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# Green Synthesis of Oligomer Calixarenes

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Additional information is available at the end of the chapter

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## Abstract

The synthesis of calixarenes can be conventionally done by heating at high temperature for a few hours and using various solvents in large quantities. The greener synthesis can be done with microwave-assisted synthesis and the solvent-free method, where both of these methods can reduce reaction time, energy use, solvent, and waste, with a higher percentage yield than that from the conventional synthesis method, making the synthesis of cyclic oligomer calixarenes and their derivatives more environmentally friendly.

**Keywords:** calixarenes, cyclic oligomer, green synthesis, microwave, solvent-free

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## 1. Introduction

A calixarene is a cup-shaped supramolecule. The name is derived from the word “calix,” which means a cup. Synthesis of calixarenes becomes very important because these molecules are widely used in various fields, especially in its use in a guest-host system molecule. The molecule was first reported in 1872 by Baeyer as a reaction product of aldehyde-phenol condensation. The same product can also be formed from benzaldehyde-pyrogallol (benzene-1,2,3-triol) condensation reaction. The structure of phenols used in this reaction has reactivity at ortho and para positions so that it can form a polymer cross-linked at three positions (two orthos and one para). In 1942, Zinke and Ziegler used para-substituted phenols so that the phenols could only react at the two ortho positions, thereby reducing the possibility of cross-link formation. By reacting *p*-*tert*-butylphenol with formaldehyde under a basic condition at 100–220°C, a waxy brown paste was produced, which was then recrystallized and formed a crystal decomposed at above 300°C. The results of the analysis showed that the product had a molecular weight that was in agreement with a cyclic tetrameric structure [1]. Similarly, Cornforth reacted *p*-*tert*-butylphenol

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with formaldehyde. However, the reaction resulted in two crystal products that were rather soluble in water with high but nonidentical melting points. Likewise, when *p*-*tert*-butylphenol was replaced with *p*-1,1,3,3-tetramethylbutylphenol, two products with different melting points were obtained. The results of X-ray showed that the four condensation products had a cyclic tetrameric structure. The different melting points, according to Cornforth, indicated that the two compounds are diastereoisomers [1, 2].

Calixarene synthesis can be done through a noncomplicated process. The compound group is commonly synthesized from 4-alkylphenol, especially 4-*t*-butylphenol, through a one-stage reaction with formaldehyde and NaOH or KOH as the base. The making of calixarenes, known as a base-induced process, results in calixarenes that may vary in their aromatic components. The reaction product between phenols or phenol derivatives and aldehydes is also known as calixarene, while the reaction product between resorcinol or resorcinol derivatives and aldehydes is known as calixresorcinarene. In addition, there are several products that use aromatic compounds in the forms of para-alkoxy-substituted benzyl alcohol derivatives, such as *p*-alkoxybenzyl alcohol, that when reacted with the aid of  $\text{AlCl}_3$  as a catalyst will result in non-hydroxylated calixarenes [3]. In general, these reactions are illustrated in **Figure 1**.

The basic structure of calixarenes consists of phenolic units or phenolic derivatives which are repeated and interconnected with Ar-C-Ar bridge to form a hollow cycle. The part with a broader hollow side is called the upper rim, and the narrow hollow part is called the "lower rim" as shown in **Figure 2** [4, 5].

The various conformations of calixarenes are caused by the free rotation of sigma bonds at methylene, Ar-C-Ar, bridges [6]. For example, calix[4]resorcinarenes have four prochiral centers on carbon atoms at the methylene bridges, causing the compound to form four different diastereoisomers. The relative configurations of the four R substituents at the methylene bridges can form a cis for all R substituents (rccc) or a cis-cis-trans to one R (rcct), cis-trans-trans (rctt), and trans-cis-trans (rtct). The configurations are determined based on their configurations to one of the R substituents on the prochiral center in a clockwise direction [4, 7, 8]. **Figure 3** illustrates the relative configurations of the four R substituents.

In reality, the cyclic tetrameric ring of a calixarene is not a planar molecule and can adopt five conformations, namely, "crown" or  $C_{4v}$ , "boat" or  $C_{2v}$ , "chair" or  $C_{2h}$ , "diamond" or  $C_s$ , and "saddle" or  $S_4$  [2, 8]. The five conformations of calixarene is shown in **Figure 4**. In fact, the rccc isomer where all R groups in the same position, so far only found with the macrocyclic ring adopted the "crown" or  $C_{4v}$  and "boat" or  $C_{2v}$  conformations. This is caused by the single bond with a tetrahedral shape of R groups so that it can rotate freely. The rccc isomers can form conformation "boat" or  $C_{2v}$  with the fourth R possesses an all axial and all-cis configuration, while the macrocyclic ring in a boat conformation. In this case, the fourth R leads into the annulus of the calixarene (endo). It was also reinforced by the result of a condensation reaction between resorcinol and 4-bromobenzaldehyde with an acid catalyst, where produced the rccc isomer of calix[4]resorcinarene in "boat" or  $C_{2v}$  conformation [7]. The rctt isomer is only found in "chair" or  $C_{2h}$  conformation. In the calculation of energy, the rccc isomer in the crown conformation ( $C_{4v}$ ) is favored over the rctt isomer in the chair conformation ( $C_{2h}$ ).

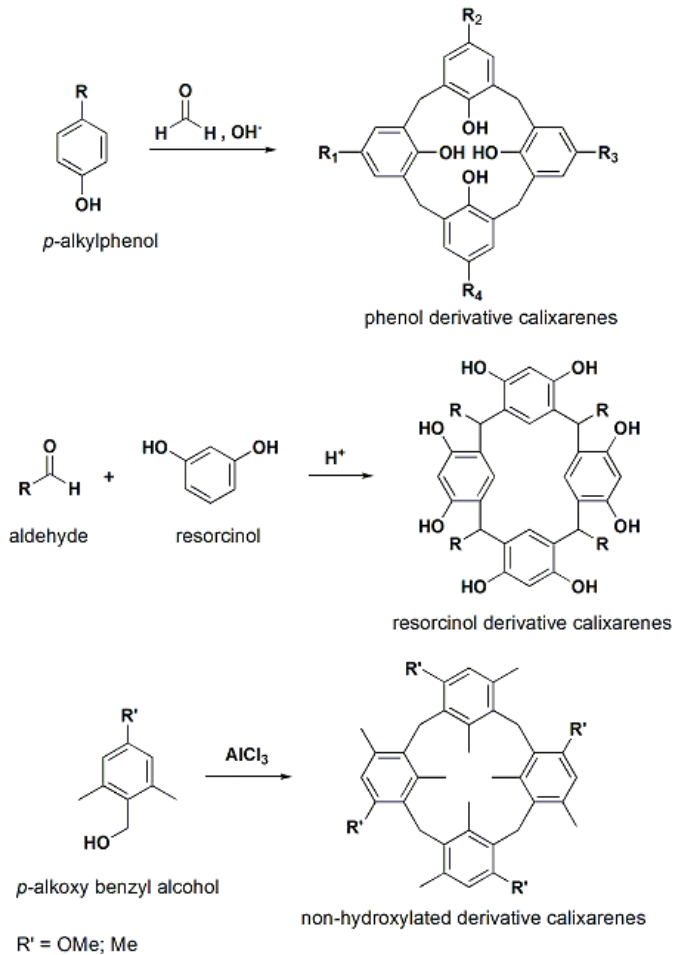


Figure 1. Basic synthesis of calixarene.

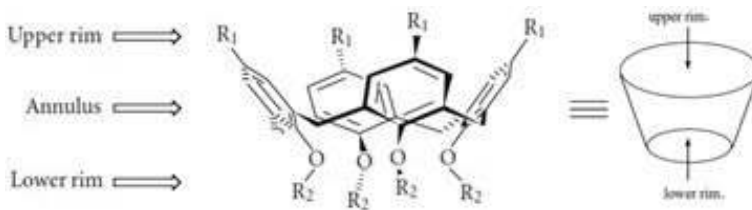


Figure 2. The “upper rim” and “lower rim” of calixarenes.

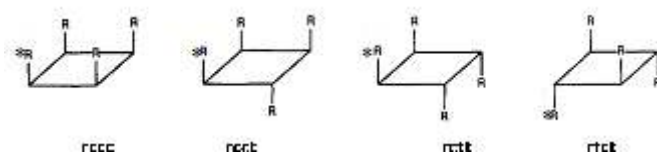


Figure 3. R relative configurations at the methylene bridge.

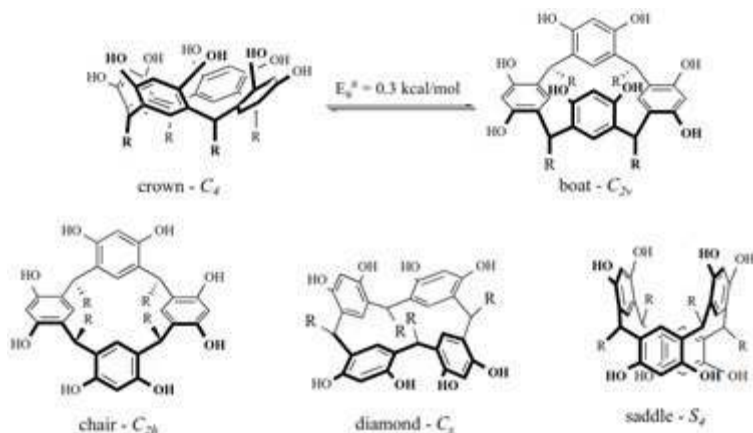
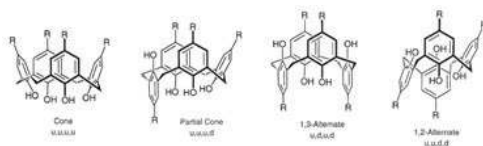


Figure 4. Calix[4]arene conformations.

Nevertheless, the rccc in boat conformation ( $C_{2v}$ ) has similar energy to the rctt in chair conformation [51]. The rcct isomer adopts the “diamond” or  $C_s$  conformation [4].

Based on the projection of aryl group on the cyclic tetramer structure of calixarenes, four different conformations can be formed depending on the forms of aryl cluster projection, which can be upward (u) or downward (d), relative to the plane. The four conformations are a cone, partial cone, 1,2-alternate, and 1,3-alternate conformations (Figure 5), each with different thermodynamic stabilities [1, 5].

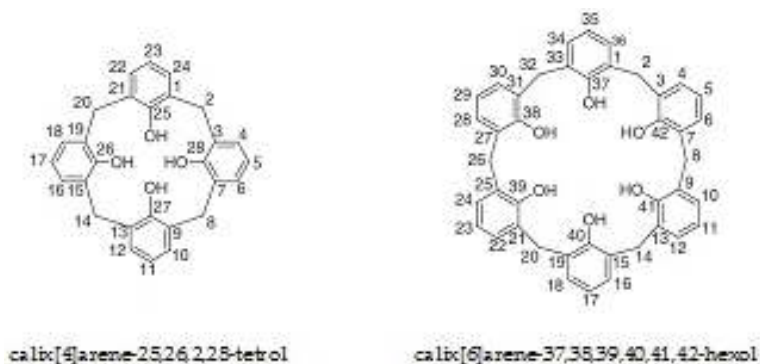
In their development, calixarenes have been successfully synthesized not only in the form of the tetramer but also hexamer and octamer. Therefore, the naming of calixarenes is developed by inserting a number inside brackets, showing the number of monomers they possess. For instance, a calixarene containing eight monomers will be written as calix[8]arene. Furthermore, to show the types of phenol used in the synthesis, para substituents are also included in the name. The cyclic hexamer of *p*-*tert*-butylphenol, for example, is named *p*-*tert*-butylcalix[6]arene. For resorcinol-derived calixarenes, the name is calix[n]resorcinarene, while the substituents of the methylene carbon are shown by the prefix of “C-substituent.” For example, the reaction yield of resorcinol with acetaldehyde is named C-methylcalix[4]resorcinarene, indicating the presence of methyl substituents in the methylene carbon. For a more systematic



**Figure 5.** Conformation based on the projection of aryl group in tetramer structure of calixarenes.

naming, especially for scientific publication, the basic name of calix[n]arene is maintained, whereas the substituent identity is shown based on its position through the number, such as shown in **Figure 6** [9].

Calixarenes have been broadly used, among others, as liquid crystal materials [10–12], sensors [13, 14], catalysts [15, 16], the stationary phase of chromatography [17], host molecules [18–25], or even semiconductors [26]. As a role in the guest-host system molecule, calix[4]arene and 4-*tert*-butylcalix[6]arene can be the host molecules for compounds such as trifluoromethyl-benzene contained in pesticides [24]. In addition, some calixarene derivatives can also be the host for the dye molecules such as orange I (OI), methylene blue (MB), neutral red (NR), and brilliant green (BG) [18]. This finding makes calixarenes as a promising candidate as a host molecule to be used in chemical sensors to measure neutral organic molecules. In addition to being the host molecules for neutral compounds, calixarene and its derivatives were also proven to be a host for the molecular ion compounds such as heavy metal ions [19, 20]. It is no wonder that calix[n]arenes have been greatly synthesized and yielded various oligomers with  $n = 4–20$  according to their purposes. Various modifications of functional clusters have also been developed in order to yield the desired molecular structures, for example, the modification of the aryl group [27] or the aldehyde. The modification can be in the form of the addition of a functional cluster such as alkyl cluster and hydroxyl cluster or the elimination of a functional cluster in the starting materials used or further modification of the calixarene molecules formed [19]. Some of the modifications make the calixarene structure more rigid,



**Figure 6.** Calixarene numbering system.

thereby forming the expected conformations [28]. To cite an example, the addition of ketone group into aryl group was done to increase the affinity of calixarene compound to the complex formation of alkali cation [29]. The modification can also be made by adjusting the hollow size formed in calix[n]arenes to match the size of a certain molecule both by modifying the functional cluster and adding other components [2, 30].

## 2. Synthesis of oligomer calixarenes

### 2.1. Conventional synthesis procedures

Various calixarene synthesis procedures and their derivations have been largely developed, for example, the procedure developed by Zinke-Ziegler, where the synthesis of calixarene started by mixing *p*-*tert*-butylphenol, 37% formaldehyde, and NaOH heated at 50–55°C for 45 h. To remove water content, the reaction compound was reheated at 110–120°C for 2 h. In the purification process, the yellow solid yielded was subsequently heated in linseed oil up to 200°C for several hours, and the process yielded tetramers. The modification to this procedure was made by Cornforth by directly heating the reaction compound (*p*-*tert*-butylphenol, formaldehyde, and NaOH) at 110–120°C for 2 h, thereby yielding a very thick product which was then refluxed with diphenyl ether for 2 h. Once the compound was cold, the product was separated with infiltration and recrystallized to produce white crystals with a melting point of 342–344°C for 50%. The procedure was later on known as the Zinke-Cornforth procedure [1, 2, 31]. The condensation of *p*-*tert*-butylphenol with formaldehyde under basic conditions (NaOH, KOH) can yield cyclic tetramers, hexamers, and even octamers with a percentage of 85–63%. **Figure 7** illustrates the reaction mechanisms of calix[n]arene formation under basic conditions.

The right mechanism to transform linear oligomer into a cyclic oligomer, according to Gutsche [1], can be predicted from the formation of hemicalixarene combined with a pair of linear oligomers. Under appropriate conditions, two linear methyl-hydroxylated tetramers combine to form hemicalix[8]arene, followed by the release of water to form calix[8]arene [1]. This process can also be seen in the synthesis of *p*-chlorocalix[4]arene, which is a “2 + 2” condensation product of *p,p'*-dichlorodiphenylmethane, such as illustrated in **Figure 8**.

Similarly, calix[6]arene formation is postulated to be the result of a combination of two linear trimers. Based on this postulation, the form of dianion hemicalix[6]arene can be the cause of the large amounts of bases required for hemicalix[6]arene synthesis. The following reaction in **Figure 9**, for example, adopts a “3 + 3” condensation that involves two trimers to obtain 9% calix[6]arene [32].

Gutsche synthesized *p*-*tert*-butylcalix[4]arene with the Zinke-Cornforth procedure to see the effect of basic conditions on the cyclic oligomer produced. The yellow thick paste (“precursor”) formed after heating the compound for 1.5–2 h at 110–120°C was diluted with chloroform and washed with aqueous HCl and water several times to neutralize the base. The results of Gutsche’s research showed that when the precursor containing a base of 0.03–0.04

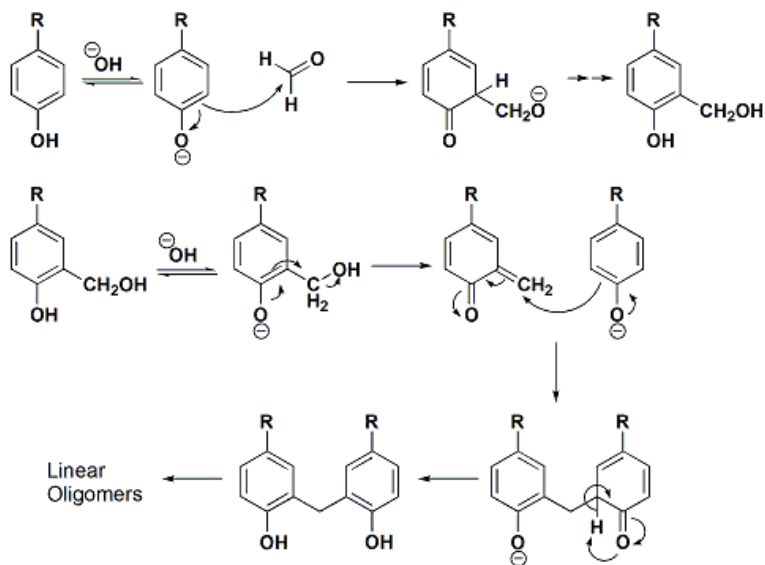


Figure 7. Reaction mechanisms of calix[n]arene formation under basic conditions.

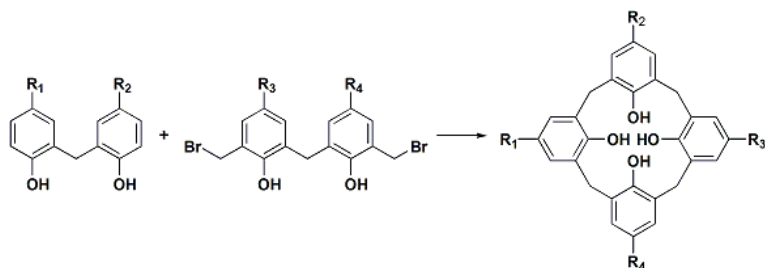


Figure 8. Cyclic tetramer formation through “2 + 2” condensation.

or equiv. (relative to the number of phenols used) was refluxed for 2 h, it could yield cyclic tetramers. However, the lower the concentration of the base used, the lower the cyclic tetramer formations; on the other hand, a higher concentration of the base will increase the formation of cyclic hexamers. The findings of this research showed that bases play a role in inducing cyclization and are vital in determining the cyclic oligomer formed [33, 34]. The cations used as the base catalyst can play the role of a “template” which determines the size or number of monomers forming oligomers.

A large cyclic oligomer enables the formation of a larger hollow, and this can be used to absorb heavy metals, as can be found in the synthesis of calix[6]arene involving *p*-*tert*-butylphenol, paraformaldehyde, and bases (KOH) with a proportion of 0.45 mole relative to the *p*-*tert*-butylphenol used. The reaction happened for 4 h by refluxing it in *p*-xylene. The compound

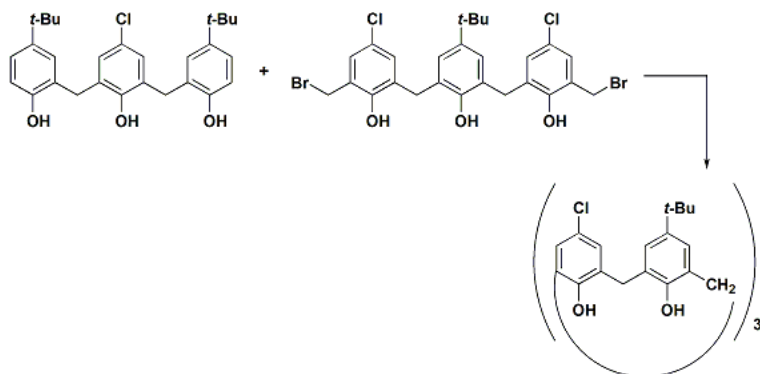


Figure 9. Cyclic hexamer formation through “3 + 3” condensation.

was separated with liquid-liquid extraction using chloroform. The organic phase obtained was then evaporated and recrystallized with methanol to yield 65.47% white solids with a melting point of 370–372°C. The analysis of the product showed that it is a cyclic hexamer of calix[6]arene [35].

Condensation of resorcinol with formaldehyde under acidic conditions formed a linear or cross-linked polymer between formaldehyde with resorcinol. This reaction also did not produce calixresorcinarene under alkaline conditions. It is not surprising since resorcinol and formaldehyde are highly reactive so that the reaction becomes uncontrollable and does not produce a cyclic oligomer. Base conditions can be applied to the synthesis of calixresorcinarene from 2-substituted resorcinols and formaldehyde. Nevertheless, resorcinol used should be substituted with an electron-withdrawing group at position 2 as shown in Figure 10. Electron-withdrawing group at position 2 will reduce the reactivity of resorcinol

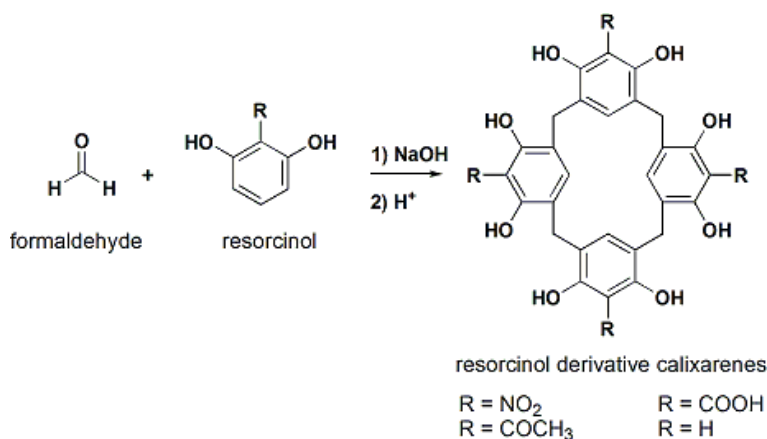


Figure 10. Synthesis of resorcinarenes from 2-substituted resorcinols and formaldehyde in basic conditions.



so that the reaction will be controlled and it will be suitably carried out under alkaline conditions. The presence of electron-withdrawing substituents such as nitro group ( $-\text{NO}_2$ ) facilitates condensation reactions that occur by directing the reaction site at the meta position of the nitro group. The reaction rate decreased from electron-withdrawing substituent nitro > acetyl > carboxylate > H due to the ability of the groups to deactivate the resorcinol. In contrast, the reaction of resorcinol substituted electron-donating group such as 2-methylresorcinol or phloroglucinol (=benzene-1,3,5-triol) with formaldehyde under base conditions did not produce a derivative of calixresorcinarene. Therefore, the acidic conditions are more suitable when used resorcinol substituted electron-donating group in position 2. The condensation reaction between formaldehyde and 2-nitroresorcinol and its analogs seems to take place in the irreversible reaction, so it is unknown whether to form a tetramer, pentamer, or hexamer [36].

Besides adding bases, the synthesis of calix[n]arenes can also be done under acidic conditions. One such example is found in the procedure of calix[n]resorcinarene synthesis developed by Niederl-Hogberg, in which resorcinol was used as an aromatic unit in the reaction. Resorcinol is more reactive compared to phenol. Resorcinol was reacted with acetaldehyde by adding hydrochloric acid. The reaction took place at  $80^\circ\text{C}$  for 16 h and yielded C-methylcalix[4]resorcinarenes for 75%. The reaction follows the following mechanism which is illustrated in Figure 11.

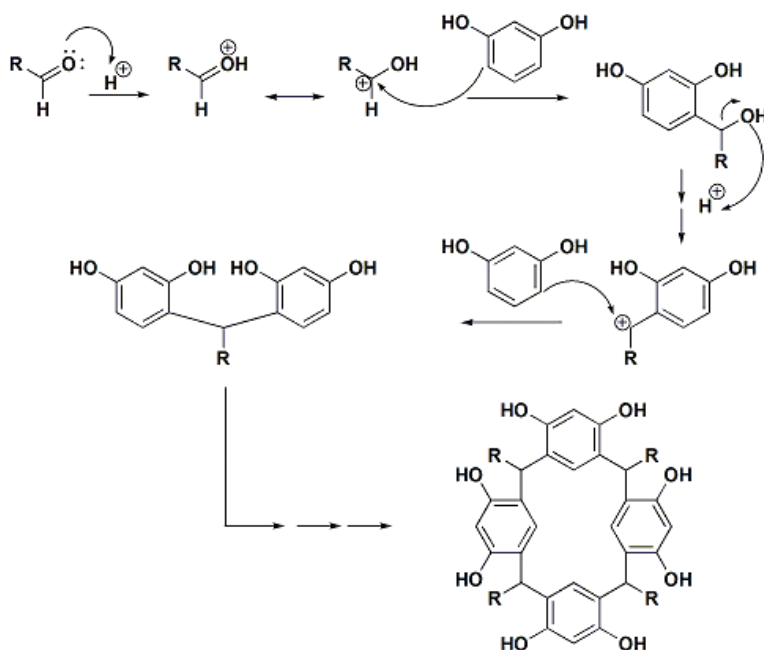


Figure 11. Reaction mechanism of calix[n]resorcinarene formation under acidic conditions.

In the condensation reaction catalyzed by acids, kinetic and thermodynamic factors compete with each other. The kinetic factor controls the oligomer rate produced, while the thermodynamic factor controls the cyclic structure formation. In this reaction, controlling the thermodynamic factor will be very determining for the formation of a small cyclic oligomer, such as the formation of calix[4]resorcinarene. To control the thermodynamic factor, less reactive aldehydes can be used to slow down the reaction rate. If the aldehyde used is very reactive (such as formaldehyde), the reaction will happen very quickly so that the kinetic factor will dominate and the majority of the products formed will be polymers with linear chains. A modified aldehyde was used in the synthesis reaction of methoxyphenylcalix[4]resorcinarene from resorcinol with *p*-anisaldehyde with the addition of HCl. The reaction happened employing reflux for 30 h, yielding 4-methoxyphenylcalix[4]resorcinarene as much as 91.54% [37].

The synthesis of calix[4]resorcinarene from resorcinol with acetaldehyde was done by Petrova et al. in 2012. The reaction was made by varying the amounts of hydrochloric acid used. The reaction occurred at 75°C for 5–24 h. The reaction product was dependent upon the amounts of hydrochloric acid used. Increasing the amount of acid can cause the formation of linear oligomers. The amount of acid catalyst effective in this reaction was 4% of the resorcinol. In addition, the polarity of the solvents used affected the composition of the yielded product. An increase in the polarity of the solvent caused an increase in the oligo cyclization. Calix[4]resorcinarene with rccc conformation was quantitatively formed very well (76.89%) when 30% water-ethanol solvent was used [38].

Calix[4]resorcinarenes synthesized through a condensation reaction between resorcinol and an aliphatic or aromatic aldehyde under acidic conditions yield products in the form of cyclic tetramer calixresorcinarenes that theoretically can contain four diastereoisomer products. However, in reality, only three have been identified to be formed by the reaction with an aliphatic aldehyde and two from the reaction of an aromatic aldehyde with resorcinol. The products with crown conformation with all side chains in the axial position (rccc) are more desirable and stable thermodynamically. Hogberg reacted resorcinol with acetaldehyde by adding hydrochloric acid. The reaction occurred at 75°C for 1 h and yielded sediment that was subsequently acetylated. The acetylated product was in the form of two isomeric cyclic tetramers, one of which formed cis (rccc) conformation of up to 47%, while the other product formed rctt conformation with a percentage yield of 13%. This indicated that products with all side chains in the axial position (rccc) are more desirable and stable thermodynamically [39]. The same result can be obtained by selectively increasing the alcohol proportion in the solvent mixtures used and increasing the reaction temperatures and time [39, 40].

Several synthesis methods of calix[n]arenes and their derivatives have been largely developed to produce high yields. However, the methods require heating at high temperatures and a long reaction time. This requirement is disadvantageous, ultimately when the synthesis is done on a large scale. The required solvents will be in a very large amount, and the reaction time needed will be much longer. This makes the synthesis of calix[n]arenes and their derivatives not environmentally friendly.

## 2.2. Green synthesis procedures

Various approaches to calixarenes and their derivatives have been attempted, one of which is by implementing the concept of “green chemistry.” The synthesis of calixarenes and their derivatives requires heating at high temperatures for quite a long time. The heating is usually done using conventional heating, where heat transfer occurs conductively. The method is relatively slow and inefficient to transfer energy into the reaction system, as it depends on the thermal conductivity of the materials used; consequently, the temperature of the reaction vessel will be greater than that in the reaction compound. Irradiation with a microwave can produce more efficient internal heating because microwave energy penetrates into the containers so that it can directly hit the reaction compound, and energy transfer becomes more efficient. The phenomenon will depend on the ability of the molecules (solvents or reagents) to absorb microwave energy and change it into heat. The thermal energy is obtained when the polar molecules try to align themselves with an electric field resulted from microwave irradiation. The amount of heat produced depends on the dielectric properties of the molecules. Dielectric constants indicate the ability of the molecules to get polarized by the electric field. The electric field received by the molecules causes reorientation of the dipolar molecules which in turn increases polarity and reactivity by reducing the activation energy. Consequently, the reaction can happen more quickly [41–43].

Organic synthesis using microwave technology has been largely employed, as it can accelerate the reaction time as a consequence of an increase in heating that cannot be achieved with conventional heating [44]. This is what happened in Baozhi's [45] synthesis of *p*-methylcalix[6]arene. A reaction compound consisting of formaldehyde, *p*-methylphenol, and KOH was heated with microwave for 2–8 min (output power at 100%). The required reaction time at this stage was faster than that when using conventional heating, which could take up to 2 h. After solids were formed, reflux was done for 40 min using dimethylbenzene. When cooled down, white crystals with a melting point of 361–362°C were yielded for up to 81.7%. The synthesis of *p*-*tert*-butylcalix[8]arene was done with the same procedure using the microwave as well, in which the compound was radiated for 4–8 min. To yield a larger cyclic reaction product, the amounts of bases used were increased with a longer reflux time. As previously discussed, bases and reflux time play a role in cyclic formation [45].

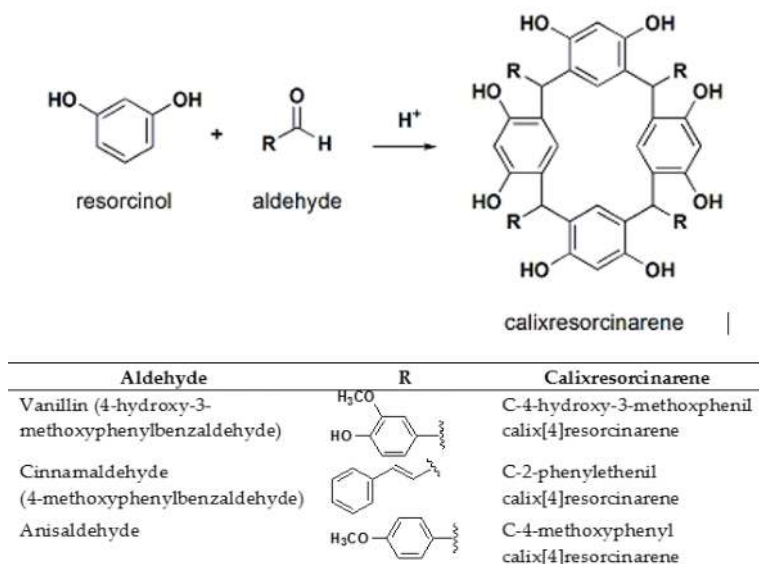
The same phenomenon was observed when calixarene synthesis was done using resorcinol, which is known to be more reactive than phenol. The reaction product in the form of cyclic tetramer calix[4]resorcinarene was obtained after the compound was heated with conventional heating for 5–10 h, with a reaction yield of around 60–90%. However, the reaction could be faster when the heating method was changed with microwave. One reaction only required 3–5 min with a greater reaction percentage yield, namely, around 80–90% [46]. This finding was put to use in the synthesis of thiocalix[*n*]arene with *n* = 4–8 [47].

Aldehyde modification can also be done by using the abundant natural products such as vanillin that can be derived from vanillin plant (*Vanilla planifolia*), cinnamaldehyde from cinnamon oil, and anisaldehyde from Indonesian fennel oil. The synthesis procedures using these materials have been developed for the synthesis of calix[*n*]arenes and their derivatives

with “green chemistry” approach. The three compounds were reacted with resorcinol to yield cyclic tetramers, calix[4]resorcinarenes. As previously discussed, the synthesis reaction of calix[4]resorcinarenes can occur for 15–30 h using conventional heating. Sardjono et al. [48] developed a microwave-assisted synthesis procedure for calix[4]resorcinarenes, where resorcinol was reacted to vanillin or cinnamaldehyde. The calix[4]resorcinarenes derivatives yielded could be up to 97.9% in 8 min with a ratio of resorcinol to vanillin or cinnamaldehyde was 1:1, and the microwave power used 332 W. Another calix[4]resorcinarenes derivatives, namely *C*-anisalcalix[4]resorcinarene could also be yielded for up to 99.5% in 5 min from the reaction of resorcinol with anisaldehyde at the ratio of 1:1.2 and 264 W microwave power [48]. The three reactions of resorcinol with various aldehydes to form calix[4]resorcinarenes is illustrated in **Figure 12**.

Vanillin in the synthesis of calix[4]resorcinarene derivatives was also employed by Nakajima and Kobayashi [20], although they still used the conventional heating method (without a microwave). The reaction compound comprised resorcinol and aldehyde (vanillin, syringaldehyde, or *p*-hydroxybenzaldehyde) with a mole ratio of 1:1 and hydrochloric acid heated at 70°C and stirred for 12 h. The reaction yield was then washed with hot water and purified using methanol and ethanol. The third reaction yield formed cyclic tetramers, namely, vanillin calix[4]arene for 32%, syringaldehyde calix[4]arene for 28%, and *p*-hydroxybenzaldehyde calix[4]arene for 37% [20].

Calixarene synthesis commonly needs a lot of solvents which results in a large amount of waste. Therefore, a synthesis approach by minimizing the use of solvents has been attempted and proved to be more effective. The solvent-free reactions that have been tried, in addition



**Figure 12.** Synthesis reaction of calix[4]resorcinarene from resorcinol with various aldehydes.

to requiring a shorter amount of time, used less energy and could produce better and more effective and selective reactions than the conventional method [49]. Solvent-free reactions have also been used for calixresorcinarene synthesis, which is a condensation reaction between aldehyde and resorcinol. The method has also been widely used in several organic reactions and sometimes gives better results than the reaction method in solvents [50].

In calixresorcinarene synthesis, the use of solvent-free method was carried out by mixing aldehyde and resorcinol (1:1) with a certain amount of acid catalysts and then ground simultaneously. Although all reagents were in solid forms, when mixed they could form a thick liquid or paste reaction compound. Isolation of the reaction product can be carried out by washing with water to remove the acid catalyst and recrystallize with the right solvent. The method was proven to effectively yield calixresorcinarene with various aldehydes. In this method, no external heating is needed; only consistent scouring is needed. The scouring can be done in order to reduce particle sizes so that the compounding will be efficient. Because the reaction forms a thick liquid, not powder compound, then scouring at high intensity is not necessary [51].

Using the solvent-free method, the reaction occurs in mere minutes, much faster than the reaction time using the conventional method, which requires hours or even days. The percentage yield of the solvent-free method is often greater than that of the conventional synthesis method. The synthesis of calix[4]resorcinarenes commonly yields isomeric products, with two forms of isomer, namely, cis-cis-cis (rccc) and cis-trans-trans (rctt) with "crown" ( $C_{4v}$ ), "chair" ( $C_{2h}$ ), or "boat" ( $C_{2v}$ ) conformation. Theoretically, without the effect of solvents, rccc isomers with "crown" ( $C_{4v}$ ) conformation are more desirable than the rctt isomers with "chair" ( $C_{2h}$ ) conformation [51]. Besides reduced reaction time, synthesis with this method uses a small amount of catalyst and does not produce solvent waste, hence meeting the principles of "green synthesis" [51, 52].

The condensation reaction between aldehyde and resorcinol (1:1) with *p*-toluenesulfonate acidic catalyst (5%) occurs for several seconds up to several minutes and yields derivatives of calix[4]resorcinarenes with rccc and rctt isomers. Four out of the six reactions were reported by Roberts et al. [51] to yield more rctt isomers with "chair" ( $C_{2h}$ ) conformation than rccc isomers with "crown" ( $C_{4v}$ ) conformation, with a ratio of 2:1. However, in one of the reactions, more rccc "crown" ( $C_{4v}$ ) isomers were yielded for up to 95%. The distribution of isomer products is very possibly related to solubility that also plays a role in the reaction with the solvent-free method. In this reaction, increased reaction or heating time of the initial materials up to 85°C for 5 h did not cause an increase in the amount of rccc isomers yielded with "crown" ( $C_{4v}$ ) conformation [51].

Employing the same method, Firdaus et al. [53] reacted vanillin with resorcinol (1:1) and yielded C-4-hydroxy-3-methoxyphenylcalix[4]resorcinarene for 52%, with a ratio of rccc isomers to rctt isomers of 1:5. However, when the aldehyde used was replaced with *p*-anisaldehyde, 63% of C-4-methoxyphenylcalix[4]resorcinarene was yielded with rccc isomers two times greater in number than rctt isomers. The distribution of the isomer products showed that each aldehyde has such a different characteristic that it can yield a different product composition. This difference may also be related to the solubility of the aldehyde used in the

reaction compound. In addition, the reaction product demonstrated that rccc isomers with "crown" ( $C_{4v}$ ) conformation are more desirable [53].

The solvent-free method is significantly faster than the conventional synthesis method. This can also be seen in the synthesis of calix[4]pyrogallolarene that is commonly done with condensation reaction of pyrogallol and aldehyde using alcohol solvent and acid catalyst and yields in rccc "cone" isomers. In the synthesis of calix[4]pyrogallolarene using the solvent-free method, an amount of aldehyde was added drop by drop to pyrogallol (1:1) with *p*-toluenesulfonate (3.7%) catalyst and scoured constantly. The reaction yielded vulnerable white solids in 2 min. The solids were easily scoured into soft yellow powder in 5 min. As was the case with the synthesis reaction of calix[4]resorcinarene derivatives, no heating was used in this synthesis [52].

The synthesis of *C*-(*p*-substituted phenyl) calix[4]resorcinarenes was carried out to see the interaction between host and guest using DMSO by mixing resorcinol with halogen-substituted benzaldehyde in *para* positions (1:1) under acidic conditions with an addition of 5% solid *p*-toluenesulfonate. The synthesis yielded a product at a percentage of 90–95% by scouring without using any solvents [54].

In the synthesis of calixresorcinarenes from resorcinol and aromatic aldehyde, Lewis acid is frequently used, such as  $\text{BF}_3\text{-OEt}_2$ ,  $\text{AlCl}_3$ , and  $\text{SnCl}_4$ . For example, in the synthesis of resorcinarene *O*-acetates from 1,3-di(alkoxycarbonylmethoxy)benzenes with aromatic or aliphatic aldehydes (1:1) can be efficiently done at room temperature with the addition of  $\text{BF}_3\text{-OEt}_2$  (boron trifluoride etherate) as a catalyst in order to produce high yields [55]. However, the amount of acid needed in this reaction is quite large (50–200% mole). Certainly, this is not good for the environment and safety, considering the sensitivity of Lewis acid to water that can yield side products in the forms of acidic oxides and metal oxides. Furthermore, the process is not efficient in terms of atom economy. The reaction also can yield two diastereoisomers. Lanthanide (III) triflates are selective acid catalysts that have been widely used for the formation of carbon-carbon and carbon-heteroatom bonds. Different from the common Lewis acid that is frequently used in stoichiometric numbers, lanthanide (III) triflates can be used in various reactions in catalytic numbers in the presence of solvents such as THF, DMSO, DMF, MeCN, and water. In addition, the stability and solubility of this catalyst in water make the compound easily separated and reused. One of the examples of lanthanide (III) triflate compounds that can be used as a catalyst is Ytterbium (III) triflate nonahydrate [ $[\text{Yb}(\text{H}_2\text{O})_9](\text{OTf})_3$ ]. In the condensation reaction of resorcinol with various aldehydes (1:1), to produce derivatives of calix[*n*]resorcinarenes only needs 8% mole of Ytterbium (III) triflate nonahydrate as a catalyst. Although the amount of the catalyst is small, the reaction product yielded can reach up to 71–94% and this reaction is stereoselective. The reaction is done by refluxing for 48 h with ethanol as solvent [56].

Tungstate sulfuric acid (TSA) can also be used in the synthesis of calix[4]resorcinarene derivatives. In the reaction of an aldehyde with resorcinol at 120°C, the addition of TSA could produce around 78–95% in 25–80 min. The use of TSA as an acid catalyst is also more environmentally friendly because this acid can be recycled and reused for up to four reaction cycles with a decrease in reaction product yield around 3–11% [57].

### 3. Conclusion

Calixarenes and their derivatives can form a cyclic oligomer with a number of monomer units ranging from 4 to 20 and a basic structure consisting of phenolic units or phenol derivatives which are repetitive and interconnected by the Ar-C-Ar bridge to form a hollow cycle. Cyclic oligomer calixarene and its derivatives have been widely used in various fields, especially as host molecules in a guest-host system. Therefore, it takes a lot of effort to synthesize calixarenes and their derivatives. Various modifications of functional groups and synthesis methods were made in order to produce the expected configuration and conformation. These compounds have largely been synthesized by conventional methods by heating at 50–120°C for 1.5–45 h, either under acidic or basic conditions. The conventional method requires the use of various solvents in large amounts. The percentage yield of the reaction employing this method can range from 50 to 91%. The conventional synthesis method that requires heating at high temperatures, a fairly long reaction time, and large amounts of solvents has encouraged many researchers to develop more environmentally friendly synthesis methods, such as microwave-assisted synthesis and solvent-free methods.

Microwave-assisted synthesis of calixarenes and their derivatives requires 2–8 min with a percentage of reaction products of up to 99%. This method has been proven to accelerate reaction time without reducing the percentage of reaction products significantly. The synthesis of calixarenes and their derivatives can also be done with the solvent-free method. The method only relies on scouring process without heating. Nevertheless, the method requires a shorter reaction time with a higher percentage yield than that from the conventional synthesis method. Both microwave-assisted synthesis method and solvent-free method can reduce reaction time, energy use, solvent, and waste, making the synthesis of oligomer calixarenes and their derivatives more environmentally friendly.

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