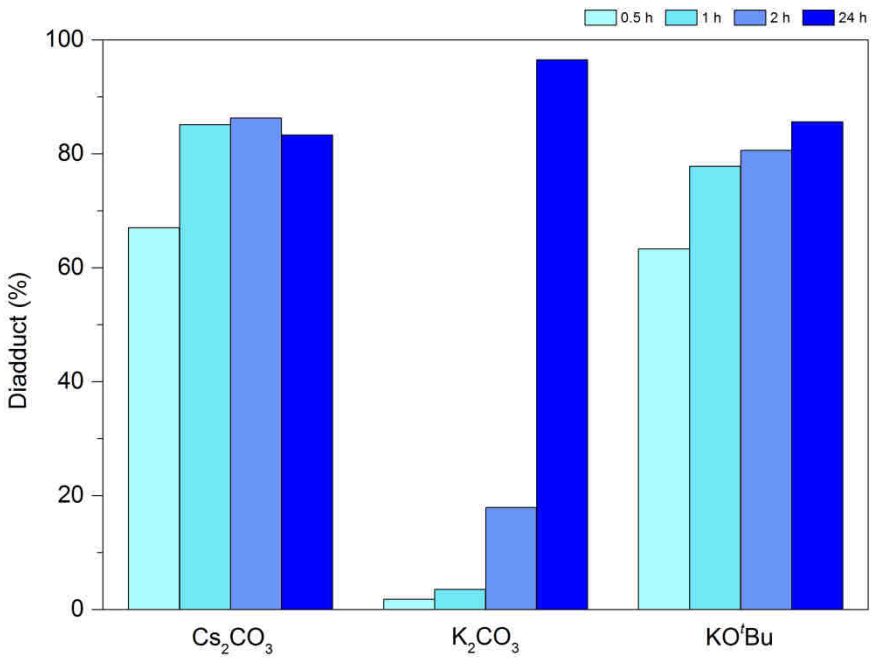


Figure 12. Formation of diadduct over time, catalyzed by different bases

Summing up the above, potassium-*tert*-butoxide is a well suited base for the oxa-Michael addition of phenol with divinyl sulfone.

3.2.1.4 Base Load Effect on the Addition of Phenol to Divinyl Sulfone

The impact of diverse base loads, employing cesium carbonate and potassium-*tert*-butoxide, was determined. A detailed list of results can be taken from Table 14 and an exemplary presentation is shown in Figure 13.

Noteworthy, the amount of base greatly affects the conversion of phenol and divinyl sulfone. In the presence of 10 mol% base, the yield of desired diadduct stays beyond that of 100 mol% within 2 h. However, after 24 h an exceeding quantity of diadduct compared to 100 mol% base is detected. Reworded, a reduction of base load is possible, but on expense of a prolonged reaction time.

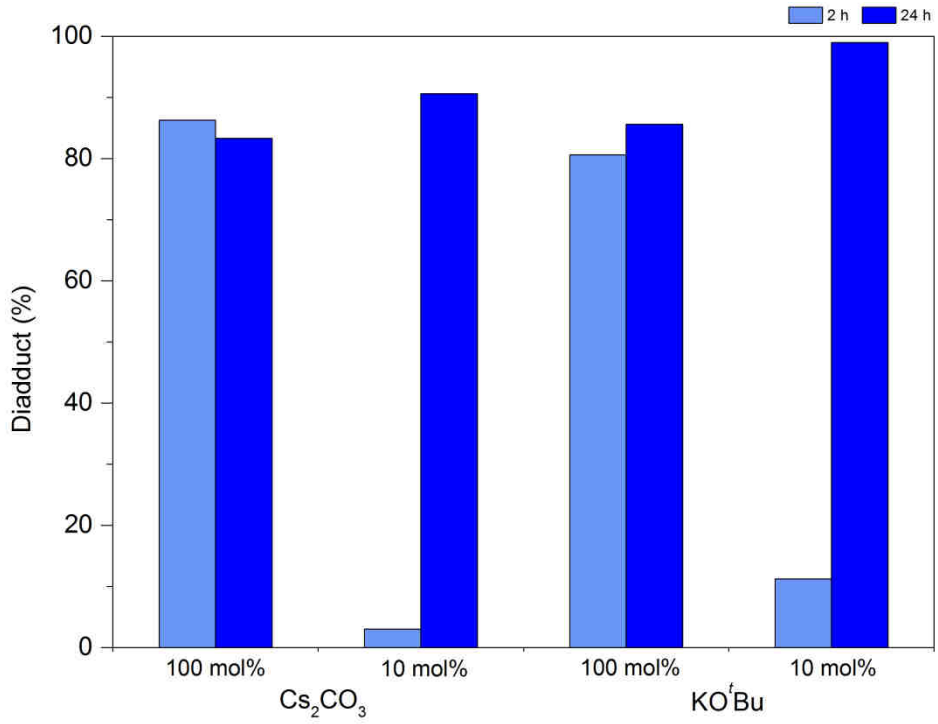


Figure 13. Formation of diadduct, catalyzed with differnt base loads of cesium carbonate and potassium-*tert*-butoxide

10 mol% of potassium-*tert*-butoxide (entry 4, Table 14) exhibit complete conversion of divinyl sulfone to the diadduct and consequently and is therefore well-suited for the model reaction.

Summarizing the findings from the previous experiments, optimized conditions for the oxa-Michael addition of phenol to divinyl sulfone encompass 10 mol% potassium-*tert*-butoxide and *tert*-butanol as solvent.

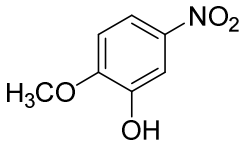
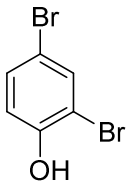
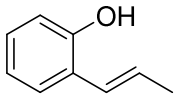
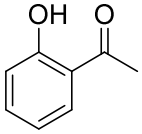
3.2.2 Application of Optimized Reaction Conditions

These optimized conditions were tested concerning the applicability on structurally different substrates and enlarged to the nucleophile-mediated oxa-Michael addition.

3.2.2.1 Substrate Scope

Table 4 depicts all tested substrates and the associated experimental findings can be taken from Table 15.

Table 4. Substrates for the oxa-Michael addition and corresponding pK_a values

Entry	Name	Structure	pK_a[a]
1	2-Methoxy-5-nitrophenol		8.31
2	2,4-Dibromophenol		7.86
3	2-Propenylphenol		10.06
4	5-Hydroxyacetophenon		10.17

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02, retrieved from Scifinder.

Under the present reaction conditions, phenolic derivatives (entry 1 – 4, Table 15) gave hardly any or no desired addition product. Low pK_a values of 2-methoxy-5-nitrophenol and

2,4-dibromophenol offer a plausible explanation for the unsuccessful conversion. In case of 2-propenylphenol and 5-hydroxyacetophenon steric hindrance due to further substituents might cause troubles. This is aggravated by the fact that 2-propenylphenol occurs as a mixture of *cis*/*trans* isomers. It remains unclear whether the substrates did undergo an addition reaction followed by an elimination reaction or no addition reaction occurred at all.

Only benzyl alcohol (entry 5, Table 15) showed a rapid and satisfying addition reaction to the diadduct. The yield of diadduct amounted 97.8 % already after 0.5 h. Interestingly a constant increase of formed monoadduct on the expense of declining diadduct over time is observed.

3.2.2.2 Base and Nucleophile Promotion of Oxa-Michael Addition

Completing the applicability experiments, the reaction set-up was enlarged to the nucleophilic-mediated oxa-Michael addition. For this purpose, 4-dimethylaminopyridine (DMAP) and triphenylphosphine (PPh_3) were chosen as nucleophilic promoters. The experimental output is listed in Table 16.

Strasser and Slugovc found out that triphenylphosphine constitutes to be an insufficient promoter for the oxa-Michael addition of phenol to divinyl sulfone in dichloromethane. After 24 h the ratio of mono-/diadduct is 21/2. [69] The topic was picked up and an evaluation of the catalytic activity in *tert*-butanol as solvent was carried out. Additionally, a second nucleophile (4-dimethylaminopyridine) was utilized and compared with potassium-*tert*-butoxide.

It must be mentioned that none of the two nucleophiles is nearly as effective as potassium-*tert*-butoxide (entry 1, Table 16), in terms of conversion within 24 h. 4-Dimethylaminopyridine (entry 2, Table 16) gave only 29.9 % diadduct and moderate 49.6 % are achieved with triphenylphosphine (entry 3, Table 16). Also, the nucleophile-mediated reaction mixtures suffer from lower product purity. Pure products were achieved employing other substrates than phenol.[69]

[69] Strasser, S.; Slugovc, C.; *Catalysis Sience and Technology*, **2015**, *5*, 5091-5094.

3.2.3 Further Investigations

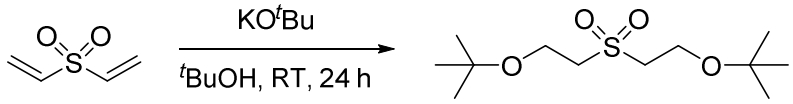
3.2.3.1 Reactivity Study of Divinyl Sulfone

The screening experiments made clear that *tert*-butanol is an appropriate solvent (section 3.2.1.1) for the oxa-Michael addition of phenol to divinyl sulfone. Consequently, the question has been raised whether *tert*-butanol is also able to act as Michael donor.

The reactivity of divinyl sulfone towards *tert*-butanol was investigated. To a mixture of *tert*-butanol and divinyl sulfone potassium-*tert*-butoxide was added. The resulting suspension was stirred at room temperature and a change of colour within 1 h from yellow to orange was observed. After 24 h the reaction was stopped and a homogeneous solution was obtained by the addition of dichloromethane. The reaction mixture was further investigated via ^{1}H-NMR spectroscopy and bis(*tert*-butyl-2-ethoxy)sulfone was identified as the major product accompanied by minor amounts of 1,4-oxathiane-4,4-dioxide[70]. In order to prove the presence of suspected *tert*-butanol diadduct, a preparative experiment was carried out (section 3.2.3.2).

The NMR sample was measured several times and also subjected to a temperature treatment for 12 h (43 °C drying cabinet). It was found that, the exposure to thermal stress does not lead to decomposition of the existing products and no formation of new products occurred. Remarkably, the addition reaction of *tert*-butanol to divinyl sulfone occurs in a satisfactory extent in the absence of phenol.
Only the combination of potassium-*tert*-butoxide and *tert*-butanol facilitates the formation of *tert*-butanol adducts in the presence of phenol, but to a very low extent. This observation refers to the results from the screening experiments and demonstrates that phenol reacts faster than *tert*-butanol.

3.2.3.2 Synthesis of Bis(tert-butyl-2-ethoxy)sulfone (5)



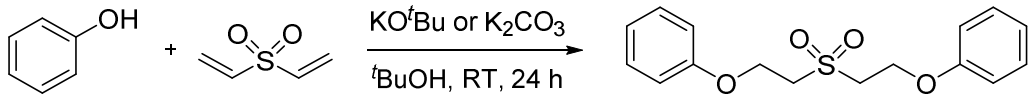
5

Scheme 11. Preparation of bis(*tert*-butyl-2-ethoxy)sulfone **5**

[70] Rous, M. V. et al.; *Journal of Organic Chemistry*, **2007**, *72*, 1143-1147.

Compound **5** was synthesized according to Scheme 11. The work up procedure gives a spongy, white interphase. This interphase was finally captured from the aqueous phase. The resulting yellow-orange oil and the interphase were subjected to ^{1}H-NMR spectroscopy in $CDCl_3$. A mixture of 90 ± 1 % diadduct and 10 ± 1 % 1,4-oxathiane-4,4-dioxide (crude product) and 2 ± 1 % diadduct and 9 ± 1 % 1,4-oxathiane-4,4-dioxide (interphase) were detected. The crude product was further purified via flash column chromatography yielding 46.7 % of **5**. The yield might be lowered since a portion of **5** has been included in the interphase which was not subjected to the chromatographic purification.

3.2.3.3 Synthesis of Bis(phenyl-2-ethoxy)sulfone (6)



6

Scheme 12. Preparation of bis(phenyl-2-ethoxy)sulfone **6**

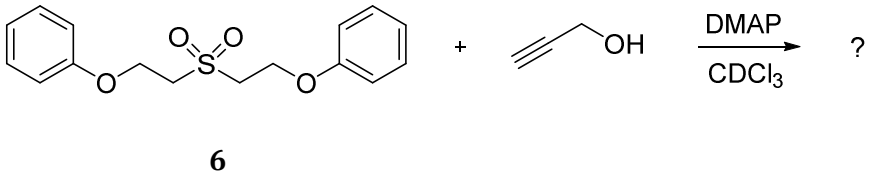
Compound **6** was synthesized according to Scheme 12. The synthesis was performed twice, in order to determine if the yields is affected by the base used. Therefore, potassium-*tert*-butoxide and potassium carbonate were utilized. Subsequently, **6** was subjected to a stability study (section 3.2.3.4). The resulting yellowish, oily solid was investigated via ^{1}H-NMR spectroscopy in $CDCl_3$ and the composition of the crude product is outlined in Table 5. In order to separate phenol, further purification was done via extraction with toluene. Both syntheses give good yields > 70 % (Table 5). Nevertheless, as indicated in the screening experiments (section 3.2.1.3), after 24 h potassium carbonate gives a higher yield than potassium-*tert*-butoxide.

Table 5. Synthesis of **6** - crude product composition and yield

Entry	Base	Phenol (%)	Monoadduct (%)	Diadduct (%)	Yield (%)[a]
1	KO^{t}Bu	27.8	1.8	70.4	70.8
2	K_2CO_3	13.3	1.2	85.5	75.7

[a] Isolated yield after purification.

3.2.3.4 *Stability Study of Bis(phenyl-2-ethoxy)sulfone (6)*



6

Scheme 13. Stability study of bis(phenol-2-ethoxy)sulfone **6**

Three approaches were performed to examine the stability of compound **6**. The reaction set-up is outlined in Scheme 13. All experiments were carried out in NMR tubes ensuring a permanent possibility for ^{1}H-NMR measurements. The NMR tubes were charged according to Table 6 and diluted with $CDCl_3$ by adjusting a filling level of 5 cm (height in NMR tube). Propargyl alcohol has shown to be a good substrate for nucleophile-mediated oxa-Michael addition[69] and was therefore used in experiment 3.

Table 6. Compositions of the reaction mixtures for the stability study of **6**

Entry	Compound 6 (mg)	DMAP (mg)	Propargyl alcohol (mg)
1	10.26	-	-
2	10.20	1.20	-
3	9.88	1.08	3.70

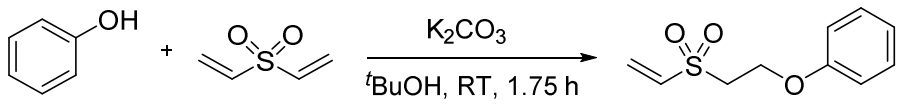
Experiment 1 (entry 1, Table 6): After approximately 96 h the reaction mixture was subjected to thermal stress (43 °C drying cabinet) for 24 h. The exposure to thermal stress did not lead to the decomposition of the existing products and no formation of new products was observed.

Experiment 2 (entry 2, Table 6): Intrusions into the experiment were performed, encompassing thermal stress at 43 °C for 24 h, addition of one droplet divinyl sulfone and again thermal stress at 43 °C for 23 h. The exposure to thermal stress did not lead to the decomposition of the existing products and no formation of new products was observed.

Experiment 3 (entry 3, Table 6): Intrusions into the experiment were performed, encompassing thermal stress at 43 °C, addition of one droplet divinyl sulfone and total removal of the solvent. After addition of divinyl sulfone, a slow conversion with progargyl alcohol to the adduct was monitored. The destruction of **6** succeeded only after generation of bulk conditions.

Under present reaction conditions, bis(phenol-2-ethoxy)sulfone **6** exhibits a great stability. Only through the combination of bulk conditions and the attendance of 4-dimethylaminopyridine, divinyl sulfone and propargyl alcohol enabled the destruction.

3.2.3.5 Synthesis of (Phenyl-2-ethoxy)vinylsulfone (7)

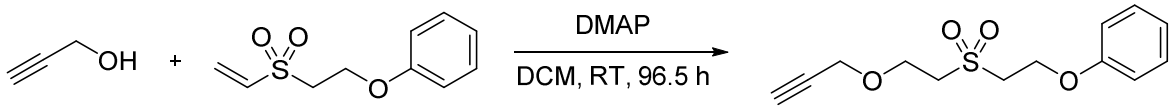


7

Scheme 14. Preparation of (phenyl-2-ethoxy)vinylsulfone **7**

Compound **7** was synthesized according to Scheme 14. The resulting yellowish oil was subjected to ^{1}H-NMR spectroscopy in $CDCl_3$ and a composition of the 32 % divinyl sulfone, 56 % monoadduct and 12 % diadduct was detected. Further purification was carried out via flash column chromatography, affording a moderate yield of 40.8 % of **7**. According to ^{1}H-NMR spectroscopy, the resulting white solid is composed of 96 ± 1 % monoadduct und 4 ± 1 % diadduct.

3.2.3.6 Synthesis of (Phenyl-2-ethoxy)propargylsulfone (8)



7 **8**

Scheme 15. Preparation of (phenyl-2-ethoxy)propargylsulfone **8**

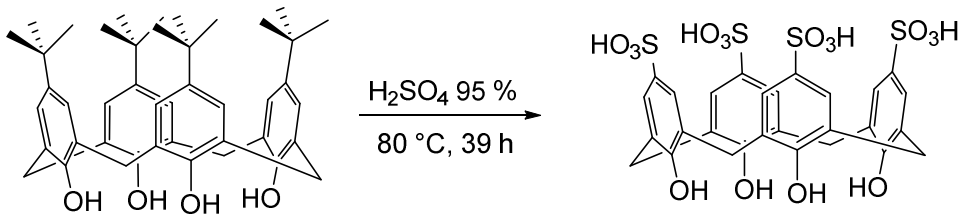
Compound **8** was synthesized according to Scheme 15. After 73 h the reaction mixture was investigated via ^{1}H-NMR spectroscopy in $CDCl_3$ and residual **7** was detected. In order to improve the conversion, the volume of the reaction mixture was reduced to 1/3 and further progargyl alcohol was added. Total conversion of **7** was observed after 96.5 h and a mixture composition of 30.4 % bis(progargyl-2-ethoxy)sulfone, 60.9 % (phenyl-2-ethoxy) propargyl-

sulfone and 8.7 % (phenyl-2-ethoxy)vinylsulfone was detected by the means of ^{1}H-NMR spectroscopy. Further purification was carried out via flash column chromatography, affording a colourless oil. The synthesis of **8** had only qualitative purposes and hence the yield was not determined.

The primary intended functionalization of calix[4]arenes via oxa-Michael addition could not be realized (section 3.1) and therefore the modification procedure is as follows. Starting from *p-tert*-butylcalix[4]arene, an *ipso*-substitution in sulfuric acid gave *p*-sulfonatocalix[4]arene which was further treated with an olefin halide to etherify the phenolic oxygen atoms.

3.3 Sulfonation of *p-tert*-Butylcalix[4]arene

Following a literature procedure[71] for *ipso*-sulfonation of *p-tert*-butylcalix[4]arene with H_2SO_4 conc. led to *p*-tetrasulfonic acid-calix[4]arene (**9**) (Scheme 16). Reaction control and one work up step have been slightly modified.



9

Scheme 16. Sulfonation of *p-tert*-butylcalix[4]arene with H_2SO_4 conc.

p-tert-Butylcalix[4]arene was added to sulfuric acid and the resulting suspension was stirred at 80 °C for 39 h. Special attention was paid to the careful and portion wise addition of *p-tert*-butylcalix[4]arene to sulfuric acid. This is particularly important as sticking to the flask wall should be avoided and a good wetting enabled. Unlike literature, reaction control was carried

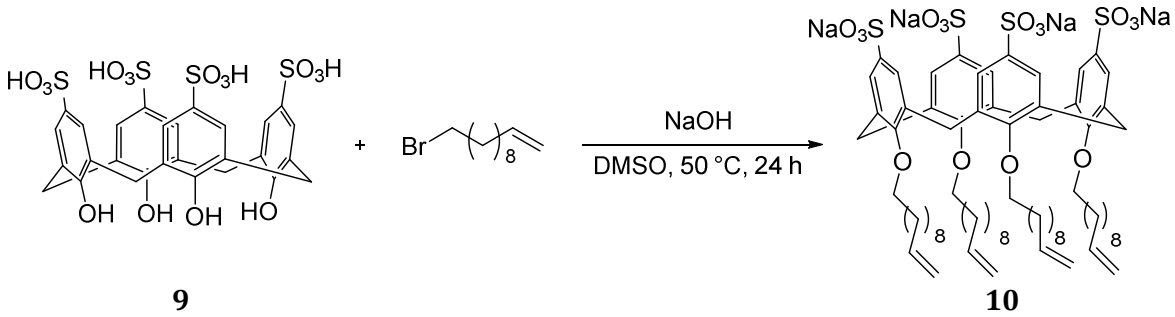
[71] EP 0 918 751 B1 *Process for the dealkylating sulfonation of p-alkyl calixarenes*.

out by an optical evaluation of residual educt in the reaction mixture, instead of a water solubility test. Once no significant variation could be noted, the reaction mixture was worked up according to the protocol. After cooling to room temperature the solid material is recovered by filtration and washed with ice-cooled ethanol. An increased volume of ethanol was used to ensure complete removal of excess sulfuric acid. The crude product was dissolved in methanol, the resulting solution treated with charcoal and then filtered on Celite. Finally, the desired product was precipitated in ethyl acetate. Compound **9** was received as pure substance in a moderate yield of 53.7 %, whereas literature reports 87 %.[71] Via this synthetic route the easy available, water-insoluble and inexpensive educt could be converted successfully into a water-soluble and more expensive product which serves a starting material for further syntheses.

3.4 *O*-Alkylation of *p*-Sulfonatocalix[4]arenes

3.4.1 Preparation of 5,11,17,23-tetrasulfonato-25,26,27,28-tetra(undec-1-ene-11-oxy)-calix[4]arene (10)

Next, with **9** in hand, the reaction with 11-bromo-1-undecene to provide additional functionality in the molecule was envisioned. *O*-Alkylation of **9**, following the literature procedure[41] with adaptions referring to the reaction performance, led to 5,11,17,23-tetrasulfonato-25,26,27,28-tetra(undec-1-ene-11-oxy)-calix[4]arene (**10**) (Scheme 17).



9 **10**

Scheme 17. Complete *O*-alkylation of *p*-tetrasulfonic acid-calix[4]arene **9** with 11-bromo-1-undecene

9 was mixed with finely crushed sodium hydroxide suspended in DMSO. Using solid sodium hydroxide instead of aqueous one should suppress an increased hydrolysis of alkylating agent. To ensure good conversion, 11-bromo-1-undecene was added slowly in three portions. During the reaction, precipitation of a beige solid was observed. The obtained solid was

investigated by the means of ^{1}H-NMR spectroscopy in DMSO-d_6 and ATR-IR spectroscopy, (**10**) residual 11-bromo-1-undecene and its hydrolysis product were detected. To promote precipitation, the reaction mixture was stored in the fridge for some time. The raw product was recovered by filtration and washed with *n*-pentane for purification. The purity of **10** could be improved but still not removable amounts of alkylating agent and its hydrolysis product remained. For economic reasons further purification steps were omitted, because the purity was already satisfactory. Good yields from 80 to 83 % of **10** were afforded using 32 – 34 eq. of the alkylating agent in the presence of 30 – 32 eq. of sodium hydroxide (entry 1 - 3, Table 11). A reduction of alkylating agent to 15.6 eq. (entry 4, Table 11), respectively 15.9 eq. (entry 5, Table 11) led to 73.4 % and 78.3 % yield. The reduction to the half of alkylating agent and sodium hydroxide in combination (entry 6, Table 11) was followed by a larger decrease in yield to 66.8 %. Also, according to the ^{1}H-NMR spectrum, it is assumed that a certain portion of **9** is less than four-fold alkylated.

It is worth mentioning that, by the means of NMR-spectroscopy, the conformation of **10** can be assigned to *cone* (Table 1).[23,24] The methylene bridge gives a pair of doublets (3.24 ppm and 4.34 ppm) with coupling constants $^{3}J_{HH}$ = 12.5 Hz and one signal at 30.60 ppm. Representative extracts of NMR-spectra for conformation assignment are depicted in Figure 14 and 15.

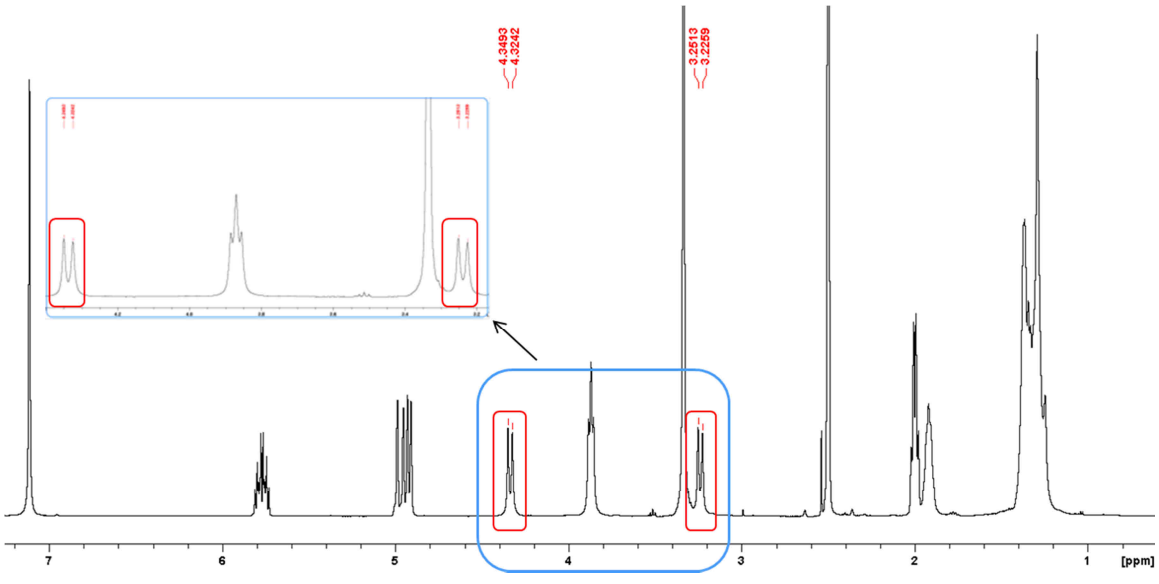


Figure 14. ^{1}H-NMR spectrum of **10**, doublets of the methylene bridge highlighted

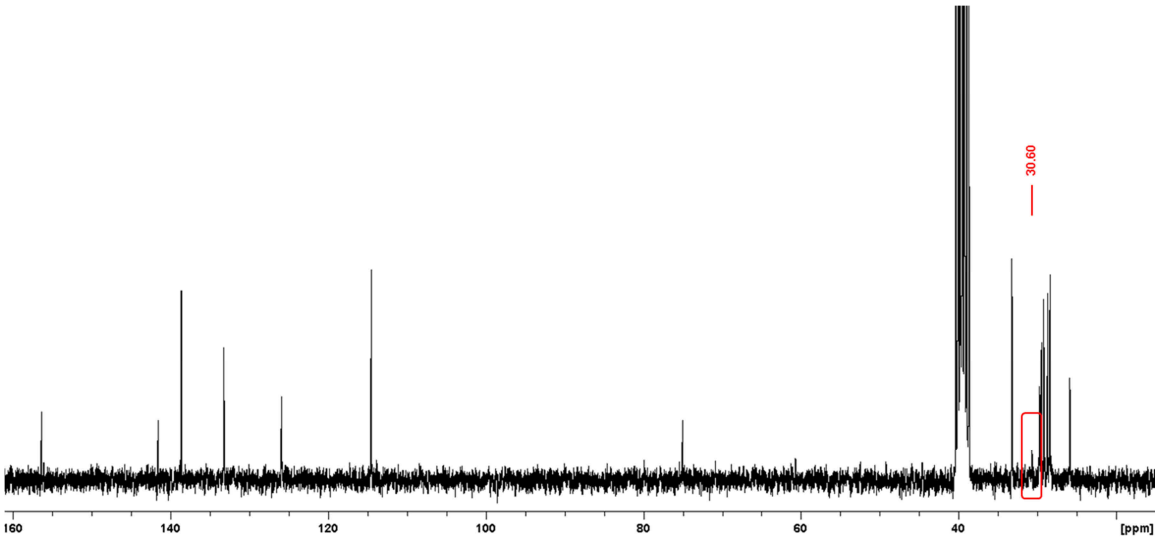


Figure 15. ^{13}C-NMR spectrum of **10**, signal of the methylene bridge highlighted

Additionally the product (entry 2, Table 11) was subjected to high resolution mass spectroscopy leading to the following spectrum (Figure 16).

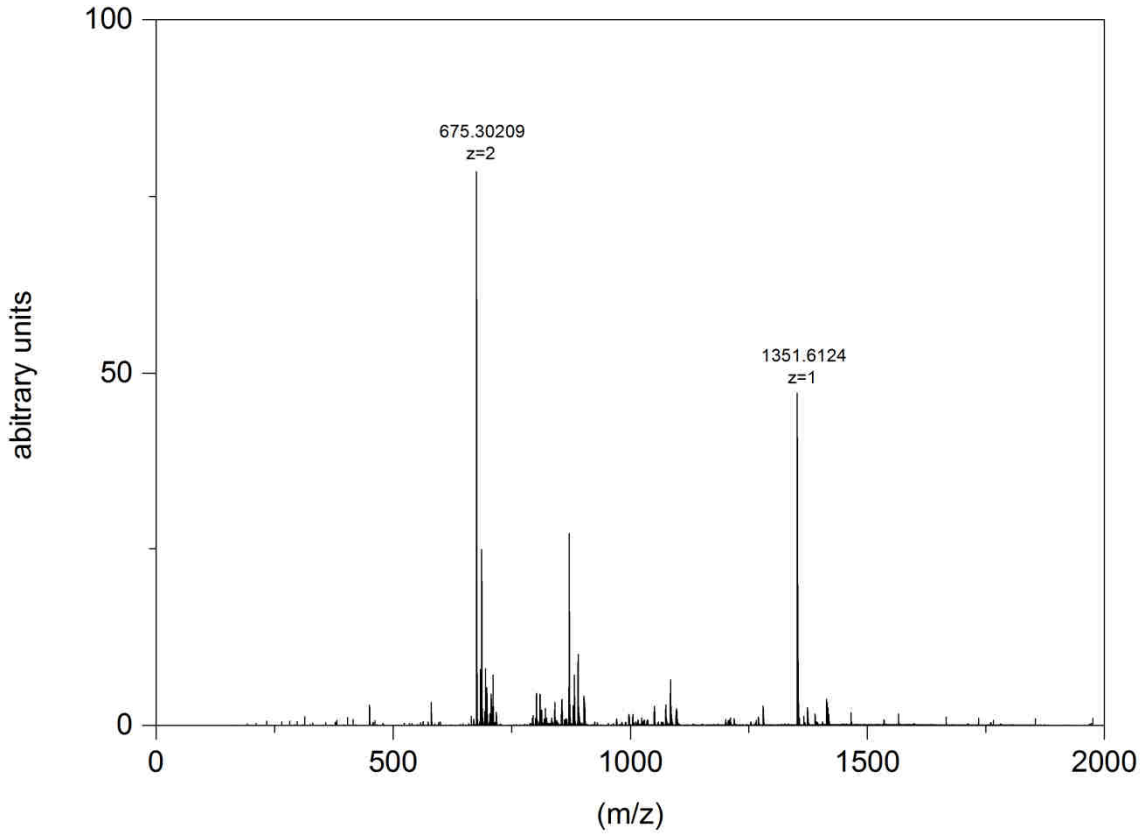
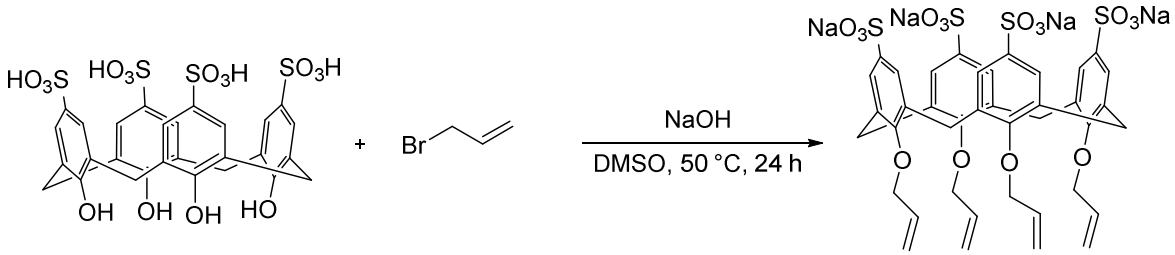


Figure 16. Mass spectrum of **10** (ESI, negative mode)

Summarizing the above, *O*-alkylation of *p*-tetrasulfonic acid-calix[4]arene (**9**) can be carried out in a good manner, even with reduced to the half of the original amount of alkylating agent. Only additional reduction of sodium hydroxide gives less satisfying results concerning yield and degree of alkylation. Consumption of base results from deprotonation of the sulfonic acid group as well as the hydroxyl group at the lower rim. Together, this leads to an increased demand for base.

3.4.2 Preparation of 5,11,17,23-tetrasulfonato-25,26,27,28-tetra(prop-1-ene-3-oxy)-calix[4]arene (11)

The furnishing of **9** with an additional functionality while maintaining its water solubility was desired. *O*-Alkylation of **9** with allyl bromide following the literature procedure[41] led to 5,11,17,23-tetrasulfonato-25,26,27,28-tetra(prop-1-ene-3-oxy)-calix[4]arene **11** (Scheme 18). The only alteration of the given protocol concerns the application of solid sodium hydroxide instead of an aqueous formulation.



9 **11**

Scheme 18. Complete *O*-alkylation of *p*-tetrasulfonic acid-calix[4]arene **9** with allyl bromide

The conversion of **9** with allyl bromide was carried out in the same manner as the synthesis of **10** (section 3.4.1). The reaction suspension showed no observable changes in appearance over time. The insoluble solid was removed by filtration and the product **11** was then precipitated from the filtrate with methanol. For the promotion of the precipitation, the mixture was stored in the fridge for some time. The obtained solid was investigated by the means of ^{1}H-NMR spectroscopy in D_2O and **11**, residual allyl bromide and its hydrolysis products were detected. The raw product was recovered by filtration and washed with ethanol for purification. The desired product was obtained in an appropriate purity but only with a low yield of 19.7 %.

Interestingly, similar to **10** the conformation of **11** can be assigned to *cone* (**Table 1**).[23,24] A pair of doublets (3.46 ppm and 4.55 ppm) with coupling constants $^{3}J_{HH}$ = 13.2 Hz (^{1}H-NMR spectrum) and one signal at 31.92 ppm for the methylene bridge (^{13}C-NMR spectrum) is compatible with the *cone*-conformation.

Summing up, *O*-alkylation of **9** with allyl bromide can be carried out, although yielding only roughly 20 % of **11**. The water solubility of the modified *p*-sulfonatocalix[4]arene is maintained due to the incorporation of a shorter alkyl chain and the conformation is assigned to *cone*.

3.5 Preparation of PolyHIPEs

Making use of the terminal functionality, **10** was connected to a solid support. So, polyHIPEs were prepared, employing **10** as polymerizable surfactant and following the literature procedure for the laboratory course.[72] The formulations can be taken from Table 7.

Table 7. Formulations for preparation of the polyHIPEs

Entry	Compound 10 (mg)	Span 80® (mg)	DCPD (g)	$H_2O_{deion.}$ (mL)	M/I[b]	Porosity[c] (%)
1	50.53	-	1.008	2.3	~12000	70
2	50.20[a]	-	1.052	2.5	12000	70
3	49.20	98.4	2.003	8.0	15.000	80

[a] Suspended in 300 µL toluene. [b] Molar ratio of monomer : initiator (Umicore M2). [c] Calculated value.

Dicyclopentadiene and the surfactant(s) (**10** and Span 80®) were mixed with the aid of a magnetic stirrer bar. Afterwards, water was added dropwise to the mixture and the formation of an emulsion was observed. A drastic increase of viscosity was noticed using the surfactant combination (entry 3, Table 7), and therefore the emulsion had to be shaken further by hand. Using **10** as the only surfactant (entry 1 and Table 7), no such observation was made. The initiator Umicore M2 was dissolved in toluene and added to the emulsion for initiating the ring opening metathesis polymerization. In order to receive polyHIPE monoliths and discs, the established emulsions are transferred quickly into the required molds. The charged molds were placed into the drying cabinet (80 °C) for curing of the polymer. Subsequent removal from molds gives the shaped polyHIPEs, which morphology and inner

[72] Wappel, J.; Slugovc, C.; *polyHIPE beads, LU und Exkursion Chemische Technologie CHE.170*, **2012**, 1-2.

structure were investigated via SEM. Qualitative information about the composition of the polyHIPE resulting from the surfactant combination (entry 3, Table 7) was received from EDX measurements. Therefore, the disc was examined at three different points and the results are listed in Table 8.

Table 8. EDX results - Weight% of the polyHIPE made from a surfactant combination

Position	C	O	S
1	94.15	5.39	0.45
2	93.33	6.10	0.57
3	94.76	4.51	0.73
Average	94.08	5.33	0.58
Calculated	91.82	6.12	2.00

Solely, the combination of **10** and Span®80 (entry 3, Table 7) gave good results in forming polyHIPEs with a high interconnected structure (Figure 17). The single application of **10** as surfactant (entry 1 and 2, Table 7), did not succeed in forming a porous inner structure.

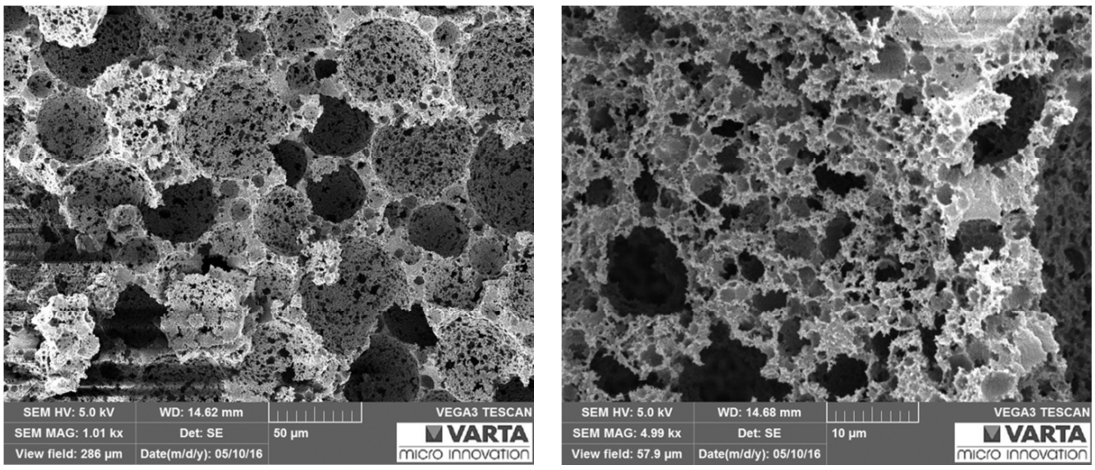


Figure 17. SEM images of polyHIPE, formed with surfactant combination.
Left: 1000x magnification, right: 5000x magnification.

Attempts to replace water by methanol in order to create polyHIPEbeads failed. The formation of a macroscopic emulsion could not be observed with the naked eye.

4 Conclusion and Outlook

The primary envisaged functionalization of calix[4]arenes via oxa-Michael addition could not be realized. However, *O*-alkylation could be carried out in a satisfactorily manner and thereby an additional functional entity was incorporated. At first, *p-tert*-butylcalix[4]arene was sulfonated, leading to *p*-tetrasulfonic acid calix[4]arene. In a second step, *O*-alkylation with alkene halogenides gained an amphiphilic molecule, furnished with a terminal functional group. Finally, making use of the terminal unsaturated bond, polyHIPEs were prepared. The thereby modified calix[4]arenes are considered as complexing units for *N*-methylated lysines. Their quality as such will be evaluated within BioTechMed-Graz.

Optimized reaction conditions for the oxa-Michael addition of phenol to divinyl sulfone were found. Also a better understanding of factors influencing the reaction behavior of those reactants was achieved, suggesting that calix[4]arenes are bad Michael donors for steric and electronic reasons.

5 Experimental Section

5.1 General and Used Chemicals

All reactions were performed under ambient conditions, unless otherwise mentioned. All chemicals from commercial source were utilized without further purification, unless otherwise stated.

Table 9. Used Chemicals and commercial sources

Reagent	Supplier
11-Bromo-1-undecene	Alfa Aeser
2,2-Bis(4-hydroxyphenyl)propane	Fluka
2,4-Dibromophenol 95 %	Fluka
2-Hydroxyacetophenon 99 %	Sigma Aldrich
2-Methoxy-5-nitrophenol 98 %	Lancaster
2-Propenylphenol 98 %	Sigma Aldrich
4,4´-Dihydroxybiphenyl	Fluka
4-Dimethylaminopyridine	Fluka
Allyl bromide 99 %	Fluka
Benzyl alcohol	Sigma Aldrich
Cesium carbonate	Sigma Aldrich
Dicyclopentadiene	ABCR
Divinyl sulfone 97 %	Sigma Aldrich
Umicore M2	Umicore
Phenol	Fluka
Potassium carbonate	Merck
Potassium *tert*-butoxide 95 %	Sigma Aldrich
Propargyl alcohol	Fluka
p-tert-Butylcalix[4]arene	Carbosynth
Sodium hydroxide	VWR Chemicals
Span 80®	Sigma Aldrich
Sulfuric acid 95 %	VWR Chemicals
Triethylamine	Sigma Aldrich
Triphenylphosphine	Sigma Alrich

5.2 Analytics

5.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 MHz spectrometer equipped with an autosampler at 25 °C (300.36 MHz (^{1}H-NMR), 75.53 MHz (^{13}C-NMR)) or on a Varian Inova 500 MHz at 25 °C (499.88 MHz (^{1}H-NMR), 125.70 MHz (^{13}C-NMR)). Chemical shifts (δ) are given in parts per million (ppm) relative to TMS (δ = 0 ppm) and the spectra were referenced to the residual solvent peak, not otherwise mentioned. Coupling constants (J) are reported in Hertz (Hz). The spectra were processed and analyzed with Bruker Topspin 3.1 software. As solvents $CDCl_3$, D_2O or DMSO-d_6 were used.

5.2.2 Infrared Spectroscopy (ATR-FTIR)

Infrared spectra were recorded on a Bruker ALPHA-P FT-IR spectrometer equipped with a diamond attenuated total reflection (ATR) unit. Fourier transformation (FT), processing and analyzation were performed with OPUS 7.5 software. Wave numbers ($\tilde{\nu}$) are given in one per centimeter (cm^{-1}). The spectra were recorded in the range from 4000 cm^{-1} to 400 cm^{-1} with a resolution of 4 cm^{-1} and a sample scan time of 48 scans per spectrum. Background spectra were performed with a scan time of 24 scans per spectrum.

5.2.3 Thin Layer Chromatography (TLC)

Silica gel plates aluminum foil from Merck (TLC silicagel 60 F_{254}) were used. Detection was done by UV at 254 nm and $KMnO_4$ (1 wt% in $H_2O_{deion.}$) or Seebach dipping solution.

5.2.4 Flash Column Chromatography

As stationary phase Silica Gel 60 was applied. Separation problem as well as column size determined the quantity of stationary phase used. A rubber hand-pump enabled pressure generation during separation.

5.2.5 Melting Point (mp)

Melting point measurements were carried out on a MEL-TEMP melting point apparatus in open capillary tubes and mercury thermometer for temperature measurement. Melting points are not corrected.

5.2.6 High Resolution Mass Spectrometry (HR-MS)

High resolution mass spectrometry spectra were recorded on a Thermo Fisher Scientific LTQ FT Ultra ion cyclotron equipped with a nano-sprayer source. The products were ionized by direct infusion Electro Spray Ionization (ESI) with 1.6 kV spray voltage, 200 °C capillary temperature and 35 V capillary voltage at a tube lens voltage of 150 V. The spectra were processed and analysed with LTQ Tune Plus 2.5.5, XCalibur 2.1 Qual browse software.

5.2.7 Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed on an ESEM Tescan 500PA with EDX, equipped with a tungsten cathode. Sputtering of gold was performed on a Cressington Sputter Coater 108auto.

5.2.8 Energy Dispersive X-Ray Spectroscopy (EDX)

Energy dispersive X-ray spectroscopy for qualitative determination of sample composition was carried out with an INCAx-act detector from Oxford Instruments, mounted on the SEM device.

5.3 Synthesis

5.3.1 Oxa-Michael Addition Attempts with Divinyl sulfone

5.3.1.1 Conversion of p-tert-Butylcalix[4]arene with Divinyl Sulfone

Experiment 1 (entry 1, Table 2)

A vial equipped with a magnetic stirrer bar was charged with *p-tert*-butylcalix[4]arene (103.0 mg, 0.159 mmol, 1.00 eq.), divinyl sulfone (97 %, 27.9 mg, 0.229 mmol, 1.44 eq.) and 700 µL ^{t}BuOH. Subsequently, cesium carbonate (80.5 mg 0.247 mmol, 1.55 eq.) was added. The resulting white suspension was stirred at room temperature and the conversion was monitored via TLC (CH/EA = 4:1 (v/v)). After 60 h the reaction mixture was heated up to 60 °C. Further cesium carbonate (54.9 mg, 0.169 mmol, 1.09 eq.) was added after 61 h 15 min. The heating was removed (63 h 40 min) and the mixture cooled to room temperature before diluting with 5 % $HCl_{aq.}$ in order to stop the reaction. Afterwards, the mixture was extracted with Et_2O and DCM. The organic phases were monitored via TLC

(CH/EA = 4:1 (v/v), 254 nm, $KMnO_4$ dipping solution), subsequently dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure giving the referring residues. Similar result as TLC can be stated via ^{1}H-NMR spectroscopy in $CDCl_3$. Et_2O phase: pearly, shimmering, oily solid. DCM phase: pearly, shimmering, fine crystals. Via ^{1}H-NMR spectroscopy in $CDCl_3$ non-converted *p-tert*-butylcalix[4]arene and divinyl sulfone adducts with water were detected, representing similar results than TLC.

Experiment 2 (entry 2, Table 2)

The reaction was performed in the same manner as experiment 1. *p-tert*-Butylcalix[4]arene (102.5 mg, 0.158 mmol, 1.00 eq.), divinyl sulfone (97 %, 142.4 mg, 1.169 mmol, 7.40 eq.), 700 µL ^{t}BuOH, first portion (78.8 mg 0.242 mmol, 1.28 eq.) and second portion (52.5 mg 0.161 mmol, 1.05 eq.) cesium carbonate.

Experiment 3 (entry 3, Table 2)

A vial equipped with a magnetic stirrer bar was charged with *p-tert*-butylcalix[4]arene (100.7 mg, 0.155 mmol, 1.00 eq.), divinyl sulfone (97 %, 82.00 mg, 0.673 mmol, 4.37 eq.) and 1.5 mL ^{t}BuOH. Subsequently, triethylamine (32.27 mg, 0.319 mmol, 2.07 eq.) followed by cesium carbonate (50.45 mg, 0.154 mmol, 1.01 eq.) was added. After 68 h 45 min the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction. Then the mixture was extracted with DCM and the organic phase was monitored via TLC (CH/EA = 4:1 (v/v), 254 nm, $KMnO_4$ dipping solution) and ^{1}H-NMR spectroscopy in $CDCl_3$. Only a mixture of educts but no conversion was detected.

5.3.1.2 O-Alkylation of p-tert-Butylcalix[4]arene followed by Conversion with Divinyl Sulfone

Synthesis of *p-tert*-butyl-25,26-bis(2-propyleneoxy)calix[4]arene (**3**)

In a round bottom flask equipped with a magnetic stirrer bar, a reflux condenser and a gas inlet *p-tert*-butylcalix[4]arene (297.4 mg, 0.458 mmol, 1.00 eq.) and potassium carbonate (70.8 mg, 0.512 mmol, 0.512 eq.) were suspended in 20 mL dry MeCN. The mixture was heated to reflux for 1 h and then allyl bromide (390 µL, 564.6 mg, 4.67 mmol, 10 eq.) was added slowly in three portions. The mixture was refluxed for 44 h 10 min before cooled to room temperature. The solvent was removed under reduced pressure and the residue was taken up in DCM (20 mL) and 1 N HCl (20 mL). The organic phase was washed with 1 N HCl

(3 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). After removing the solvent, the resultant solid (yellow, oily crystals) was dissolved in a minimum amount of DCM and precipitated to large amount of MeOH. Very tiny and fine crystals were obtained and the solution was placed in the freezer (-18°C). Due to no progress in crystallization over the weekend, the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography (Silica Gel 60, CH/EA = 10:1 (v/v)) and the purification was monitored via TLC (CH/EA = 4:1 (v/v), 254 nm, $KMnO_4$ dipping solution). Two different species were separated (fractions 3 – 5 and fractions 6 – 9) and characterized via ^{1}H-NMR spectroscopy in $CDCl_3$.

Fractions 3 – 5 (residual *p-tert*-butylcalix[4]arene and *p-tert*-butyl-25,26-bis(propyl-1-ene-2-oxy)-calix[4]arene): white crystals.
Fractions 6 – 9 *(p-tert*-butyl-25,26-bis(propyl-1-ene-2-oxy)-calix[4]arene): white crystals.

Conversion of *p-tert*-Butyl-25,26-bis(propyl-1-ene-2-oxy)calix[4]arene (**3**) with Divinyl Sulfone

A vial equipped with a magnetic stirrer bar was charged with **3** (fractions 6 – 9) (30.30 mg, 0.046 mmol, 1.00 eq.), divinyl sulfone (97 %, 11.59 mg, 0.098 mmol, 2.15 eq.) and 1.5 mL ^{t}BuOH. Subsequently, cesium carbonate (15.16 mg, 0.047 mmol, 1.02 eq.) was added. The resulting suspension was stirred at room temperature and the conversion was monitored via TLC (CH/EA = 4:1 (v/v), 254 nm, $KMnO_4$ dipping solution). After 75 h 10 min the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction. Afterwards, the mixture was extracted with DCM (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford a white-yellowish solid. A mixture of possible by-products of divinyl sulfone but no adduct **3** was detected via ^{1}H-NMR spectroscopy in $CDCl_3$ and TLC (CH/EA = 4:1 (v/v)).

5.3.2 Oxa-Michael Addition Model Reaction

5.3.2.1 General Procedure for the Oxa-Michael Addition of Phenol and Phenylic Derivatives with Divinyl Sulfone in the Presence of a Base

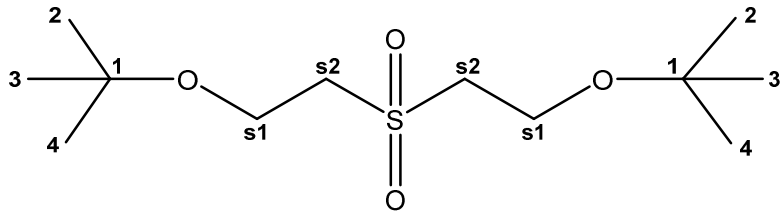
A vial equipped with a magnetic stirrer bar was charged with phenol, divinyl sulfone (97 %) and 1.5 mL solvent. Subsequently, the base was added. The resulting suspension was stirred at room temperature. After defined intervals an aliquot part of the reaction mixture was

withdrawn and worked up. Therefore, the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction and extracted 3 times with DCM. The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting product was analyzed via ^{1}H-NMR spectroscopy in $CDCl_3$.

5.3.2.2 Reactivity Study of Divinyl Sulfone

A vial equipped with a magnetic stirrer bar was charged with divinyl sulfone (97 %, 99.29 mg, 0.815 mmol, 1.00 eq.) and 1.50 mL ^{t}BuOH. Subsequently potassium-*tert*-butoxide (95 %, 10.61 mg, 0.090 mmol, 0.11 eq.) was added. The resulting suspension was stirred at room temperature. After 24 h the reaction mixture was diluted with 5 % HCl_{aq} in order to stop the reaction and diluted with DCM. A composition of < 0.1 % divinyl sulfone, 82.4 % *tert*-butanol diadduct and 17.6 % 1,4-oxathiane-4,4-dioxide was detected by ^{1}H-NMR spectroscopy in $CDCl_3$. This NMR sample was left at room temperature for 125 h and finally put into the drying cabinet at 43 °C for 24 h and ^{1}H-NMR spectra were measured at different times.

5.3.2.3 Bis(tert-butyl-2-ethoxy)sulfone (5)



A vial equipped with a magnetic stirrer bar was charged with divinyl sulfone (97 %, 170.0 mg, 1.396 mmol, 1.00 eq.) and 2.58 mL ^{t}BuOH. Subsequently, potassium-*tert*-butoxide (95 %, 18.22 mg, 0.142 mmol, 0.10 eq.) was added. The resulting suspension was stirred at room temperature. After 24 h the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction and extracted with DCM (3 x 20 mL).The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. A composition of < 0.1 % monoadduct, 89.6 % diadduct and 10.4 % 1,4-oxathiane-4,4-dioxide was detected by ^{1}H-NMR spectroscopy in $CDCl_3$. The crude product was purified by flash column chromatography (Silica Gel 60, CH/EA = 20:1 → 3:1 (v/v)) and the purification was monitored via TLC (CH/EA = 1:1 (v/v), 254 nm, Seebach dipping solution). The purification afforded 173.1 mg (0.650 mmol) of a white solid (sampling of fractions with R_f = 0.67).

Diadduct: Bis(^{t}butyl-2-ethoxy)sulfone, $C_{16}H_{18}O_4S$, [266.40].

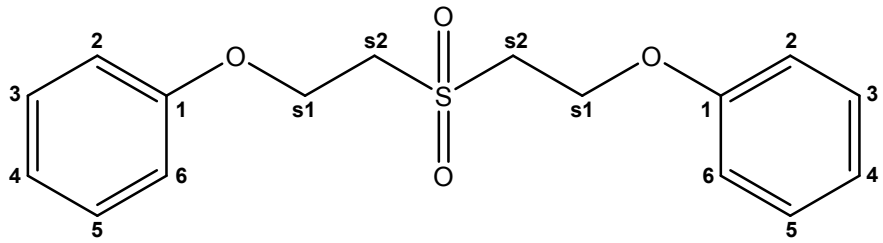
Yield: 173.1 mg (0.650 mmol, 46.7 % o.th.), white solid.

^{1}H-NMR (300 MHz, $CDCl_3$,) δ: 3.79 (t, 4H, $^{3}J_{HH}$ = 5.70, CH_2^{s1}), 3.28 (t, 4H, $^{3}J_{HH}$ = 5.70, CH_2^{s2}), 1.21 (s, 18H, $CH_3^{2,3,4}$).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$,) δ: 73.98 (2C, C^{1}), 55.90 (2 signals merged, 4C, $C^{s1,s2}$), 27.48 (6C, $C^{2,3,4}$).

mp = 33 °C

5.3.2.4 Bis(phenyl-2-ethoxy)sulfone (6)



A vial equipped with a magnetic stirrer bar was charged with phenol, divinyl sulfone (97 %) and ^{t}BuOH. Subsequently, the base was added and the resulting suspension was stirred at room temperature. After 24 h the reaction mixture was diluted with 5 % HCl_{aq} in order to stop the reaction, mixed with 30 mL saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. A composition of 27.8 % phenol, 1.8 % monoadduct and 70.4 % diadduct was detected by ^{1}H-NMR spectroscopy in $CDCl_3$. The crude product was purified by extraction with toluene and saturated $NaHCO_3$ solution. Again, the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The purification afforded a white solid which according to the NMR spectra can be assigned as followed:

Entry 1, Table 10: 2 ± 1 % monoadduct (4.3 mg, 0.020 mmol) and 98 ± 1 % diadduct (212.5 mg, 0.679 mmol).

Entry 2, Table 10: 2 ± 1 % monoadduct (4.7 mg, 0.022 mmol) and 98 ± 1 % diadduct (228.4 mg, 0.745 mmol).

mp = 98 °C

Diadduct: Bis(phenyl-2-ethoxy)sulfone, $C_{16}H_{18}O_4S$, [306.38], beige solid.

^{1}H-NMR (300 MHz, $CDCl_3$,) δ: 7.30 (t, 4H, $^{3}J_{HH}$ = 8.10, $^{3}J_{HH}$ = 7.29, C$H^{3,5}$), 7.01 (t, 2H, $^{3}J_{HH}$ = 7.29, CH^{4}), 6.89 (d, 4H, $^{3}J_{HH}$ = 8.10, C$H^{2,6}$), 4.48 (t, 4H, $^{3}J_{HH}$ = 5.59, CH_2^{s1}), 3.61 (t, 4H, $^{3}J_{HH}$ = 5.52, CH_2^{s2}).

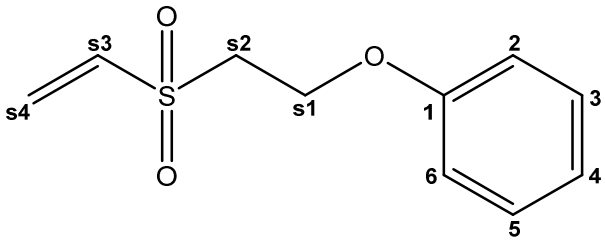
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$,) *δ:* 157.74 (2C, C^{1}), 129.83 (4C, C^{3,5}), 121.98 (2C, C^{4}), 114.75 (4C, C^{2,6}), 61.89 (2C, C^{s1}), 54.75 (2C, C^{s2}).

Table 10. Used quantities for preparative oxa-Michael addition of phenol with divinyl sulfone

Entry	DVS (mg)	Phenol (eq.[a])	Base	Base (eq.[a])	^{t}BuOH (mL)	Yield (%)[b]
1	118.2	3.03	KO^{t}Bu 95 %	0.10	1.84	70.8
2	120.0	2.97	K_2CO_3	0.84	1.84	75.7

[a] With respect to DVS. [b] o.th.

5.3.2.5 (Phenyl-2-ethoxy)vinylsulfone (7)



A vial equipped with a magnetic stirrer bar was charged with phenol (391.1 mg, 4.16 mmol, 2.91 eq.), divinyl sulfone (97 %, 174.0 mg, 1.43 mmol, 1.00 eq.) and 2.65 mL ^{t}BuOH. Subsequently, potassium carbonate (192.72 mg, 1.39 mmol, 0.97 eq.) was added. The resulting suspension was stirred at room temperature. After 1 h 45 min the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction and extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. A composition of 32 % phenol, 56 % monoadduct and 12 % diadduct was detected by ^{1}H-NMR spectroscopy in $CDCl_3$. The crude product was purified by flash column chromatography (Silica Gel 60, CH/EA = 10:1 → 3:1 (v/v)) and the purification was monitored via TLC (CH/EA = 3:1 (v/v), 254 nm, Seebach dipping solution, $R_{f(mono)}$ = 0.25, $R_{f(di)}$ =0.32). The purification afforded 130.7 mg of a white solid which, according to the ^{1}H-NMR spectra, can be assigned as followed: 96 ± 1 % monoadduct (124.0 mg, 5.842 mmol) and 4 ± 1 % diadduct (6.7 mg, 0.022 mmol).

mp = 68 – 74 °C

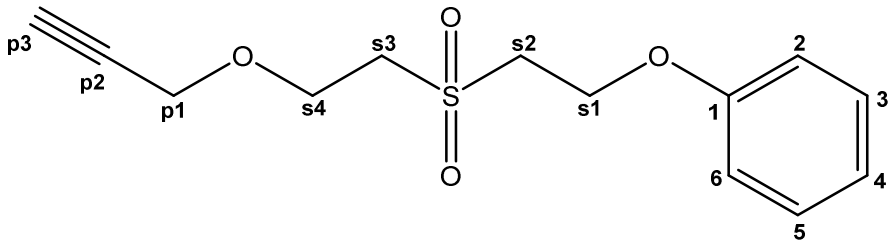
Monoadduct: (Phenyl-2-ethoxy)vinylsulfone, $C_{10}H_{12}O_3S$, [212.26].

Yield: 124.0 mg (5.842 mmol, 40.8 % o.th.), white solid.

^{1}H-NMR (300 MHz, $CDCl_3$,) δ: 7.31 (t, 2H, $^{3}J_{HH}$ = 8.07, $^{3}J_{HH}$ = 7.74, C$H^{3,5}$), 7.01 (t, 1H, $^{3}J_{HH}$ = 7.40, CH^{4}), 6.89 (d, 2H, $^{3}J_{HH}$ = 7.74, C$H^{2,6}$), 6.77 (dd, 1H, $^{3}J_{HH(z)}$= 9.75, $^{3}J_{HH(E)}$= 16.5, CH^{s3}), 6.45 (d, 1H, $^{3}J_{HH}$ = 16.5, C$H_2^{s4(Z)}$), 6.15 (d, 1H, $^{3}J_{HH}$ = 9.75, C$H_2^{s4(E)}$), 4.40 (t, 2H, $^{3}J_{HH}$ = 5.69, CH_2^{s1}), 3.47 (t, 2H, $^{3}J_{HH}$ = 5.69, CH_2^{s2}).

^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$,) δ: 157.70 (1C, C^{1}), 137.50 (1C, C^{s3}), 129.85 (2C, $C^{3,5}$), 129.71 (1C, C^{s4}), 121.99 (2C, C^{4}), 114.66 (2C, $C^{2,6}$), 61.80 (1C, C^{s1}), 54.92 (1C, C^{s2}).

5.3.2.6 (Phenyl-2-ethoxy)propargylsulfone (8)



A vial equipped with a magnetic stirrer bar was charged with propargyl alcohol (41.57 mg, 0.742 mmol, 1.27 eq.), DMAP (7.31 mg, 0.060 mmol, 0.10 eq.) and 2 mL DCM. Subsequently, **7** (124.00 mg, 0.584 mmol, 1 eq.) was added. The resulting mixture was stirred at room temperature. After 73 h residual **7** was observed via ^{1}H-NMR spectroscopy and therefore the mixture was reduced to 1/3 of the volume and further propargyl alcohol (0.04 ml, 37.96 mg, 0.677 mmol, 1.16 eq.) was added. After 96 h 30min the reaction mixture was diluted with 5 % $HCl_{aq.}$ in order to stop the reaction. A composition of 30.4 % dipropargylsulfone, 60.9 % (phenyl-2-ethoxy)propargylsulfone and 8.7 % (phenyl-2-ethoxy)vinylsulfone was detected by ^{1}H-NMR spectroscopy in $CDCl_3$. The crude product was purified by flash column chromatography (Silica Gel 60, CH/EA = 10:1) and the purification was monitored via TLC (CH/EA = 2:1 (v/v), 254 nm, Seebach dipping solution). The purification afforded a colourless oil (sampling of fractions with R_f = 0.32), containing approximately 7 % phenol- and propargyldiadduct.

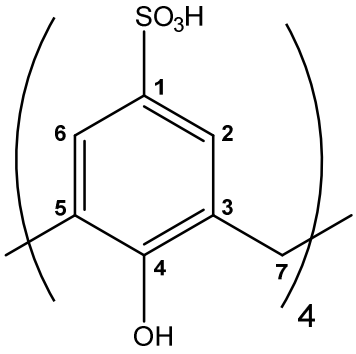
The product is characterized by:

Mixed adduct: (Phenyl-2-ethoxy)propargylsulfone, $C_{12}H_{24}O_4S$, [284.11]

^{1}H-NMR (300 MHz, $CDCl_3$,) δ: 7.31 (t, 2H, $^{3}J_{HH}$ = 7.99 Hz, C$H^{3,5}$), 7.00 (t, 1H, $^{3}J_{HH}$ = 7.32 Hz, CH^{4}), 6.92 (d, 2H, $^{3}J_{HH}$ = 7.99 Hz, C$H^{2,6}$), 4.44 (t, 2H, $^{3}J_{HH}$ = 5.80 Hz, CH_2^{s1}), 4.20 (d, 2H, $^{3}J_{HH}$ = 2.26 Hz, CH_2^{p1}), 4.02 (t, 2H, $^{3}J_{HH}$ = 5.64 Hz, CH_2^{s4}), 3.55 (t, 2H, $^{3}J_{HH}$ = 5.77 Hz, CH_2^{s2}), 3.42 (t, 2H, $^{3}J_{HH}$ = 5.61 Hz, CH_2^{s3}), 2.48 (t, 1H, $^{4}J_{HH}$ = 2.21 Hz, CH^{p3}).

$^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$,) *δ:* 157.81 (1C, C^1), 129.82 (2C, $C^{3,5}$), 121.95 (1C, C^4), 114.80 (2C, $C^{2,6}$), 78.70 (1C, C^{p2}), 75.66 (1C, C^{p3}), 63.45 (1C, C^{s4}), 61.83 (1C, C^{s1}), 58.65 (1C, C^{p1}), 55.09 (1C, C^{s3}), 54.63 (1C, C^{s2}).

5.3.3 5,11,17,23-Tetrasulfonic acid-calix[4]arene (9)



A round bottom flask equipped with a magnetic stirrer bar, a reflux condenser and a drying tube was charged with sulfuric acid (20 mL, 95 %). *p-tert*-Butylcalix[4]arene (5.0102 g, 7.72 mmol) was added portion wise under stirring. The formed suspension which is formed was heated to 82 °C for the duration of 39 h. Then, heating and stirring were stopped and the mixture was allowed to cool down to room temperature. The precipitate was recovered by filtration through a glass frit (porosity 3). The brown pasty solid on the frit was washed with ice-cooled ethanol (3 x 25 mL). Subsequently, the remaining residue was dissolved in 100 mL methanol. The obtained solution was treated with charcoal (1.0190 g), filtered on Celite and added to 500 mL ethyl acetate under stirring. The resulting precipitate was recovered by filtration through a glass frit (porosity 3) and dried under reduced pressure.

Yield: 3.0640 g (4.114 mmol, 53.7% o.th., Lit. 87 %[71]), grey-brownish solid.

$C_{28}H_{24}O_{16}S_4$, [744.74]

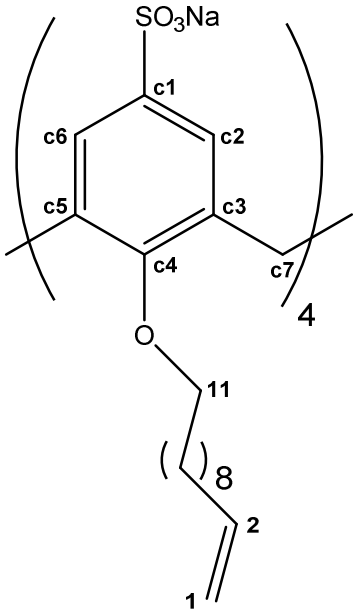
^{1}H-NMR (300 MHz, D_2O) *δ:* 4.40 (s, 8H, Ar-CH_2^7-Ar), 7.95 (s, 8H, Ar-$H^{2,6}$).[73]

$^{13}C\{^{1}H\}$-NMR (75 MHz, D_2O) *δ:* 32.13 (1C, Ar-C^7-Ar), 128.15 (2C, Ar-$C^{2,6}$), 129.82 (2C, Ar-$C^{3,5}$), 137.57 and 153.09 (2C, C^4-OH and C^1-SO_3H).[73]

ATR-IR $\tilde{\nu}$: 3224 (b) (O-H); 1595 (w) (C=C); 1454 (m), 1365 (w) (C-H); 1269 (m) (O-H); 1157 (s) (S=O); 1119 (s) (Ar-O); 1030 (s) (S=O); 810 (w), 786 (m) (Ar-H).

[73] Spectrum was referenced to the methyl group of the remaining ethanol (^{1}H-NMR: 1.17 ppm, ^{13}C-NMR: 17.47 ppm) according to *Journal of Organic Chem*istry, **1997**, *62*, 21, 7513-7514.

5.3.4 5,11,17,23-Tetrasulfonato-25,26,27,28-tetra(undec-1-ene-11-oxy)-calix[4]arene (10)



A round bottom flask equipped with a magnetic stirrer bar was charged with finely crushed sodium hydroxide and DMSO and subsequently, **9** was added. 11-Bromo-1-undecene was added in 3 portions while the mixture was stirred at 50 °C (oil bath temperature) for 24 h. After cooling, the reaction mixture was diluted with methanol and placed in the freeze (-18 °C) in order to promote precipitation. The solid was recovered by filtration through a glass frit (porosity 3) and afterwards dissolved in $H_2O_{deion.}$. The insoluble material was recovered by filtration again through a glass frit (porosity 3). The remaining residue was washed with *n*-pentane und dried under reduced pressure. The desired product was detected via ^{1}H-NMR spectroscopy and contains not removable amounts of alkylating agent and its hydrolysis product.

m_p > 360 °C

The product is characterized by:

$C_{72}H_{100}Na_4O_{16}S_4$, [1441.78], beige solid.

^{1}H-NMR (500 MHz, DMSO-d_6) *δ:* 1.25-1.37 (m, 48H, CH_2^{4-9}), 1.96 (m, 8H, CH_2^{10}), 2.00 (q, 4H, $^3J_{HH}$ = 6.95, CH_2^3), 3.24 (d, 4H, $^3J_{HH}$ = 12.4, Ar-CH_2^{c7}-Ar), 3.87 (t, 8H, CH_2^{11}), 4.34 (d, 4H, $^3J_{HH}$ = 12.5, Ar-CH_2^{c7}-Ar), 4.95 (dd, 8H, $^3J_{HH(Z)}$ = 10.2, $^3J_{HH(E)}$ = 17.1, CH_2^1), 5.77 (dquint, 4H, $^3J_{HH}$ = 10.2, $^3J_{HH}$ = 16.9, $^3J_{HH}$ = 6.67, CH^2), 7.11 (s, 8H, Ar-H^{c2,c6}).

^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6) *δ*: 25.86-29.73 (28C, C^{4-10}), 30.60 (4C, Ar-C^{c7}-Ar), 33.21 (4C, C^3), 75.00 (4C, C^{11}), 114.51 (4C, C^1), 125.88 (8C, Ar-$C^{c2,c6}$), 133.21 (8C, Ar-$C^{c3,c5}$), 138.60 (4C, C^2), 141.56 (4C, Ar-C^{c1}), 156.35 (4C, Ar-C^{c4}).

ATR-IR $\tilde{\nu}$: 3428 (b) (O-H); 1639 (m), 1588 (w) (C=C, aromatic ring); 1461 (m), 1382 (w) (C-H, aliphatic and aromatic), 1262 (m) (O-H), 1183 (s) (S=O), 1120 (s) (Ar-O), 1049 (s) (S=O).

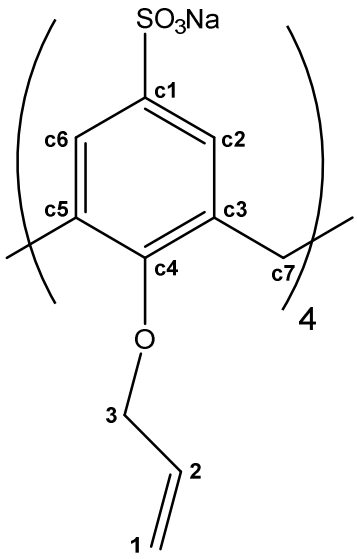
HR-MS (ESI, negative mode) (*m/z*): $[M-4Na+3H]^-$ calculated: 1351.6129, found: 1351.6124, $[M-4Na+2H]^{2-}$ calculated: 675.3025, found: 675.3029.

Table 11. Used quantities of reagents for *O*-alkylations of **9**

Entry	Compound 9 (g)	11-Bromo-1-undecene (eq.[a])	NaOH (eq.[a])	DMSO (mL)	Yield (%)[b]
1	0.1009	32.2	30.5	5	83.2
2	0.1011	32.4	31.5	5	80.2
3	0.1017	34.6	30.3	5	81.6
4	1.2910	15.6	30.4	25	73.4
5	1.2831	15.9	30.1	50	78.3
6	0.9941	15.4	16.5	25	66.8

[a] With respect to 5,11,17,23-tetrasulfonic acid-calix[4]arene (**9**). [b] o.th.

5.3.5 5,11,17,23-Tetrasulfonato-25,26,27,28-tetra(prop-1-ene-3-oxy)-calix[4]arene (11)



A round bottom flask equipped with a magnetic stirrer bar was charged with finely crushed sodium hydroxide (1.58580 g, 39.6 mmol, 29.5 eq.) and 40 mL DMSO. Subsequently, **9** (0.9996 g, 1.342 mmol, 1.00 eq.) was added. Allyl bromide (5.15 g, 3.7 mL, 40.1 mmol, 31.4 eq., 99 %) was added in 3 portions. The mixture was stirred at 50 °C (oil bath temperature) for 24 h. After cooling, the insoluble material was removed by filtration. The filtrate was diluted with methanol and placed in the freezer (-18 °C) in order to promote

precipitation. The solid was recovered by filtration through a filter paper, washed with ethanol und dried under reduced pressure. The desired product was detected via ^{1}H-NMR spectroscopy.

Yield: 0.26214 g (0.264 mmol, 19.7% o.th.), white solid.

$C_{40}H_{36}Na_4O_{16}S_4$, [992.91]

^{1}H-NMR (500 MHz, D_2O) *δ:* 3.47 (d, 4H, $^{3}J_{HH}$ = 13.2, Ar-CH_2^{c7}-Ar), 4.55 (d, 4H, $^{3}J_{HH}$ = 13.2, Ar-CH_2^{c7}-Ar), 4.68 (d, 8H, $^{3}J_{HH}$ = 6.7, CH_2^{3}), 5.34 (dd, 8H, $^{3}J_{HH(Z)}$ = 10.1, $^{3}J_{HH(E)}$ = 17.2, CH_2^{1}), 6.46 (dquint, 4H, $^{3}J_{HH}$ = 10.3, $^{3}J_{HH}$ = 17.1, CH^{2}), 7.37 (s, 8H, Ar-H^{c2,c6}).

^{13}C{^{1}H}-NMR (75 MHz, D_2O) *δ*: 31.92 (4C, Ar-C^{c7}-Ar), 76.73 (4C, C^{3}), 119.29 (4C, C^{1}), 126.43 (8C, Ar-$C^{c2,c6}$), 135.62 (8C, Ar-$C^{c3,c5}$), 136.00 (4C, C^{2}), 137.71 (4C, Ar-C^{c1}), 158.62 (4C, Ar-C^{c4}).[74]

ATR-IR $\tilde{\nu}$ (cm^{-1}): 3447 (b) (O-H); 1646 (m), 1590 (w) (C=C, aromatic ring); 1463 (m), 1420 (w) (C-H, aliphatic and aromatic), 1263 (m) (O-H), 1189 (s) (S=O), 1122 (s) (Ar-O), 1053 (s) (S=O).

5.3.6 Preparation of PolyHIPEs

A vial equipped with a magnetic stirrer bar was charged with dicyclopentadiene (2.003 g, 15.15 mmol), 100 µL toluene, Span 80® (98.4 mg) and **10** (49.2 mg) and mixed. $H_2O_{deion.}$ (8.000g) was added drop wise under vigorous stirring in order to achieve a highly viscous emulsion, which has further been shaken by hand. The initiator Umicore M2 (0.96 mg) was dissolved in 100 µL toluene, added to the created HIPE and the emulsion was briefly mixed. Afterwards the emulsion was transferred quickly into the required molds and placed into the drying cabinet (80 °C) for a 2 h. The removal from the molds afforded the desired polyHIPEs, which were further dried for approximately 24 h at 40 °C.

[74] Spectrum was referenced to the methyl group of the remaining dimethyl sulfone (^{13}C-NMR: 39.39 ppm) according to *Journal of Organic Chem*istry, **1997**, *62*, 21, 7513-7514.

6 Appendix

6.1 Abbreviations

aq.	aqueous
AR	aryl residue
asym.	asymmetrical
ATR-IR	attenuated total reflection infrared spectroscopy
^{t}BuOH	tertiary butanol
CH	cyclohexane
conc.	concentrated
d	doublet
DCM	dichloromethane
DCPD	dicyclopentadiene
dd	doublet of doublet
deion.	deionized
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
dquint	doublet of quintet
DVS	divinyl sulfone
e.g.	*exempli gratia* (for example)
EA	ethyl acetate
EDX	energy dispersive X-ray spectroscopy
eq.	equivalent
ESI	electrospray ionization
et al.	*et alii* (and co-workers)
Et_2O	diethylether
Et_3N	triethylamine
EtOH	ethanol

EWG	electron withdrawing group
FT	Fourier Transform
HIPE	high internal phase emulsion
HLB	hydrophobic-lipophilic balance
HR-MS	high resolution mass spectrometry
i.e.	*id est* (that is to say)
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
KO^{t}Bu	potassium tertiary-butoxide
lit.	literature
m	multiplet
m/z	mass/charge ration
MeCN	acetonitrile
MeOH	methanol
mp	melting point
N	normale
n	linear
n.e.	not evaluated
NMR	nuclear magnetic resonance spectroscopy
(n/n)	mole/mole
o	*ortho*-position
o.th.	of theory
p	*para*-position
Ph	phenyl residue
pK_a	negative decimal logarithm of the acidic constant
PPh_3	triphenylphosphine
ppm	parts per million
R	organic residue
R_f	retention factor

RT	room temperature
s	singlet
SEM	scanning electron microscopy
sym.	symmetrical
t	triplet
tert (t)	tertiary
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	tetramethylsilane
UV	ultraviolet
$\tilde{\nu}$	wave number
viz	*videlicet* (that is, namely)
(v/v)	volume/volume
X	halide
δ	chemical shift

6.2 Model Reaction Data

6.2.1 Solvent Scope

Table 12. Influence of the solvent on the oxa-Michael addition of phenol to divinyl sulfone in the presence of Cs_2CO_3 (1 eq. with respect to DVS)

Entry	Solvent	Time (h)	Ratio (%)[a]			By-products[b]
			DVS	Monoadduct	Diadduct	
1	^{t}BuOH	2	< 0.1	13.7	86.3	n.e.
		24	< 0.1	16.7	83.3	-
2	CH_2Cl_2	2	67.5	31.0	1.5	n.e.
		24	14.4	46.0	39.6	+
3	THF	2	23.1	48.7	28.2	n.e.
		24	18.9	54.6	26.5	-
4	MeOH	2	No quantitative determination.			
		24				
5	H_2O	2	28.4	68.9	2.8	n.e.
		24	< 0.1	67.2	32.8	-

[a] Remaining DVS and its conversion towards the mono- and diaddition products were determined by ^{1}H-NMR spectroscopy. [b] Determination by ^{1}H-NMR spectroscopy in the range of 3 – 4.8 ppm; integral ratio by-product/(mono+di)product. Evaluation key: n.e. (not evaluated), + (< 3 %), +/- (3 – 5 %), - (> 5 %).

6.2.2 Base Scope

Table 13. Influence of the base (1 eq. with respect to DVS) on the oxa-Michael addition of phenol to divinyl sulfone in ^{t}BuOH

Entry	Base	Time (h)	Ratio (%)[a]			By-products[b]
			DVS	Monoadduct	Diadduct	
1	Cs_2CO_3	0.5	< 0.1	33.0	67.0	n.e.
		1	< 0.1	14.9	85.1	n.e.
		2	< 0.1	13.7	86.3	n.e.
		24	< 0.1	16.7	83.3	-
2	K_2CO_3	0.5	59.8	38.4	1.8	n.e.
		1	55.7	40.8	3.5	n.e.
		2	11.0	71.1	17.9	n.e.
		24	< 0.1	3.5	96.5	+/-
3	$KO^{t}Bu$	0.5	6.5	30.2	63.3	n.e.
		1	3.8	18.4	77.8	n.e.
		2	3.02	16.2	80.6	n.e.
		24	< 0.1	14.4	85.6	-

[a] Remaining DVS and its conversion towards the mono- and diaddition products were determined by ^{1}H-NMR spectroscopy. [b] Determination by ^{1}H-NMR spectroscopy in the range of 3 – 4.8 ppm; integral ratio by-product/(mono+di)product. Evaluation key: n.e. (not evaluated), + (< 3 %), +/- (3 – 5 %), - (> 5 %).

6.2.3 Base Load Scope

Table 14. Influence of the base load on the oxa-Michael addition of phenol to divinyl sulfone in ^{t}BuOH

Entry	Base	(eq.)	Time (h)	Ratio (%)[a]			By-products[b]
				DVS	Monoadduct	Diadduct	
1	Cs_2CO_3	1	0.5	< 0.1	33.0	67.0	n.e.
			1	< 0.1	14.9	85.1	n.e.
			2	< 0.1	13.7	86.3	n.e.
			24	< 0.1	16.7	83.3	-
2	KO^{t}Bu	1	0.5	6.5	30.2	63.3	n.e.
			1	3.8	18.4	77.8	n.e.
			2	3.02	16.2	80.6	n.e.
			24	< 0.1	14.4	85.6	-
3	Cs_2CO_3	0.1	0.5	84.9	15.1	< 0.1	n.e.
			1	69.7	22.1	8.2	n.e.
			2	48.8	48.2	3.0	n.e.
			24	< 0.1	9.4	90.6	+/-
4	KO^{t}Bu	0.1	0.5	55.8	42.6	1.7	n.e.
			1	53.3	43.7	3.0	n.e.
			2	25.7	63.1	11.2	n.e.
			24	< 0.1	< 1	> 99	+/-

[a] Remaining DVS and its conversion towards the mono- and diaddition products were determined by 1H-NMR spectroscopy. [b] Determination by 1H-NMR spectroscopy in the range of 3 – 4.8 ppm; integral ratio by-product/(mono+di)product. Evaluation key: n.e. (not evaluated), + (< 3 %), +/- (3 – 5 %), - (> 5 %).

6.2.4 Substrate Scope

Table 15. Oxa-Michael addition of various substrates (3 eq. with respect to DVS) to divinyl sulfone in the presence of KO^{t}Bu (0.1 eq. with respect to DVS) and in ^{t}BuOH

Entry	Substrate	Time (h)	Ratio (%)[a]			By-products[b]
			DVS	Monoadduct	Diadduct	
1	2-Methoxy-5-nitro-phenol	0.5[c]	No quantitative determination.			
		1[c]				
		2[c]				
		24[c]				
2	2,4-Dinitrophenol	0.5[d]	No quantitative determination.			
		1[d]				
		2[d]				
		24[d]	95.7	4.3	0.0	-
3	2-Propenylphenol	0.5[e]	No quantitative determination.			
		1[e]				
		2[e]				
		24[e]				
4	2-Hydroxy-acetophenon	0.5	>99	< 1	0.0	n.e.
		1	>99	< 1	0.0	n.e.
		2	98.2	1.8	0.0	n.e.
		24	90.8	9.2	0.0	-
5	Benzyl alcohol	0.5	0.0	2.2	97.8	n.e.
		1	0.0	3.7	96.3	n.e.
		2	0.0	4.0	96.0	n.e.
		24	0.0	14.1	85.9	-

[a] Remaining DVS and its conversion towards the mono- and diaddition products were determined by ^{1}H-NMR spectroscopy. [b] Determination by ^{1}H-NMR spectroscopy in the range of 4.8 - 3 ppm; integral ratio by-product/(mono+di)product. Evaluation key: n.e. (not evaluated), + (< 3 %), +/- (3 – 5 %), - (> 5 %).[c] Only formation of by-products observed. DVS is nearly converted totally within 2 h but is released again after 24 h reaction time. [d] Hardly any conversion observed, but large amount of remaining educts. [e] Qualitative statement: conversion observed.

6.2.5 Base and Nucleophilic Promotion

Table 16. Base-catalysis *vs.* nucleophilic mediation of the oxa-Michael addition of phenol to divinyl sulfone in ^{t}BuOH (0.1 eq. base resp. nucleophile with respect to DVS)

Entry	Base/Nucleophile	Time (h)	Ratio (%)[a]			By-products[b]
			DVS	Monoadduct	Diadduct	
1	KO^{t}Bu	0.5	55.8	42.6	1.7	n.e.
		1	53.3	43.7	3.0	n.e.
		2	25.7	63.1	11.2	n.e.
		24	< 0.1	< 1	> 99	+/-
2	DMAP	0.5	3.3	93.9	2.8	n.e.
		1	5.2	92.1	2.6	n.e.
		2	37.8	60.5	1.7	n.e.
		24	2.1	68.8	29.9	+
3	PPh_3	0.5[c]	No quantitative determination.			
		1[c]				
		2[c]				
		24	3.7	46.7	49.6	-

[a] Remaining DVS and its conversion towards the mono- and diaddition products were determined by 1H-NMR spectroscopy. [b] Determination by 1H-NMR spectroscopy in the range of 3 – 4.8 ppm; integral ratio by-product/(mono+di)product. Evaluation key: n.e. (not evaluated), + (< 3 %), +/- (3 – 5 %), - (> 5 %). [c] Qualitative statement: conversion observed.

6.3 Indices

6.3.1 Index of Figures

6.3.2 Index of Tables

6.3.3 Index of Schemes