Calix[4]arenes in the 1,3-Alternate Conformation

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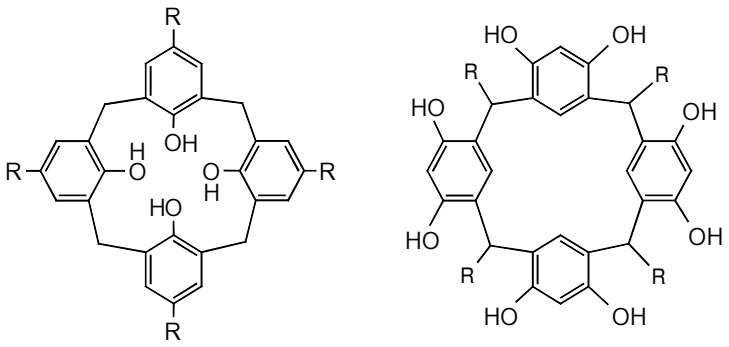
Contents

Chapter 1

Basics of Calix[4]arenes

1. Definition and nomenclature.

In 1872, Adolph von Baeyer[1] studied reactions of phenols with aldehydes, but the products of these reactions remained uncharacterized for nearly 70 years. Then, in the 1940s, Zinke and Ziegler[2] suggested a cyclic tetrameric structure for the product of the based-induced reaction between *p*-substituted phenols with formaldehyde (**I**). A similar structure was proposed by Niederl and Vogel[3] for the product of the acid-induced reaction between resorcinol and aldehydes (**II**).



I II

About 40 years later, Gutsche[4,5] and Högberg[6,7] studied these base- and acid-induced condensations showing that both are extremely useful methods to synthesize these cyclic oligomers. C. D Gutsche has chosen name "calixarenes" for the cyclic oligomers since they look like an ancient Greek vase, known as "calix crater", while "arene" refers to the aromatic rings. So, the term "calixarene" describes the shape of the cyclic tetra- or pentamers, when they assume the "*cone*" conformation and is added as an extension to the name. Larger cyclic oligomers are also called calix[n]arenes. The [n] represents the number of the aromatic units.

The analogy with an ancient vase reveals the edges of the molecule as *upper*- and *lower*-rim and the ring is called *annulus* (Fig. 1). Replacing the terms *upper* and *lower* by *wide* and *narrow* rim is preferable because this is independent of the orientation.

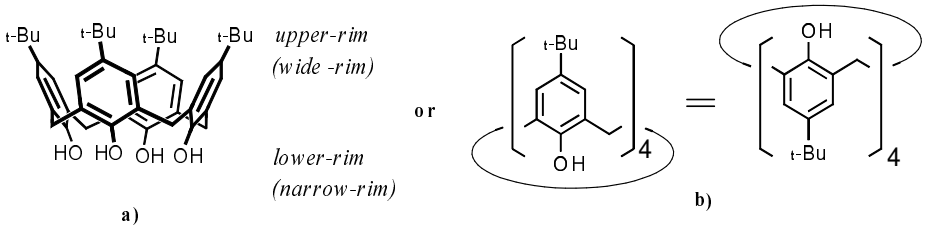


Figure 1. Formula of *p-tert*-butylcalix[4]arene in the *cone* conformation in a) spatial and b) planar representation.

To indicate from which phenol *p*-substituent calix[4]arene is derived, often is mentioned also the substituent. For example the product derived from *p-tert*-butylphenol in the abbreviated nomenclature is *p-tert*-butylcalix[4]arene. In a more detailed nomenclature of calix[n]arenes this name is retained and the substituents are named also specifying their positions by numbers as shown the figure 2.

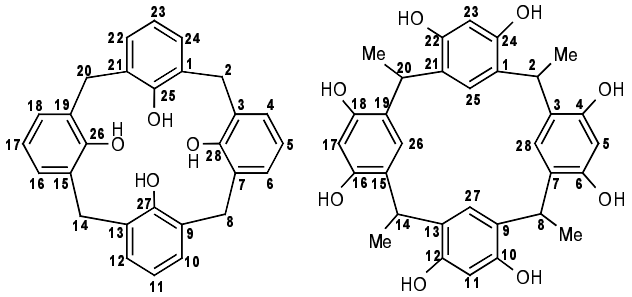
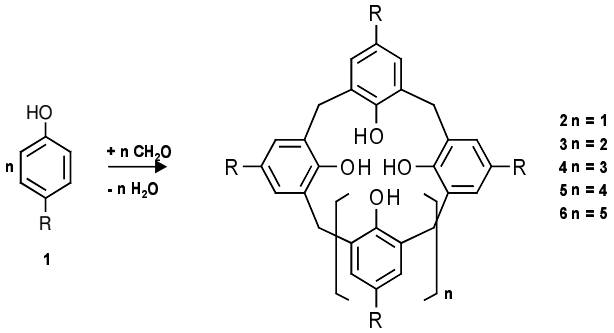


Figure 2. Structure and numbering of calix[4]arenes: 25, 26, 27, 28-tetrahydroxycalix[4]arene; 2, 8, 14, 20-tetramethyl-4, 6, 10, 12, 16, 18, 22, 24-octahydroxy calix[4]arene.

1.1. Synthesis.

1.1.1 One–pot procedure.

On a laboratory scale the *tert*-butyl-calixarenes are available by alkali-catalysed condensation of *p-tert*-butylphenol with formaldehyde (scheme 1).



Scheme 1. Formation of calix[n]arenes by one-pot condensation of *tert*-butylphenol with formaldehyde.

Under proper reaction conditions (solvent, temperature, base, aldehydes), the cyclic tetra-, penta-, hexa- hepta- and octamer can be formed.

a) the pre-condensation of **1** with aqueous CH_2O using 0.045 eqv. NaOH with respect to the phenol followed by 2 h refluxing in toluene yields about 50 % of **2**[8].
b) the heating of **1** with formalin with 0.034 eqv. KOH with respect to the phenol followed by 4 h refluxing in xylene yields about 83-88 % of **4**[9].

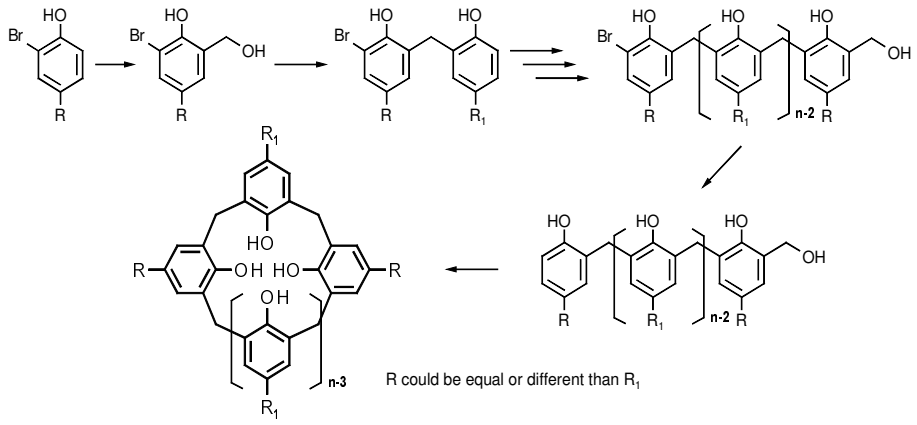
c) the refluxing of a solution of **1** in xylene with paraformaldehyde and 0.03 eqv. NaOH with respect to the phenol yields about 62-65 % of **6**[10].

It is generally accepted that the *tert*-butylcalix[8]arene is the kinetically and the *tert*-butylcalix[4]arene the thermodynamically controlled product, while a template effect seems to be the reason for the formation of the calix[6]arenes.

The yields are remarkable if we consider that for example in the synthesis of calix[8]arenes 16 covalent bonds are newly formed. The less favorably obtained cyclic penta- and heptamers are available now also in multigram quantities in yields of 15-20 % for **3**[11] and 11-17 % for **5**[12] (LiOH as base).

1.1.2. Stepwise Syntheses.

This method has the principal advantage to allow the preparation of calix[n]arenes having n different *p*-substituted alkyl phenol units. One of *ortho*-position is protected (usually by bromination) and a sequence of hydroxymethylation and condensation steps build up a linear oligomer, which after deprotection is cyclized under high dilution conditions. Thus, 2n+2 steps are required to obtain a calix[n]arene.



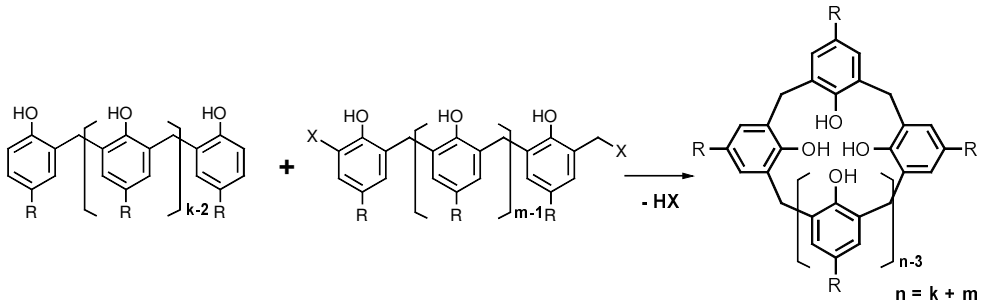
Scheme 2. The synthesis of calix[n]arenes by stepwise condensation.

1.1.3. Fragment condensation.

Two independently synthesized fragments can build up a calix[n]arene by condensation as outlines scheme 3. Various calix[4]arenes have been obtained by 3+1 or 2+2 (numbers of the phenolic units in the two fragments) attempts using $TiCl_4$ as catalyst in yields up to 25-30 %[13].

This method usually does not allow the synthesis of larger calix[n]arenes due to side reactions such as cleavage of the existing methylene bridges. However, some calix[5]- and calix[6]arenes[14,15] were obtained by fragment condensation. In the series of larger calix[n]arenes one example for n=8 is

known which was obtained in 9 % yield via 7+1 condensation of a linear heptamer with the bishydroxymethylated phenol[16]. Also, many calix[4][17]- and calix[5]arenes[14,18] having various substituents at their bridges (-CHX-) were prepared using the same strategy.



Scheme 3. The synthesis of calix[n]arenes by fragment condensation "k + m".

1.2. Conformations of calix[4]arene.

The phenolic units of calixarenes can rotate around the σ-bond of the methylene bridge. In the case of calix[4]arenes the hydroxyl group can pass through the annulus, while in the case of calix[8]arenes also the passage of the *p*-substituent through the annulus is possible.

Considering the position of the phenolic OH groups (and the *p*-positions) with respect to the main plane (the plane of the methylene bridges) four main conformations are possible in the case of calix[4]arene named by Gutsche *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* (figure 3). Due to mobility of the phenolic units these conformations may be interconverted.

In solution, the tetrahydroxy parent *tert*-butyl-calix[4]arene is exclusively found in the so called *cone* conformation, which is stabilized by an intramolecular array of hydrogen bonds, in which all hydroxyl groups are orientated in the same direction. This could be shown by ^{1}H-NMR spectrum as follows. The four methylene groups are equivalent, but the two protons of each CH_2 group are nonequivalent in the *cone* conformation. In the ^{1}H-NMR spectrum in $CDCl_3$, at low temperature a pair of doublets appears (with a coupling constant of 12-14 Hz, typical for the geminal protons) for the methylene protons which is due to their different orientations (H_A-*axial* and H_B-*equatorial*, Figure 3). These signals become broader when the temperature is increased and collapse in one sharp singlet at higher temperature. This can be explained by a rapid exchange between two opposite (but identical) *cone* conformations (Figure 4). Thus, the originally *equatorial* protons become *axial* and vice versa. Thus, the ^{1}H-NMR spectrum shows an averaged signal.

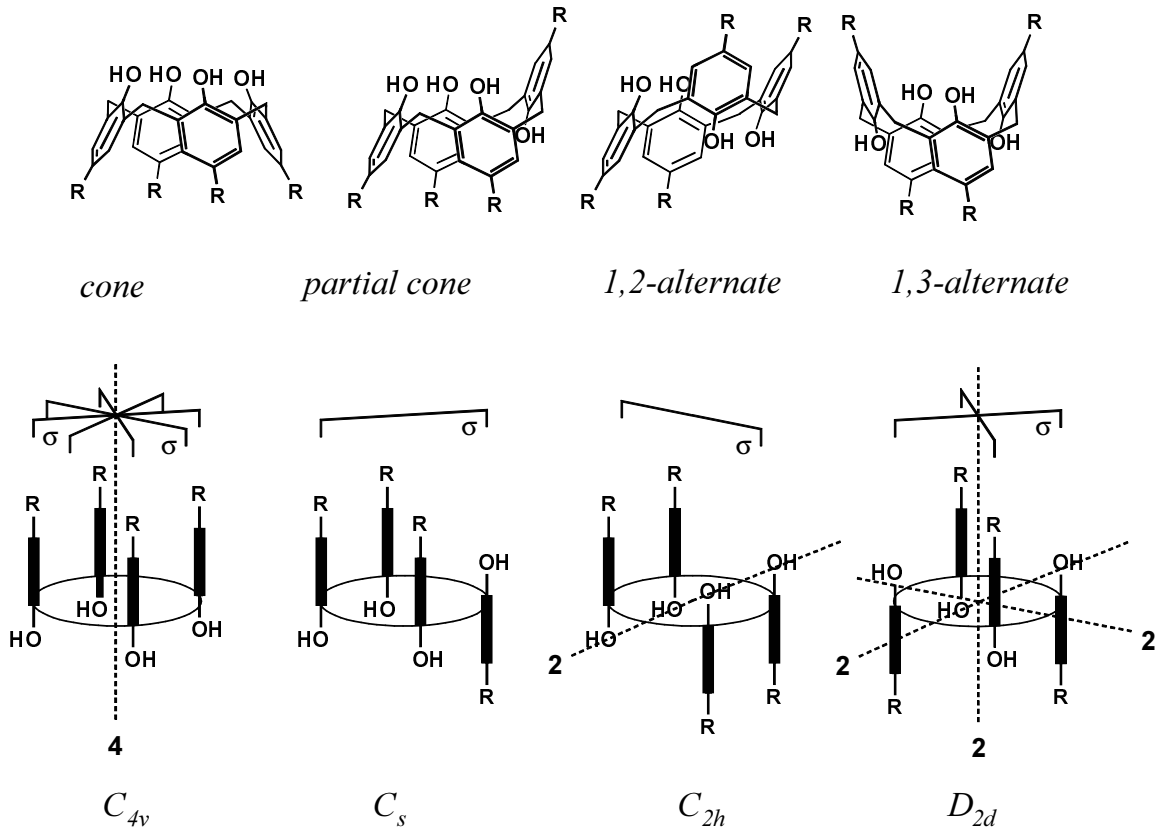


Figure 3. The four basic conformations of calix[4]arene and their symmetry classes.

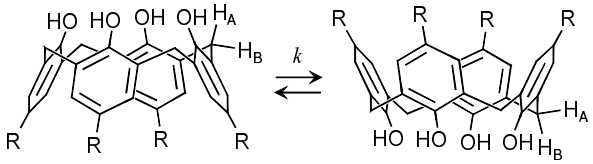


Figure 4. *Cone-cone* ring inversion of calix[4]arenes.

To restrict the conformational mobility of calix[4]arenes a bridge between phenol units can be introduced. Also, the incorporation of O-alkyl or O-acyl larger than ethyl group will fix the calix[4]arenes in a certain conformation.

Table 1. ^{1}H-NMR signals in conformational isomers of the tetraether *tert*-butyl calix[4]arene, with ether residue R^1 (R^1 shows no coupling with the adjacent CH_2 group).

Conformation / protons	*cone* C_{4v}	*partial cone* C_s	*1,2-alternate* C_{2h}	*1,3-alternate* D_{2d}
Ar-H	1s	2s, 2d[a]	2d[a]	1s
O-CH_2-R^1	1s	2s, 2d[b]	2d[b]	1s
Ar-CH_2-Ar	2d[b]	4d[b,c]	1s, 2d[b] (2:1:1)	1s
tert-butyl	1s	3s (1:2:1)	1s	1s

[a] meta-coupling, [b] geminal coupling, [c] one pair of doublets shows a small difference in chemical shift.

The structure of tetra-O-alkylated calix[4]arene fixed in one of the above mentioned conformations can be identified by ^{1}H-NMR spectrum, where for each conformer the aromatic part, methylene bridge and aliphatic area shows distinct pattern (Table 1).

To obtain a certain conformation the factors which influence the process depend mainly on:

a) the residue Y to be attached

b) the existent *p*-substituents

c) the alkylation conditions (base, temperature and solvent).

Template effects by metal cations (from the used base) have been especially used to control the formation of a certain conformer. Usually, the *cone* isomer is formed in the presence of Na^+ cations. NaH in DMF or in DMF/THF are conditions under which the exhaustive O-alkylation with alkylhalides of normal reactivity or tosylates[19] takes place, while Na_2CO_3 in boiling acetonitrile or acetone allows the O-akylation with alkylhalides of higher reactivity.

Larger cations (K^+, Cs^+) favor the formation of the *1,3-alternate* and *partial cone* conformations, while the *1,2-alternate* isomer is seldom formed and usually occurs only as a by-product accompanying the *1,3-alternate* and *partial cone* isomers.

Tetraethers with different ether residues may be obtained from partially O-alkylated compounds (see later). The stereochemical result depends on the sequence of *O*-alkylation steps.

In the tetramethoxy ethers, the methoxy groups are small enough to pass through the annulus of phenolate rings making the molecule flexible. Due to the absence of hydrogen bonds between ether residues the most stable conformation adopted by tetramethoxy calix[4]arenes is the *partial cone* (see figure 5). Also, the other conformers are found[20] in 6.1 % *1,2-alternate*, 5.5 % *cone*, 2.8 % *1,3-alternate* together with 85.6 % *partial cone* as shown by the ^{1}H-NMR spectra in $CDCl_3$ at 243 K[21].

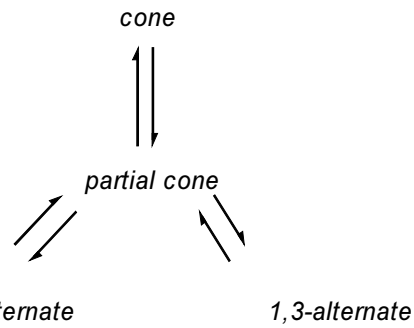


Figure 5. Conformational interconversion for tetramethyl ethers of calix[4]arenes.

1.3. Funtionalization of calix[4]arenes.

Generally, all the reactions characteristic for phenols may be applied also to calix[n]arenes. Their chemical modification does not permit only the synthesis of new molecules. Especially for

calix[4]arenes it allows also a control of their conformation and the preparation of derivatives fixed in a certain conformation.

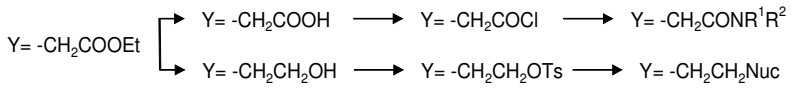
There are two main places where the skeleton of the calix[4]arene can be independently modified namely: the phenolic hydroxy groups (modification at the narrow rim) and the *para*-position to the hydroxyl groups (modification at the wide rim). Once a calix[4]arene is fixed in a certain conformation it can be used as skeleton for further attachment of various groups either at the narrow or at the wide rim or at the both sides.

1.3.1. Modification of calix[4]arenes at the narrow rim.

a) Complete conversions.

The exhaustive O-alkylation or O-acylation is usually not difficult. To introduce simple O-alkyl groups (from methyl to octadecyl) usually requires the presence of a strong base (NaH in DMF/THF), an excess of alkylating agent and sometimes elevated temperatures. When more reactive reagents are used (e.g allylbromide, benzylbromide or pycolylchloride/bromide) the presence of carbonates (e.g K_2CO_3) as weaker base in boiling acetonitrile (or acetone) is sufficient.

Functional groups attached to the narrow rim via ether linkage can be further modified. Ester groups, for instance are used to introduce a variety of functional groups (see below).



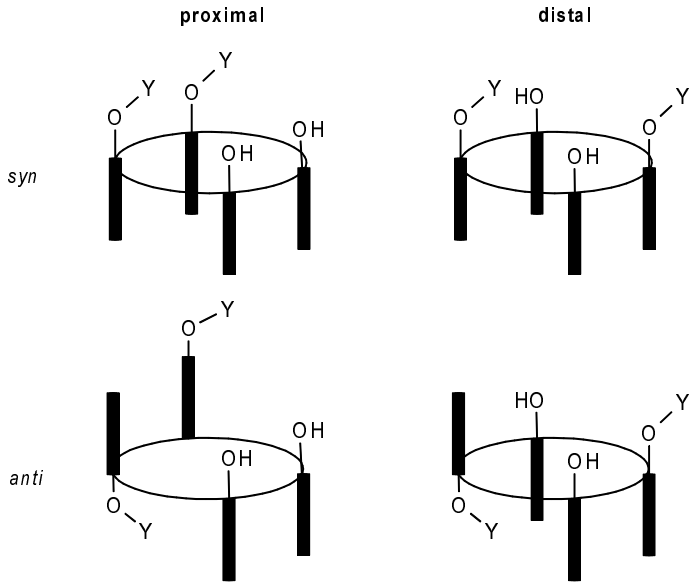
The aminoethyl ether groups were obtained by using azide (the tosilate group from ethoxytosilate is substituted by azide–from sodium azide) as a nucleophile and subsequent reduction. Longer aminoalkyl ethers were prepared by O-alkylation with ω-bromonitriles[22] or ω -bromoalkyl-phthalimides[23] followed by reduction or hydrazinolysis, respectively. Amino groups attached to the narrow rim of calix[4]arenes via a spacer (-CH_2-) represent a versatile starting material to which further residues can be attached easily via amide[24](CMPO derivatives ligands for lanthanides and actinides-[23] see the chapter 3), imide[25], (thio)urea[26] or azomethine[27] links.

b) Partial conversion.

Mono-O-alkylated derivatives are available from the reaction of tetrahydroxy calix[4]arene with 1.1 eqv. of weak base (e.g K_2CO_3, CsF), 1.1 eqv. alkylating agent in acetonitrile[28]. A different strategy to obtain the mono-O-alkylated compound was reported[29] which starts from the much easier accessible

1,3-diethers or tetraethers by controlled cleavage of the ethers groups with trimethylsilyl iodide (1 or 3 mol).

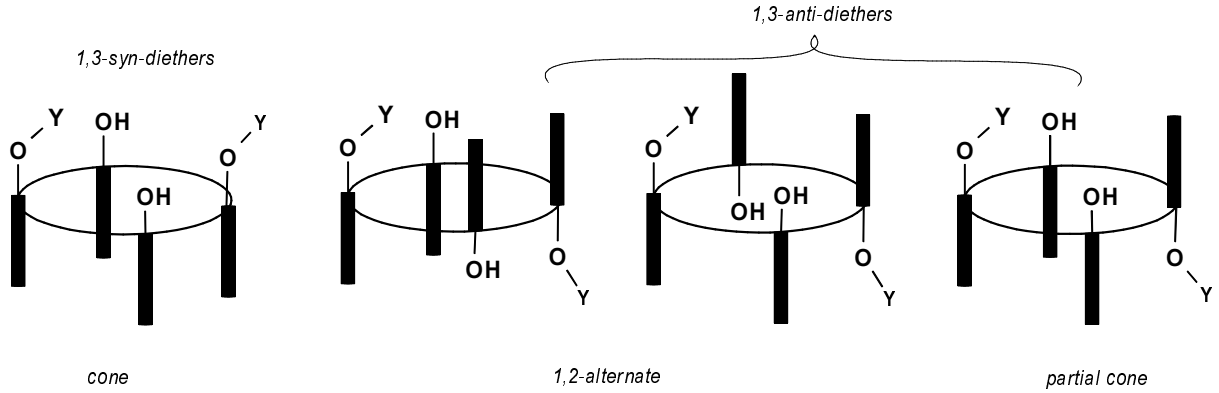
The di-O-alkylation of the hydroxy groups from calix[4]arene may lead to the formation of two regioisomers, the 1,2- or 1,3-diethers (proximal or distal positions). Two ether groups of sufficient size can be situated at the same side or at different sides of the macroring leading to *syn*/*anti* isomers. It must be pointed out that in such partial ethers/esters the orientation of Y should not be confused with the conformation of the compound, since free OH groups still can pass through the ring. Therefore, some examples are illustrated below.



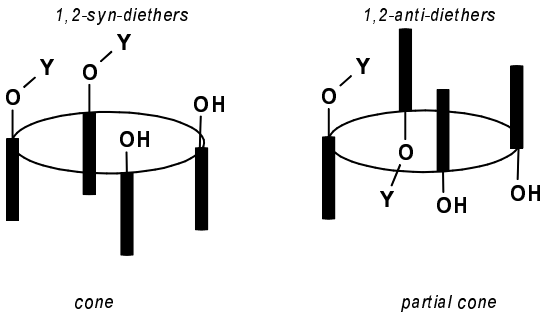
The most often ether calix[4]arene derivatives used in this thesis are the 1,3-*syn* – diethers. They are used especially when two kind of ether residues in calix[4]arenes are needed. The 1,3-*syn*-diethers can be easily synthesized in high yields under a variety of conditions, often K_2CO_3 or Na_2CO_3 in boiling acetone or acetonitrile. In this way could be obtained various di-ethers or di-esters with the same or with different residues. In the last case a two step synthesis is required via the mono-O-alkylated derivative.

The 1,3-*syn* – diethers still can assume the *cone*, *partial cone* or 1,2-*alternate* conformations. Usually the most stable conformation is *cone* conformation for which its 1,3-*syn*-diether calix[4]arene derivatives can be easily recognized by a pair of doublets (AX system, $\Delta\delta \sim 0.5\text{-}0.6$ ppm), in the ^{1}H-NMR spectrum corresponding to the methylene bridge.

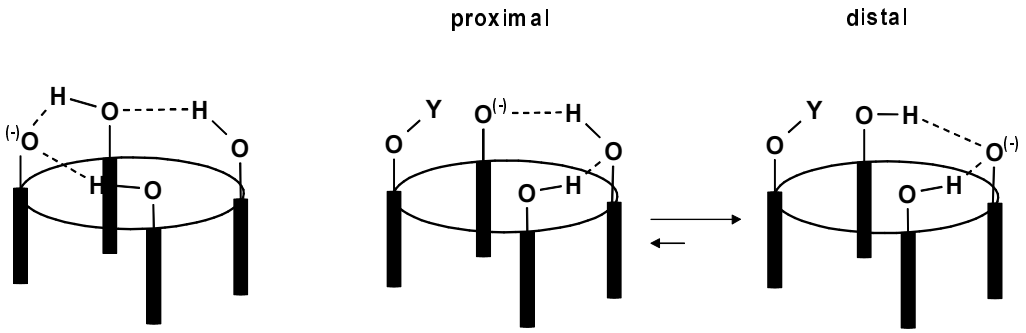
The 1,3-*anti*-diethers are obtained via protection/deprotection strategies[30]. They exist in rapid equilibrium between the two *1,2-alternates* and *partial cone* conformation (see the representation below).



The 1,2-*syn*-diethers adopt the *cone* conformation and the *anti* isomers the *partial cone* respectively (see the representation below). This can be explained by the formation of a maximum OH-OH hydrogen bonds[31].



The selective formation of 1,3-diethers can be explained by the formation of a monoanion of the mono-alkylated intermediate which is stabilized by two hydrogen bonds of the remaining hydroxyl neighboring groups (see below).



Steric reasons are in favor of the formation of 1,3-diether, while 1,2-diether is statistically favored. The optimal conditions for the formation of 1,2-diether is an excess of strong base (NaH in DMF) and 2.2 eqv. of alkylation agent.

An alternative way to obtain a 1,2-diether is the selective cleavage of neighboring *syn*-ether groups from tetraethers by $TiCl_4$[32] or Me_3SiI[33]. Here the tetraether in the *partial cone* conformation leads to the chiral 1,2-a*nti*-diether.

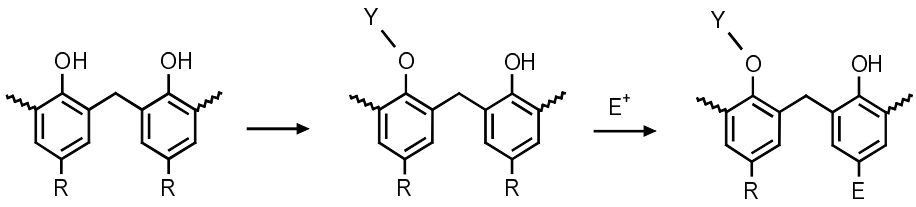
Recently an easy way to achieve the 1,2-diether was reported using a protection of two adjacent oxygens by capping with a disiloxane bridge[34].

The tri-O-alkylated[35] derivatives can be obtained as a *syn*/*syn* isomers using BaO, $BaO/Ba(OH)_2$ or CsF as base in DMF.

1.3.2. Modification of calix[4]arenes at the wide rim.

Since the one-pot synthesis of calixarenes works best with the *p-tert*-butylphenol, often the *tert*-butylcalix[n]arenes are used as starting materials for most calixarene derivatives. Therefore, one of the most important exhaustive modification at the wide rim is transbutylation with $AlCl_3$ in toluene (as solvent and acceptor), converting *tert*-butylcalix[n]arenes in unsubstituted calix[n]arenes. Thus, the *p*-positions are available for theoretically all kinds of electrophilic substitution reactions possible with phenols[36]. Sulphonation, nitration, bromination (or iodination), bromomethylation, aminomethylation, formylation, acylation and coupling with diazonium salts[37,38] are such examples. The introduction of nitro-[39] and sulphonic acid groups[40] has been achieved also in excellent yields by *ipso*-substitution of *tert*-butylcalix[4]arenes.

Partial (*ipso*-) substitutions at the wide rim can be achieved on a statistical way under appropriate reaction conditions or using the difference in reactivity between phenol and phenol ether or ester units (see scheme 4). In a direct *ipso*-nitration of calix[4]arene tetraethers the mononitro derivative is obtained in up to 75 % yield[41]. While the dinitro and trinitro derivatives can be only chromatographically isolated. In contrast to this the dinitro derivative is obtained in up to 75 % yield via selective *ipso*-nitration of the 1,3-diethers[42]. Also, an nitro-attack of the methylene bridge was found as a side product.



Scheme 4. Schematic representation of the principle of the selectivity transferred from the narrow to the wide rim.

This selectivity available in O-alkylation or O-acylation reactions can thus be transferred from narrow to the wide rim. The principle can be applied also to the larger calixarenes where less examples have been realized.

Based on this principle of selectivity, the transbutylation of the mono-, di-, tri-ethers or esters of calix[4]arenes can lead to tri-, di-, mono-*tert*-butyl-calix[4]arene derivatives. Examples of the selective substitution at the wide rim in partially O-alkylated or (O-acylated) calixarenes are the bromination[43,44], iodination[45], nitration[46], formylation[47], chloromethylation[48], and coupling with diazonium salts[49].

1.4. Characteristics of the *1,3-alternate* conformation, potential modifi-cations.

Generally, calixarenes are ideal starting materials for the synthesis of various types of host molecules and building blocks for the construction of larger molecular systems with defined structures and functions. Their potential applications range from highly specific ligands for analytical chemistry, sensor techniques and medical diagnostics to the decontamination of waste water. It includes the construction of artificial enzymes and the synthesis of new materials for nonliniar optics or for ultrathin layers and sieve membranes with molecular pores.

The general topic of this thesis is the functionalization of the calix[4]arene skeleton in the *1,3-alternate* conformation. This conformation was chosen, on the one side because was much less frequently used as platform than the *cone* one. Few examples can be enumerated here e.g di-urea derivatives as anion receptor[50,51], or self assembled dimers[52], derived from the respective amino calix[4]arenes. On the other side the *1,3-alternate* conformation offers an interesting geometrical arrangement. The two distal aromatic units which are inverted make both sides of the molecule identical with respect to methylene bridges plane. Therefore, both sides of the *1,3-alternate* platform can be functionalizated further (in identical or different ways).

For a better understanding of the geometry of the *1,3-alternate* conformation, a comparison of the single crystals of *cone* and *1,3-alternate* isomers is illustrated below (Figure 6). The both crystals which are illustrated below, are tetraether *t*-butylcalix[4]arene derivatives, where ether residues and *t*-butyl groups are avoided for a better visualization of the core. In the *cone* conformation all oxygen atoms are situated on the same plane/level, while in the *1,3-alternate* isomer they are oriented pairwise in both sides. This gives various possibilities for the introduction of amino groups (as chosen here) either on one or both sides of the molecule.

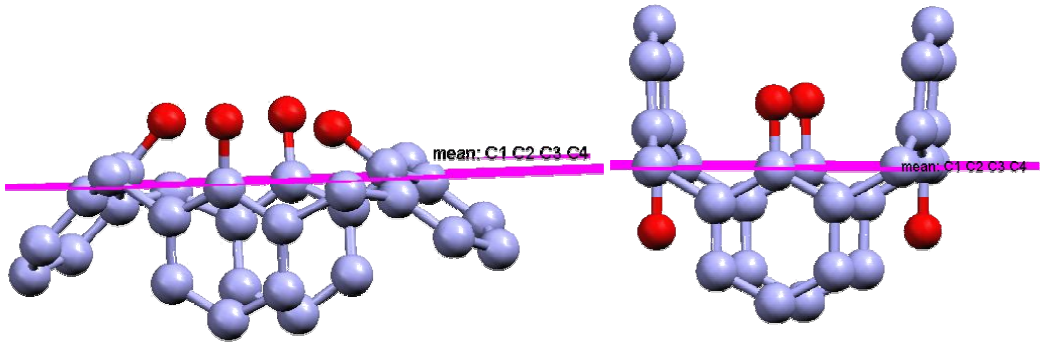


Figure 6. A comparison of the single crystal of the *cone* (left) and the *1,3-alternate* (right) conformations (blue-C atoms, red-O atoms, the violet plane is the main plane through methylene bridges).

As can be observed two distal aromatic rings in the *cone* conformation (right-left, in figure) are titled with the oxygen atoms inward. Therefore, the *p*-substituents of these rings are divergent oriented. In the case of the *1,3-alternate* conformation the rings are almost parallel, the same orientation corresponding also for the *p*-substituents. These are the differences in orientation of ether/*p*-position residues for the both isomers.

If two adjacent *p*-positions or oxygen atoms would bear identical groups the symmetry of the resulting compound differs from one to another isomer. Thus, a C_S-symmetry is shown by the *cone* isomer, while a C_2-symmetry corresponds to the *1,3-alternate* isomer (inherently chiral). Therefore, many possibilities for further functionalization of calix[4]arene can be followed using also the *1,3-alternate* as skeleton. These are developed and reported in this thesis.

1.5. References.

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Chapter 2

1,3-Alternate calix[4]arenes, selectively functionalized by amino groups

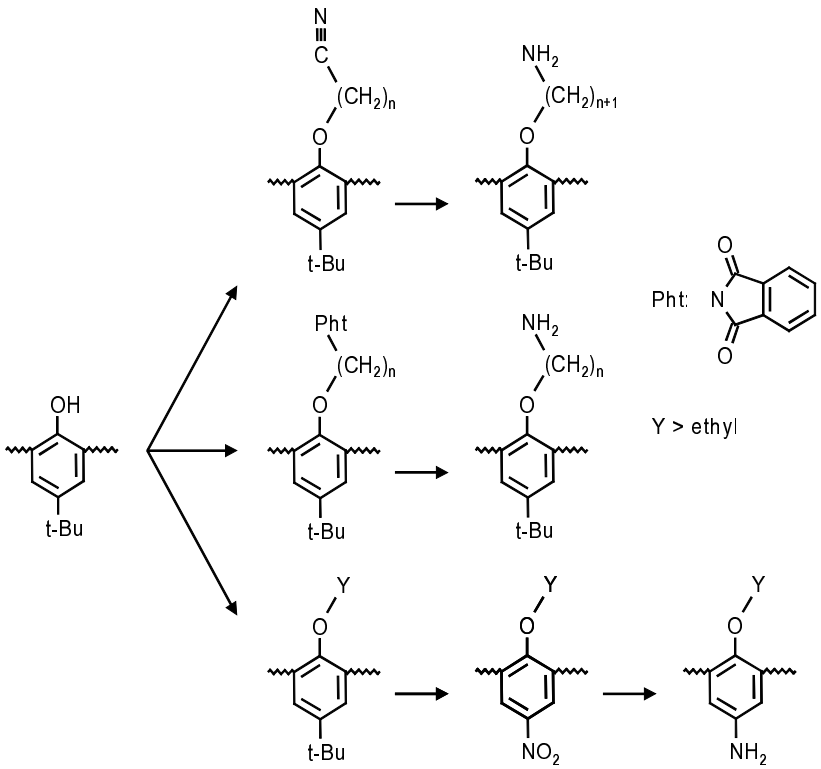
2. Introduction

Generally the calixarenes can be modified either at the narrow rim by esterification or etherification of the phenolic hydroxyl groups or at the wide rim by electrophilic or *ipso*-substitution of the *p*-positions. Our topic is focused on the functionalization of calix[4]arenes by amino groups. They could be attached to the narrow rim, via a spacer or to the wide rim by direct attachment to the phenolic unit. A direct attachment of amino groups to the narrow rim was made by Biali et al[1] eliminating the *endo*-OH groups and replacing them by NH_2. And of course, it is possible also, to attach amino groups to the *p*-position of the aromatic rings via a spacer[2,3] $-(CH_2)_x-$. Scheme 1 outlines the reaction sequences for the introduction of amino groups to the narrow or wide rim of calixarenes.

The preparation of the narrow rim amino derivatives of calix[4]arenes fixed in the *cone* conformation via selective etherification with ω-bromonitriles/ω-bromoalkyl-phthalimides is well established. A (selective) (*ipso*)nitration[4] followed by hydrogenation furnishes amino groups attached to the wide rim. This strategy may be applied either to all four phenolic units, or selectively only to one, two or three units and also, for all conformations of calixarene derivatives.

Among the ω-bromoalkylphthalimides the N-(2-bromoethyl)phthalimide cannot be used since elimination of HBr takes place under basic condition (the N-ethenylphthalimide was isolated[5]). However, hydroxyethylphthalimide has been used recently to obtain the 1,3-di-ether calix[4]arenes derivatives under Mitsunobu conditions[6].

Among the alkylnitriles the bromopropionitrile cannot be used for the O-alkylation because the elimination to acrylonitrile is the predominant reaction. O-alkylation with bromoacetonitrile[7] is possible but the cyanomethoxy residue can pass through the annulus of the phenolic unit, and a tetraether with $O-CH_2-CN$ residues is conformationally unstable[8].



Scheme 1. Main strategies for the introduction of amino functions to the narrow or wide rim of calixarenes, shown for a single unit.

The conformational mobility of calix[4]arenes is restricted, if the ether residues are larger than ethyl. In this case the resulting tetraether can be fixed in one of the four possible isomeric forms (*cone*, *partial cone*, *1,2-* and *1,3-alternate*). Among them the *cone*–conformation is the most explored. For example it was used to obtain extractants for lanthanides and actinides, CMPO (carbamoylmethylphosphine oxides) as ligating functions[9] were attached either to the narrow rim[5] or to the wide rim[10]. Anion receptors such as narrow/wide rim di or tetra-(thio)urea derivatives[11] or cobaltocenium[12] attached via amido groups were obtained. Dimeric capsules formed by self-assembly via hydrogen bonds of the wide rim tetra-urea derivatives were studied,[13] as well as capsules formed from calix[4]arenes carrying dipeptide residues at the wide rim[14].

The *1,3-alternate* conformation was by far less frequently used as platform or building block. Few examples can be enumerated here e.g. di-urea derivatives as anion receptor[15,16], or self-assembled dimers[17] which were derived from the respective amino calix[4]arenes.

In this chapter, we propose strategies for the functionalization of tetraamino calix[4]arene fixed in the *1,3-alternate* conformation where the amino groups are attached to the narrow rim via spacers. They could be equal or different and pairwise oriented in opposite sides. The amino groups can be also attached to the wide rim where again a pairwise orientation of amino groups in opposite directions is characteristic. Here, a distal or adjacent functionalization of tetraamines in *1,3-alternate* conformation

is possible. When all four amino groups are placed on the same side of the *1,3-alternate* skeleton, they should be attached at the wide and at the narrow rim (via spacer) of calix[4]arene. Both sides of the *1,3-alternate* platform can be also functionalized by eight amino groups linked to the wide and to the narrow rim via spacers. They could be equal on both sides achieving compounds with a high D_{2d}-symmetry or could be different in pairwise where the symmetry is turned in C_{2v} one.

Narrow/wide rim tetraamino and octaamino calix[4]arenes fixed in *1,3-alternate* conformation are prepared for further attachment of CMPO as extractants for actinides and lanthanides. Narrow rim tetraamino derivatives are prepared to complete the series of amino calix[4]arenes in the *1,3-alternate* conformation which provide a further attachment of different groups oriented as pairwise in opposite directions. Concerning the wide rim tetraamines in the *1,3-alternate* conformation further fuctionalization by amino groups could provide compounds which have C_{2v}-symmetry (a distal functionalization) or chiral C_2-symmetry (adjacent functionalization). The variety of possibilities of the functionalization by amino groups of calix[4]arene fixed in the *1,3-alternate* conformation is detailed in this chapter.

2.1. Tetraamines, *narrow rim*.

Having four amino groups attached to the narrow rim of the calix[4]arene in the *1,3-alternate* conformation means, that two pairs of amines are pointing in opposite directions as illustrated in Figure 1.

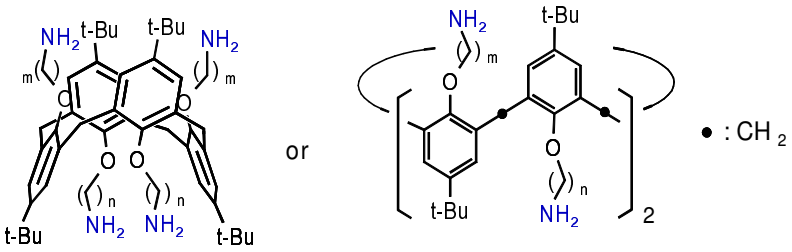


Figure 1. Four amino groups attached to the narrow rim of the *1,3-alternate* skeleton.

For the introduction of the alkyl with protected amine at the narrow rim of calix[4]arenes two step synthesis (see scheme 2) is needed. The first step is the di-O-alkylation (e.g. ω-bromoalkylphthalimides / γ-bromoalkylnitrile) of **1** in the presence of K_2CO_3[18] as base which occurs with the formation of 1,3-*syn*-diethers (**2** or **3**) in high yields. If Cs^+ (Cs_2CO_3) would be used as countercation in the first O-alkylation step a tetra-O-alkylated compound is reported[19] to be obtained also. The next step requires the presence of Cs^+ cation from Cs_2CO_3, used as template which due to cation-π interactions can invert the two distal aromatic rings. The conformation is fixed in the *1,3*

alternate since the introduced groups cannot pass through the annulus (e.g. γ-bromoalkylnitrile / ω-bromoalkylphthalimides). Always, the *partial cone* isomer accompanies the target one.

The four alkyl residues with protected amino functions can be introduced at the narrow rim also in one step by direct O-alkylation of the **1** in the presence of Cs_2CO_3. Tetraethers in *cone*, *partial cone* and *1,2-alternate* conformations can be obtained as by-products. However, tetraethers in the *1,3-alternate* conformation are not as selectively formed as tetraethers in the *cone*. In this case all the ether residues are identical.

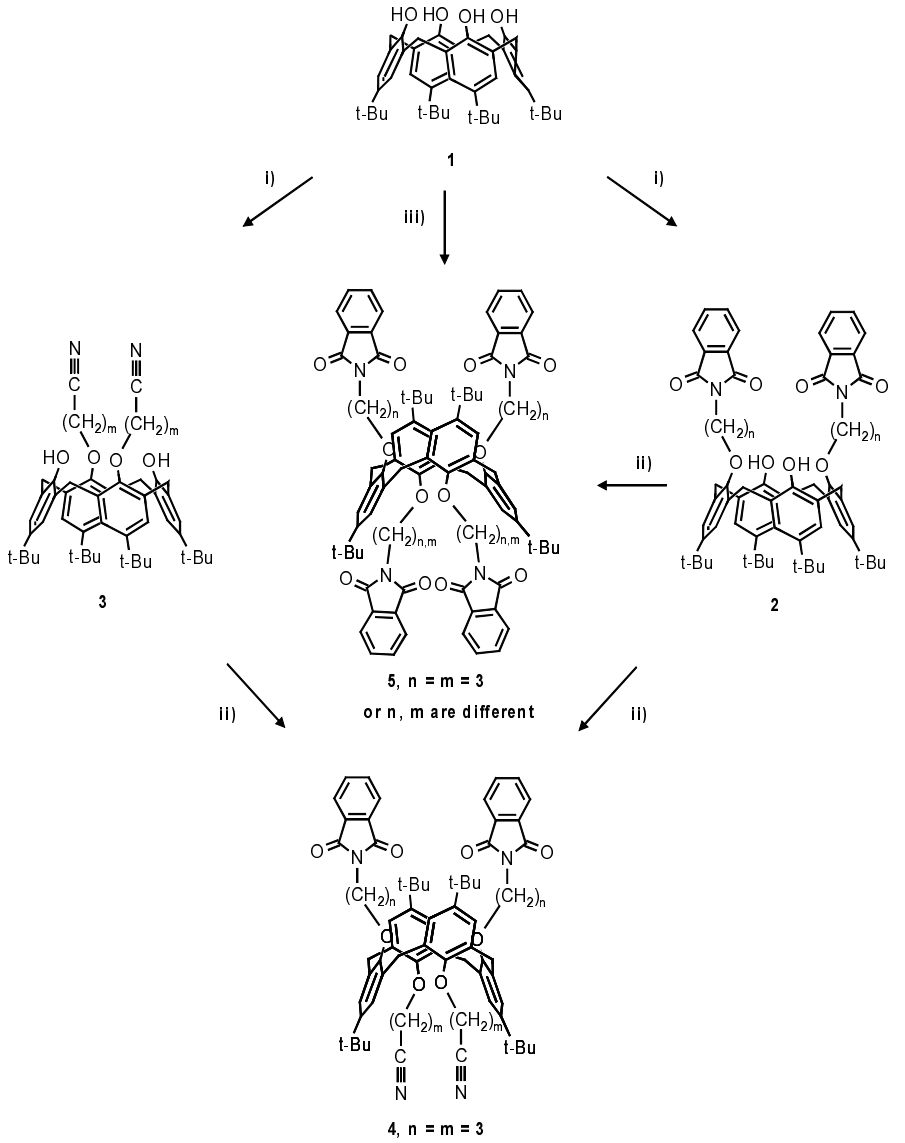
The amount of Cs_2CO_3 (as base and template) can vary between the 8- and 15-fold, with respect to the hydroxyl groups, depending on the nature of the *p*-substituent in the phenolic unit. A higher excess of Cs_2CO_3 is needed when a withdrawing group is situated in *p*-position of the phenolic unit.

Our experience shows that it is preferable to introduce the four ether residues in two steps. First the *syn* diametricallysubstituted calix[4]arenes (**2** or **3**) are obtained in up to 85-90 % yields. In the second step the remaining hydroxyl groups are alkylated (e.g. ω-bromoalkylphthalimides, γ-bromoalkylnitrile) to fix the calixarene in the *1,3-alternate* conformation. The two O-alkylation steps offer the possibility to distinguish between the two pairs of amino groups not only by a different spacer, but also by a different precursor group (e.g. phthalimide, nitrile) allowing independent further functionalization.

The tetraamine precursor **4** as an example was obtained by two pathways. In the first di-O-alkylation step either N-(3-bromopropyl)-phthalimide[5] or the γ-bromobutironitrile[11a] were used as alkylating agents. The *syn* diametrically substituted calix[4]arenes **2** or **3** were obtained in up to 90 % yield. To fix the calix[4]arene in the *1,3-alternate* conformation a further O-alkylation in the presence of Cs_2CO_3 using as reagent the γ-bromobutyronitrile or N-(3-bromopropyl)-phthalimide, respectively is required. Here, the desired *1,3-alternate* isomer is always accompanied by the *partial cone* isomer.

In our hands, the precursor **4** is obtained in 40 % yield when the starting material is the di-phthalimide **2**, while the yield of **4** was 60 % starting from the di-nitrile **3**. In the former reaction the *partial cone* isomer was not isolated, but could be identified in the ^{1}H-NMR spectrum of the mother liquor together with the *1,3-alternate*. In the last mentioned reaction the *partial cone* isomer **4** is isolated in 11 % yield.

The structure of the *1,3-alternate* isomer **4** was confirmed by the ^{1}H-NMR spectrum and additionally by X-ray analysis. In the precursor **4** both protected amino groups (phthalimide and nitrile) can be independently converted to amino groups.



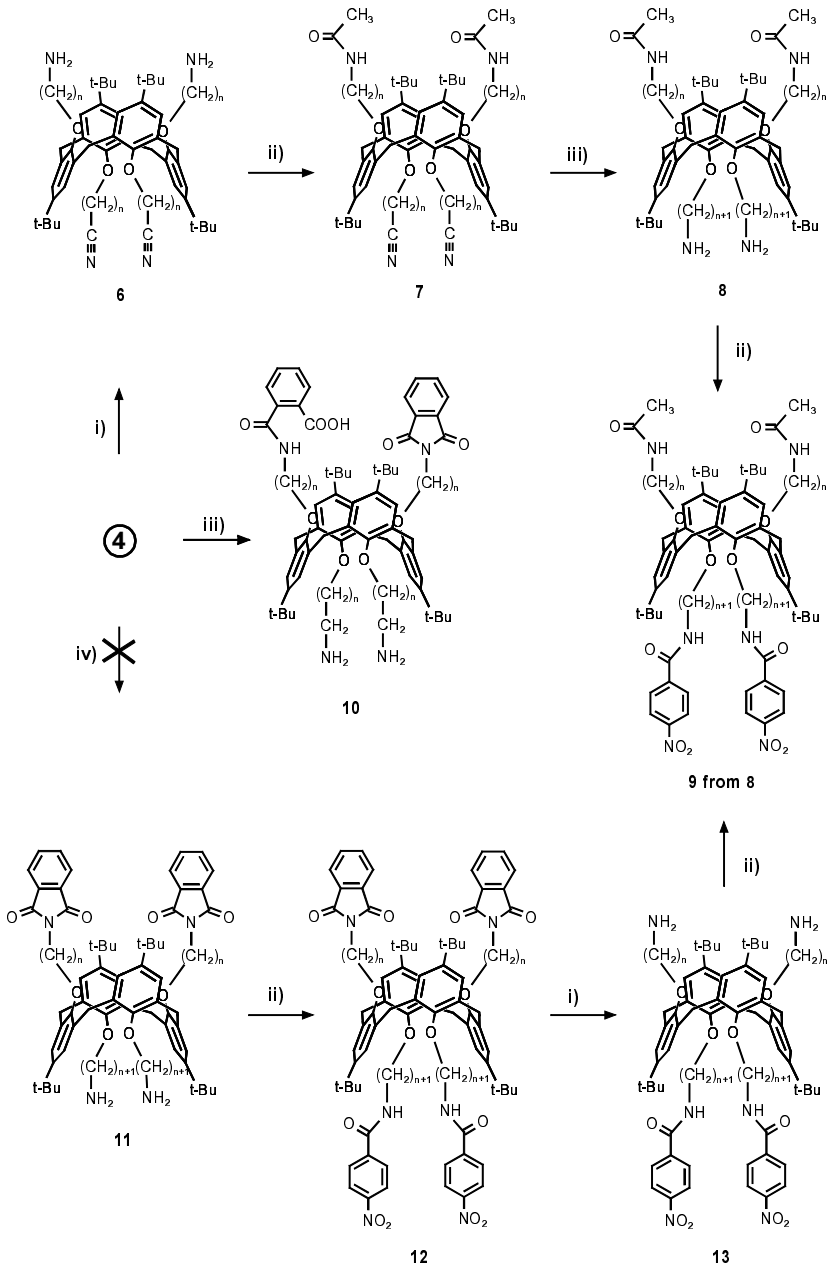
Scheme 2. The synthesis of a precursor (**4**) for a narrow rim tetraamine in the *1,3-alternate* conformation.

i) alkylating agent, K_2CO_3, CH_3CN, reflux, ii) alkylating agent, 40-50 °C, Cs_2CO_3, DMF, iii) alkylating agent, Cs_2CO_3.

Deprotection (of the phthalimide groups) and a first N-acylation with acid chloride (or anhydride) for instance followed by reduction of the nitrile groups and a second N-acylation with anhydride (or acid chloride) gives the possibility to introduce two different amido groups oriented in opposite directions. Alternatively the reduction of the nitrile groups in the first step followed by a first N-acylation (anhydride/acid chloride), subsequent deprotection of the phthalimide groups and a second N-acylation (acid chloride/anhydride) leads to the same product. Scheme 3 summarizes these reaction sequences.

The deprotection of the phthalimido groups with hydrazine leads to the di-amines **6** in 88 % yield and leave intact the nitrile groups. The di-amine was quantitatively N-acetylated to **7**. Subsequent reduction of the nitrile groups with Ra-Ni as catalyst in a mixture of EtOH and THF containing

aqueous NaOH solution (4 %) leads to the di-amine **8** in 50 % yield. The final N-acylation with *p*-nitro benzoyl chloride gives after column separation (chloroform) the tetraamide **9** in 50 % yield.



Scheme 3. The pathways for the independent functionalisation of the narrow rim tetraamines.
i) hydrazine, EtOH, reflux, ii) N-acylation, NEt_3, $CHCl_3$, rt, iii) Ra-Ni, H_2, EtOH, THF, iv) NaOH aq. sol., THF/EtOH, hydrogen atmosphere.

When the other pathway was attempted the reduction of the nitrile groups (in the presence of the phthalimido groups) the conditions mentioned above lead to compound **10** (see scheme 3). The hydrolysis of one phthalimide cycle was deduced from the ^{1}H-NMR spectrum and from the mass-spectrum which shows a peak corresponding to the mass of compound **10**. Several conditions were

tried to keep the phthalimide groups intact during the reduction of the nitrile groups: lowering of the temperature from 50 °C to rt, replacing of the Ra-Ni by Pd/C or using LiOH, a weaker base than NaOH, but the results were similar. Attempts to reduce the nitrile groups with Raney-Ni in toluene at 60 °C left the starting material unreacted[20]. In this case the pathway **4**-**11**-**12**-**13**-**9** is not possible.

2.2. Tetraamines, *wide rim.*

Here we discuss only compounds with amino groups directly linked to the aromatic units (see fig. 2).

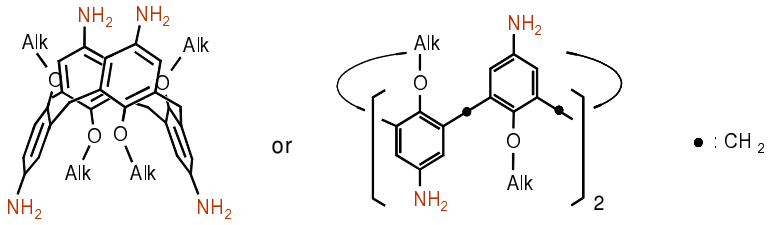


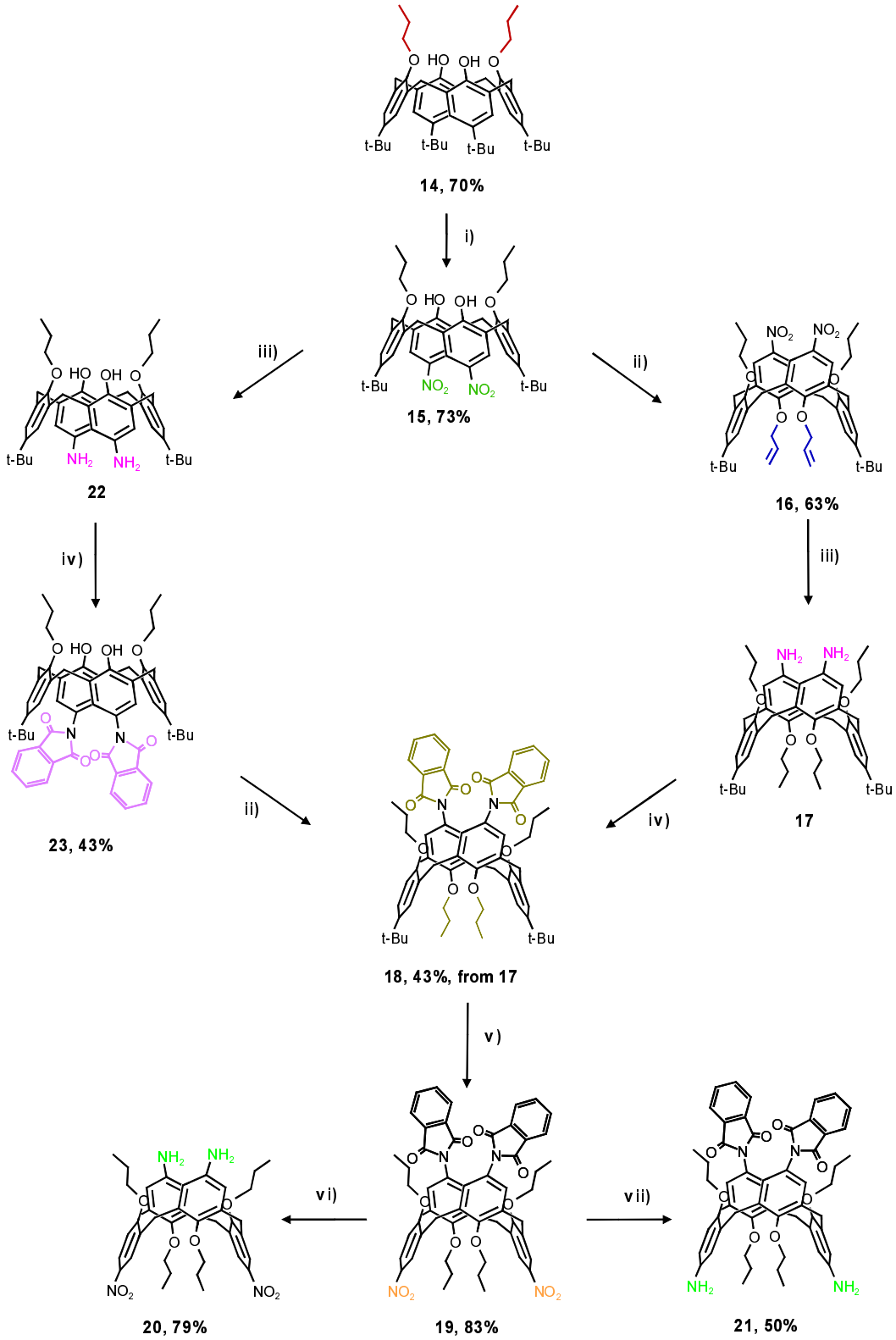
Figure 2. Four amino groups attached to the wide rim of the *1,3-alternate* skeleton.

If the wide rim tetraamino calix[4]arenes derivative fixed in the *1,3-alternate* conformation has identical ether residues no distinction between amino groups is possible. Hereby, it is reported two kind of strategies for functionalization of the wide rim tetraamino calix[4]arenes in the distal and in adjacent positions.

2.2.1. Distally functionalization of the wide rim tetraamines.

The attachment of amino groups directly to the wide rim can be possible by *ipso*-nitration of the tetraether followed by reduction. This sequence is possible for tetraethers in all conformations including the *1,3-alternate* conformation[21] and leads to tetraamines where no differentiation between amino groups can be distinguished. We developed strategies which allow a differentiation between aromatic rings e.g. AC versus BD (distal rings) and also AB versus CD (proximal rings) as discussed below.

The first step of the strategy where amino groups are distally functionalizated consists in a 1,3 di-O-alkylation of **1** in the presence of K_2CO_3. In the next step the remaining *p-tert*-butyl phenol units are *ipso*-nitrated[22] leading two masked amino groups in opposite positions.



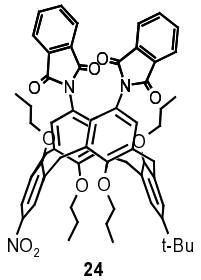
Scheme 4. The synthesis of the precursor of the wide rim tetraamines and independent treatment of the amino protected groups to release the amines. The coloured functions represent the newly groups introduced in each step.
i) HNO_3, 65 %, AcOH gl., CH_2Cl_2, rt, ii) the alkylating agent, 40-50 °C, Cs_2CO_3, DMF, iii) H_2, Ra-Ni, THF, EtOH or toluene, rt, iv) phthalic anhydride, NEt_3, toluene, reflux, v) HNO_3, 100 %, AcOH gl., CH_2Cl_2, rt, vi) hydrazine, EtOH, reflux.

In the next step the conformation of calixarene is fixed in *1,3-alternate* arrangement using Cs_2CO_3 as template. A reactive alkyl halide (e.g. allyl bromide) is required as alkylating agent due to the lower nucleophilicity of the *p*-nitrophenolate. Benzylbromide and ethylbromacetate can also be used, but the allylbromide is preferable because the O-allyl ether is easily hydrogenated to O-propyl ether (tetraether with identical ether residues **17**) in the next step. The reduction (Ra-Ni) of the nitro groups of **16** occurs simultaneously with the hydrogenation of the C=C- double bond and leads to the di-amine **17**, which is protected as phthalimide (**18**) in the next step. *Ipso*-nitration of the *p-t*-butyl phenolate units was done leaving the phthalimido[23] units intact and achieving the compound **19**.

The di-nitro derivative **19** (C_{2v}-symmetry) contains two independent precursors of amino groups oriented pairwise in opposite directions. In this way, a distal functionalization in opposite positions of the of wide rim tetraamines can be achieved.

Derivatives with two different amide residues are available from **19** by deprotection (or reduction), acylation, reduction (or deprotection) and final acylation. The appropriate reaction sequence may be chosen with respect to the special example.

In our hands 63 % of the desired *1,3-alternate* isomer **16** was obtained together with 11 % of the *partial cone* isomer. Both isomers are easily distinguished by their ^{1}H-NMR spectra. In addition to the ^{1}H-NMR spectrum, the X-ray analysis prove the structure of the *partial cone* isomer of **16**. The di-amine **17** is not isolated, but directly protected as phthalimide. After column separation the distal di-phthalimido calix[4]arene derivative **18** is obtained in 43 % yield. Regarding the *ipso*-nitration of **18**, we even found conditions which favour the formation of the mono-nitro derivative. A large volume of dichloromethane as solvent (100 ml / 1 mmol starting material), fuming nitric acid (0.44 ml / 1 mmol starting material) and short reaction time (15 min) leads to the mono-nitro **24** in 79 % yield. This compound having a pair of phthalimido groups oriented in one direction and a single nitro group in the opposite one may be considered as precursor for wide rim triamines in the *1,3-alternate* conformation (see Figure3).



24

Figure 3. A precursor for a triamino derivative in the *1,3-alternate* conformation.

Excess of fuming nitric acid (0.66 ml HNO_3 / 1 mmol starting compound) and longer reaction time (4-5 h, according to tlc) lead to the di-nitro compound **19** in 45 % yield (not optimized). Also the mono-*t*-butyl compound **24** can be further *ipso*-nitrated to the di-nitro compound **19** in 83 % yield.

Regarding the precursor **19** (in analogy to similar derivatives in the *cone*-conformation[26] either the phthalimide groups can be cleaved by hydrazine (**20**, 79 %) or the nitro groups can be reduced (**21**, 50 %). The amino calixarene formed (**20**, **21**) can be used for the further attachment of different type of dyes for instance (see the chapter dyes).

An alternative way of the synthesis of **19** is to reduce first the nitro groups. The formed di-amines **22** are protected as phthalimides **23** (43 %). During the further O-alkylation in the presence of Cs_2CO_3, the calixarene should be fixed in the *1,3-alternate* conformation. Since *p*-N-phthalimido phenyl units are more reactive than *p*-nitro phenyl ones, an alkylating reagent with normal reactivity can be used. This offers the possibility to introduce various alkyl groups which are different then the two already introduced. Unfortunately, the tetraether **18** was not isolated in this way, since the difficulties appeared in the step of second O-alkylation. The two opposite p-phthalimido phenyl units could be inverted. These may be due to hindrances induced by phthalimido moieties.

2.2.2. Proximally functionalization of the wide rim tetraamines.

The other strategy which allows a distinction between AB and CD aromatic rings is based on the selectivity of di-Boc protection reaction of the tetraamine[24] **25**, which is available in large quantity. Around this reaction others as mono-, tri- and tetra-Boc protections were also tried.

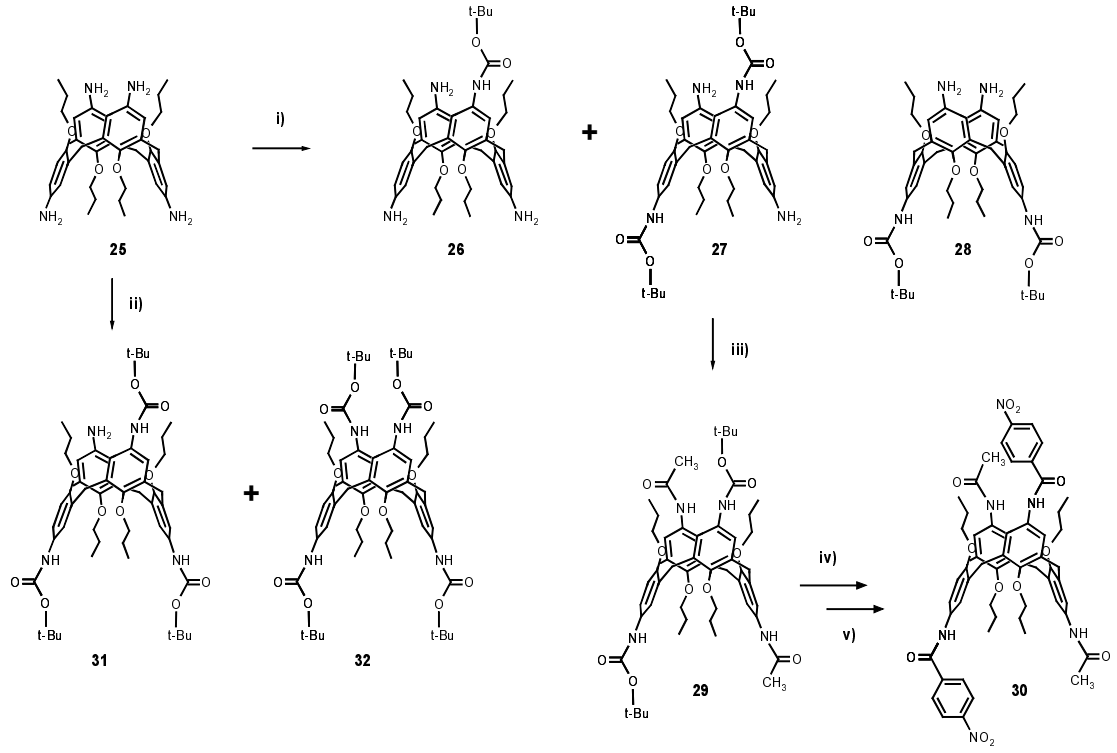
Thus, when 1 mol of tetraamine **25** is treated with 1.9 moles of Boc-anhydride (di-*t*-butyl-dicarbonate) a 1,2-di-Boc protected compound **27** is formed in addition to the mono-Boc protected compound **26**. This is in agreement with the result obtained for the di-Boc protection of the wide rim tetraamines of the *cone* isomer[25]. Similar to the *cone*-derivative the formation of the 1,3-di-Boc compound **28** was not detected. This could be explained by the formation of a transcavity hydrogen bond between the nitrogen amidic of first Boc-protected group with the lone pair electrons of distal amine group. Thus, the distal amino group is capped in this interaction, while the next available amino group is the adjacent one in the other side of *1,3-alternate* skeleton.

We could improve the yield of **27** in the di-Boc protection reaction of tetramine **25** from 58 % to 63 % using 2 moles instead of 1.9 moles of Boc-anhydride. In addition the amount of the mono- protected compound **26** decreases from 23 % to 18 %.

When 3 moles of Boc-anhydride are used for the protection of tetraamines **25**, the tri-Boc protected compound **31** is obtained in 63 % yield with the tetra-Boc protected compound **32** as a by-product.

In the 1,2-di-Boc protected compound **27** the two protected amino groups as well as the unprotected amino groups point into different directions, in contrast to **19**. The di-Boc protected compound **27** has C_2-symmetry and is chiral (see fig. 4). Tetraamides with two different amide functions are available from **27** by acylation, deprotection and a second acylation as shown for one example. The acylation of **27** with acetanhydride (for example) leads quantitatively to **29** which after deprotection is acylated to the tetraamide **30** as shown in scheme 5.

All the compounds derived from **27** (e.g. **29**, **30**) by acylation, deprotection and second acylation keep the chirality. Their optical resolution requires individual conditions for each derivative (or pair of enantiomers).



Scheme 5. Boc-protection of wide rim tetraamines in the *1,3-alternate* conformation and further functionalization of the di-amino, di-Boc-protected derivative **27**.

i) 2 moles Boc_2O, ii) 3 moles Boc_2O, iii) Ac_2O, iv) CF_3COOH, $CHCl_3$, 0°C, v) *p*-nitrobenzoylchloride, $CHCl_3$, NEt_3, rt.

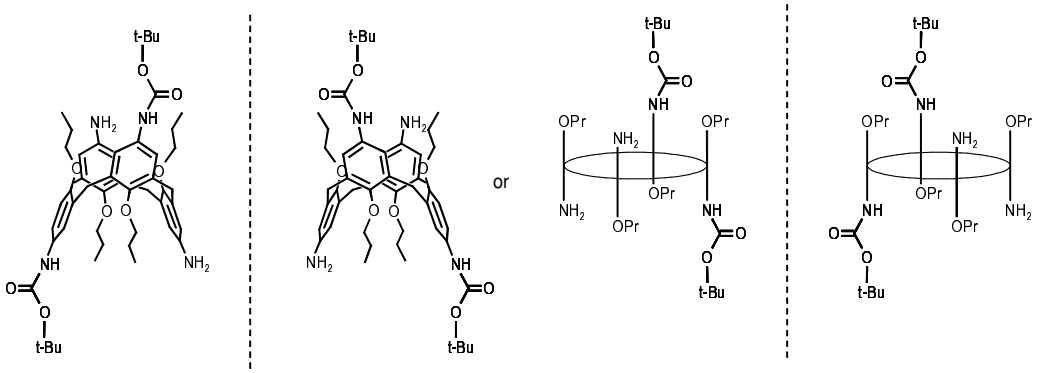
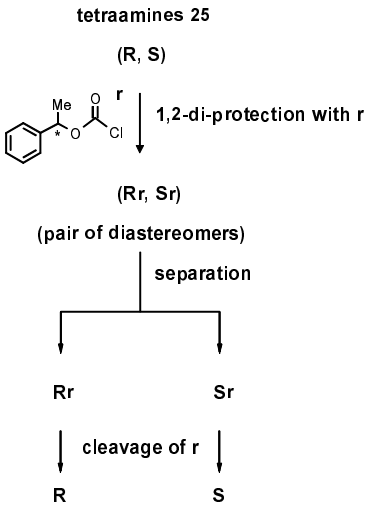


Figure 4. The pair of enantiomers of the 1,2-di-Boc-protected compound **27**.

More rational would be to resolve **27** itself. Chromatography with chiral stationary phase is expansive giving only small amounts from enantiomers. A most expeditious method is to convert the racemate **27** to diastereomers. So, a pure reagent enantiomer for instance **r** [e.g. (+)-(R,R)-tartaric acid or other optically active acid -e.g. mandelic acid, camphoric acid] is attached itself to the racemate **27** yielding a pair of diastereomers (**Rr**, **Sr**) which may be separated (in principle) in its components. However, the "binding" of this reagent is, this must be reversible under conditions, under which the Boc-groups are "stable". Thus, amide bonds are not suitable, while the "salt like" interactions have a chance. Since the diastereomers are isolated either by chromatography or several crystallizations the bond between **R** (or **S**) and **r** should be cleaved yielding the pure enantiomers **R**, **S** (could be also, just one enantiomer isolated). In addition, the optically active agent **r** may be recovered and reused in further resolution.



Scheme 6. Proposal for the resolution of enantiomers using a chiral protective group.

Ideal would be a 1,2-di-protection of tetraamines **25** with chiral protective group (e.g. methyl benzyl chloroformate) instead of Boc-anhydride. Since now the 1,2-di-protected derivative is directly a pair of diastereomers, the proposal for separation of them in its components is illustrated in scheme 6. Each

separated diastereomer is further N-acylated (e.g. acid chloride), followed by cleavage of the chiral groups which would lead to pure entantiomers.

2.3. Tetraamines, *narrow/wide rim.*

If four amino groups attached to the narrow and the wide rim of the calix[4]arene in the *1,3-alternate* are pointing in one direction then two of them must be attached to the narrow rim and two to the wide rim (see Figure5).

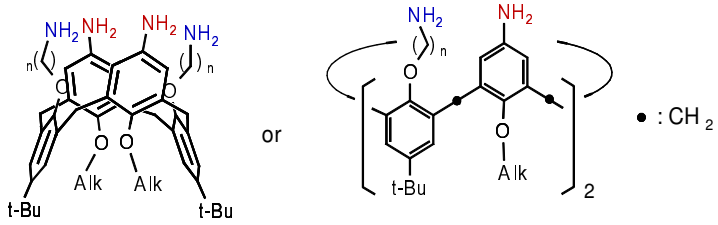
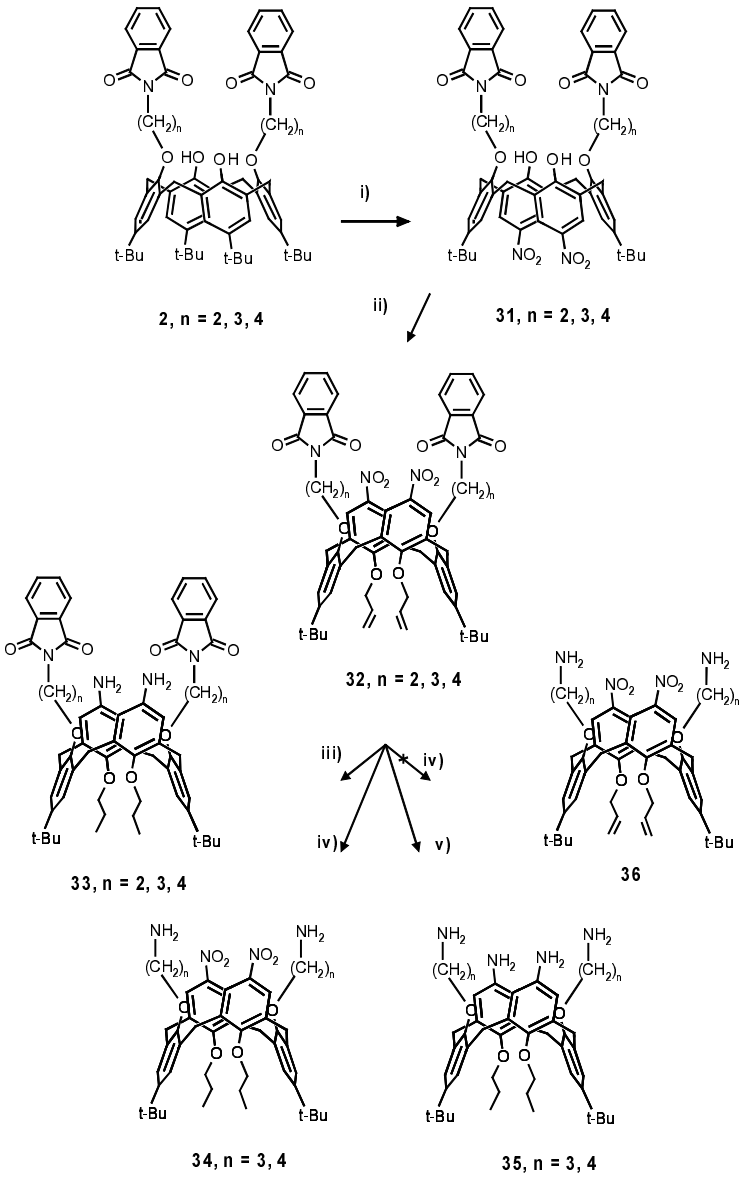


Figure 5. **N**arrow/wide rim teraamines of *1,3-alternate* calix[4]arene.

A reaction sequence to prepare such tetraamines is outlined in Scheme 7. The compounds **2 (n=3, 4)** were obtained in up to 74 % yield by di-O-alkylation of **1** with ω-bromophthalimides, while in the case of **2 (n=2)** hydroxyethylphthalimide was used as reagent under Mitsunobu conditions [diisopropyl diazodicarboxylate (DIAD), triphenylphosphine in THF]. The di-ether is selectively *ipso*-nitrated at lowered temperature (0-5 °C) (similar to **15**) with a 65 % nitric acid affording **31**.

The O-alkylation of the di-nitro compound **31** in the presence of Cs_2CO_3 is a crucial step which requires the reactive allybromide (see wide rim tetraamines). Several conditions were tried to obtain and improve the yield of **32 (n=3)** fixed in the *1,3-alternate* conformation. We succeeded in finding the optimal conditions to obtain desired compound as main product. These conditions were applied also for the homologous compounds **31 (n=2, 4)**. However, *partial cone* and *cone* isomers always accompanied the *1,3-alternate* derivative. These conditions are summarized in Table 1.

According to our experience, the reaction leads at room temperature to the tetra-O-alkylated compound **32 (n=3)** with a low rate while an increase in the temperature favors the formation of the *partial cone* isomer over the *1,3-alternate.* The optimal yield of the *1,3-alternate* isomer **32 (n=3)** is obtained under the following conditions: a ratio between di-nitro derivative **31**, alkylating agent and base of 1:6:6, DMF as solvent and a long reaction time (5-6 days) at 40-50 °C. A chromatographic separation (dichloromethane) is needed to isolate 19 % of *1,3-alternate* isomer **32 (n=3)** beside of 19 % of *partial cone* and 2 % *cone*. For the compound **32 (n=2)** just 1.6 % of tetra-O-alkylated compound fixed in the *1,3-alternate* was obtained together with 9 % of the *partial cone* isomer.



Scheme 7. The synthesis of the precursor **32** for the tetraamines pointing in one direction of the *1,3-alternate* conformation and further functionalization.

i) HNO_3, AcOH, CH_2Cl_2, ii) allylbromide, Cs_2CO_3, DMF, 40-50°C, iii) H_2, Raney-Ni, THF, rt, iv) hydrazine, EtOH, reflux, v) hydrazine, Pd/C, EtOH, reflux.

Entry	ratio between comp. **31 (n=3)** /allylbromide/ Cs_2CO_3	solvent	reaction temperature	reaction time	ratio between obtained isomers *1,3 alternate / partial cone / cone*(the last one could not be always isolated)
1.	1:6:6	DMF[7]	40°C	40h	1:1.5
2.	1:6:6	DMF	40-50°C	6days	1:1:0.1
3.	1:15:15	DMF	120°C	6days	1:2:0
4.	1:15:15	DMF	90°C	6days	1:2:0
5.	1:10:15	Acetone[13]	reflux	4 days	1:2:1
6.	1:8:8	DMF	rt	1.5days	starting material still present

Table 1. The conditions applied for the O-alkylation with allylbromide of the di-nitro compound **31 (n=3)**.

When four carbon atoms separate the oxygen from the phthalimide group, 53 % of the *1,3-alternate* isomer, 11 % of the *partial cone* and just traces of the *cone* isomer were obtained.

This increase of the amount of the *1,3-alternate* isomer **32** with increasing length of the alkyl chain could be due to some (steric) hindrance between the phthalimido group and the nitro groups of the inverted phenolic units. This can explain the increasing amount of the *partial cone* isomer in respect to the *1,3-alternate* isomer for decreasing length of the spacer (see Table 2).

The structure of the *1,3-alternate* isomers of **32** (**n=2, 3 and 4)** and of the *cone* isomer of **32 (n=3)** is confirmed by ^{1}H-NMR spectrum and additionally by X-ray analysis. The other compounds which are involved in the synthesis are characterized by the ^{1}H-NMR spectra.

n	*1,3-alternate / partial cone*
2	1:5.6
3	1:1
4	1:0.2

Table 2. Ratio between *1,3-alternate / partial cone* isomers with respect to the number of the carbon atoms of the alkyl chain, (**n**).

The compound **32** (the structure of which can be compared with **16**) represents a precursor for the tetraamino calix[4]arenes narrow/wide rim, which has again two independent pairs of di-protected amino groups, pointing in the same direction of the *1,3-alternate* platform. Catalytic reduction of the nitro groups leads to di-amines **33 (n=2, 3, 4)** which can be N-acylated at the wide rim. Further deprotection and N-acylation at the narrow rim would furnish a tetraamide with two different residues on the same side of the platform. Also, the other pathway is to cleavage the phthalimdo groups by hydrazine in boiling ethanol leads to the aliphatic di-amines **34 (n=3, 4)**. In di-amines **34** the nitro groups are retained. It is a first N-acylation at the narrow rim, reduction of the nitro groups followed by a second acylation at the wide rim will lead to mixed tetraamides again. The chosen pathway will depend on the nature of the acyl residues which should be the first introduced.

It is worth to note that during the cleavage of the phthalimdo groups the allyl groups were converted to propyl and di-amines **36** were not obtained.

In principle, the tetraamines **35** can be directly obtained by treating of precursor **32** with hydrazine and Ra/Ni or Pd/C as catalyst in boiling ethanol over 2 h. Theoretically, the deprotection, reduction and hydrogenation of double bond should take place simultaneously.

In the case of **n=3** a mixture of compounds (shown by t.l.c) is obtained under several conditions applied: Ra-Ni, excess of hydrazine in boiling ethanol (in 2.5 h) and replacing of the Ra-Ni with Pd/C (in 5-6 h) give a mixture of compounds.

In the case of compound with **n=4** several attempts were made as followed:

a) excess of hydrazine, Ra/Ni as catalyst in refluxing ethanol over 24 h lead to amines which kept intact the allyl functions, as the ^{1}H-NMR spectrum shows. An integration of double bond and aromatic proton signals reveals a ratio of proton signals as –C*H*=CH$_2$: –CH=C*H*$_2$: Ar*H* about 1:2:4. These observations correspond to compound which has intact both allyl groups.

b) replacing the Ra-Ni by Pd/C and 7 h were changes in the reaction conditions under which **32 (n=4)** was reacted. After the catalyst was filtered off and the solvent evaporated yellow oil was formed. It was further acylated with N-AE (active ester, *p*-nitrophenyl (diphenyl phosphoryl)-acetate) affording a compound ^{1}H-NMR spectrum which shows a mixture of two compounds. It contains mainly in a tetraCMPO derivative having allyl groups converted to the propyl groups. The minor compound represents a tetraCMPO compound which has double bonds. It tetraCMPO derivative is described later in the next chapter.

2.4. Octaamines.

It is also possible to attach four amino groups on each side of the *1,3-alternate* skeleton of the calix[4]arene as is presented in the Figure 6.

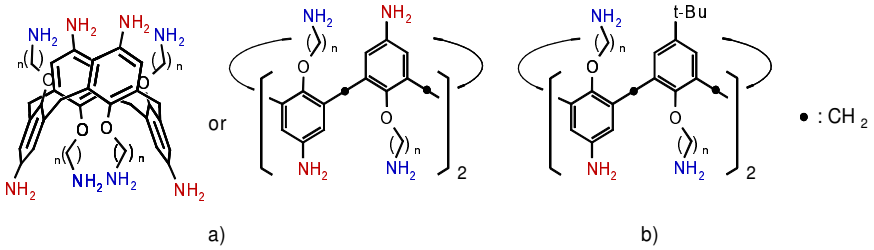
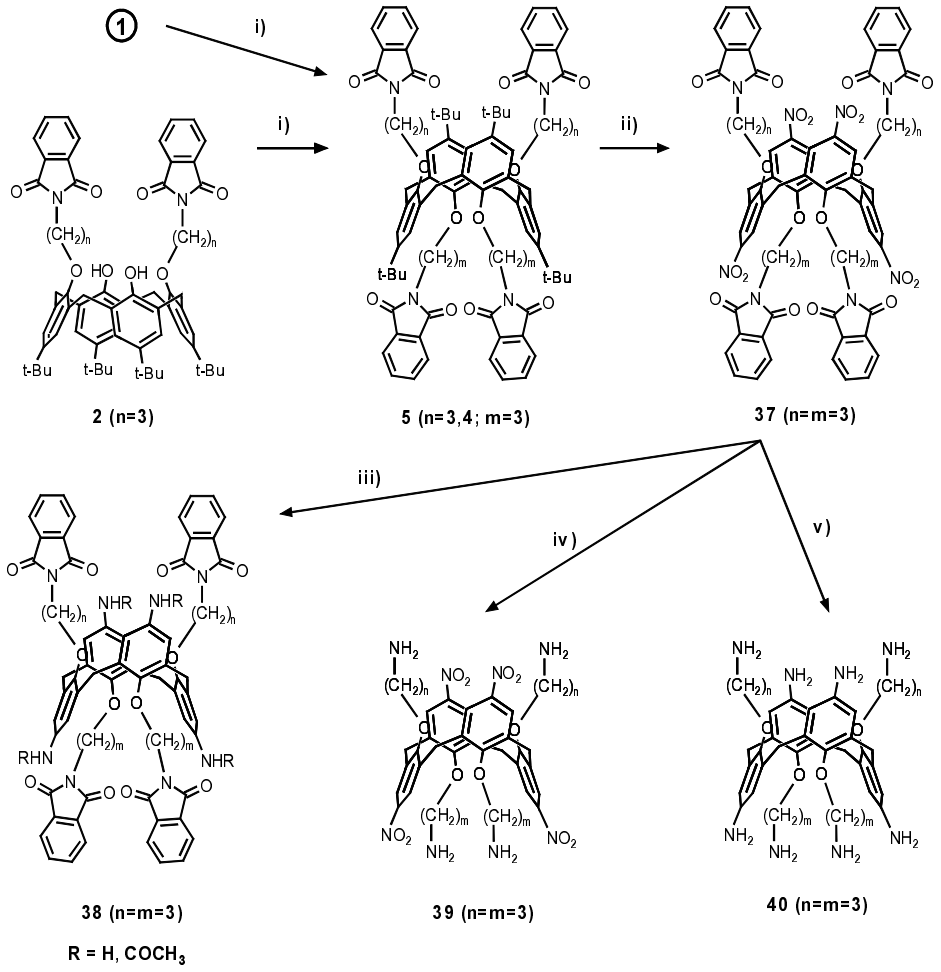


Figure 6. a) octaamines and b) hexaamines of *1,3-alternate* calix[4]arene.

The tetraether **5 (n=m=3)** can be obtained either from the *syn*-1,3-diether or directly in one step from the **1** (scheme 8). The tetraether **5 (n=4, m=3)** with two different spacer lengths is available in 60 % yield in two steps via the di-ether **2 (n=4)**. *Ipso*-nitration leads to the precursor **37** (64 %) for the octaamines, which contains two kind of protected amino groups.

Due to the low solubility of **37 (n=3)** in usual solvents or mixture of solvents the catalytic hydrogenation of the nitro groups was difficult. Therefore, the wide rim tetraamines thus formed were directly reacted with acetic anhydride and characterized as acetamides (see compound **38**). The cleavage of the phthalimido groups gives the narrow rim tetraamines **39**. A direct conversion of the **37** to the octaamines **40** was done by simultaneous reduction of the nitro- and deprotection of the phthalimido groups with hydrazine in boiling ethanol and Pd/C as catalyst.

It is worth to note that other isomers were obtained as side products in the O-alkylation step, which inspired us to synthesize octaCMPO derivatives (see the next chapter) in all possible conformations. Thus, if the **1** is exhaustive O-alkylated in the presence of Cs_2CO_3, 33 % of the target *1,3-alternate* isomer is isolated together with 31 % of *partial cone* and 22 % of *1,2-alternate* isomer **5 (n=3)**. The latter two isomers were isolated by several crystallizations. If the alkylation starts from the 1,3-*syn*-diether **2 (n=3)** (Cs_2CO_3) 36 % of *1,3-alternate* isomer **5 (n=3)** is isolated, while a mixture of such isomers as *partial cone*, *cone* and the target one are identified by ^{1}H-NMR spectrum of the mother liquor. They were not further isolated.



Scheme 8. The synthesis of the precursor **37** for the octaamines and the variety of amines from it.
i) alkylbromide, Cs_2CO_3, THF reflux or DMF 50°C, ii) HNO_3, CH_2Cl_2/AcOH, iii) H_2, Raney-Ni, THF/DMF, 50°, then Ac_2O, iv) hydrazine, EtOH, reflux, v) hydrazine, Pd/C, EtOH, reflux.

Two step synthesis of **5 (n=3)** is preferable for the obtaining of the *1,3-alternate* isomer because this isomer is much easier isolated then in the direct alkylation step of **1**. In this case, all isomers excepting cone one were detected by ^{1}H-NMR spectrum and isolated.

The structure of the isomers was proved by ^{1}H-NMR spectra (see later, Figure 12) and in the case of the *1,2-alternate* and *1,3-alternate* isomers **5 (n=3)** and *1,3-alternate* isomer **37 (n=3)** additionally by X-ray analysis (see subchapter *Single Crystal X-Ray Analyses*).

2.5. Characterization by ^{1}H-NMR.

^{1}H-NMR spectroscopy is the most valuable tool to distinguish these different isomers, especially during their separation, while the ^{13}C signals of the methylene bridges are of limited value[26]. The attribution of the structure is mainly based on the well known pattern of the Ar-CH_2-Ar bridges, of the aromatic protons[27]. Substituents in *p*-position and ether residues may furnish additional information.

For a better understanding of how the ^{1}H-NMR spectra should look for each conformers, we present hereby a comparison of them. Tetraether **5 (n=3)** is taken as an example, where the ether residues are identical making an easer interpretation of proton signals due to highest symmetry in each case (see Figure 7).

The ^{1}H-NMR spectrum of the *1,3-alternate* isomer shows one singlet for methylene protons in the *axial* and *equatorial* positions due to their magnetical equivalence. Also, one singlet for the aromatic protons and another one for the *t*-butyl protons is characteristic for such a high D_{2d}-symmetry.

Here, **5 (n=3)** in *cone* conformation has C_{4v}-symmetry and its ^{1}H-NMR spectrum shows a pair of doublets for the methylene bridges (*J* 12.5 Hz; $\Delta\delta$ 1.26 ppm,) and two singlets one for the aromatic protons and one for the *t*-butyl protons.

Regarding the *partial cone* isomer the highest symmetry which this can achieve is C_s-symmetry. A vertical mirror plane is passing through the inverted aromatic ring and the opposite one. Therefore, an AX system corresponds to the methylene bridges ($\Delta\delta$ around 1 ppm) linked to the alkylated phenol rings in a *syn* orientation (*J* 12.9 Hz; δ 2.99, 4.01 ppm) and an AB system corresponds to the methylene bridge signals between aromatic rings in *anti* position (overlapped with O-CH_2- signals in area of 3.54-3.87 ppm). The ^{1}H-NMR spectrum displays two *m*-coupled doublets (*J* 1.9 Hz; δ 6.53, 6.78 ppm,) and two singlets (δ 7.02, 7.17 ppm, corresponding to the inverted and the opposite unit) for the aromatic protons. Three singlets in a ratio 1:1:2 corresponding to the *t*-butyl protons are displayed in the ^{1}H-NMR spectrum.

The *1,2-alternate* isomer has a C_{2h}-symmetry with an inversion centre. The ^{1}H-NMR spectrum shows a pair of doublets for the methylene bridges linked to the alkylated phenol rings in *syn* orientation (*J* 12.6 Hz; δ 3.0, 4.07 ppm) and one singlet for the methylene bridges linked to the aromatic ring in *anti* position (3.80 ppm). A pair of *m*-coupled doublets (*J* 2.21 Hz; δ 7.05, 7.09 ppm) for the aromatic protons is displayed in the ^{1}H-NMR spectrum.

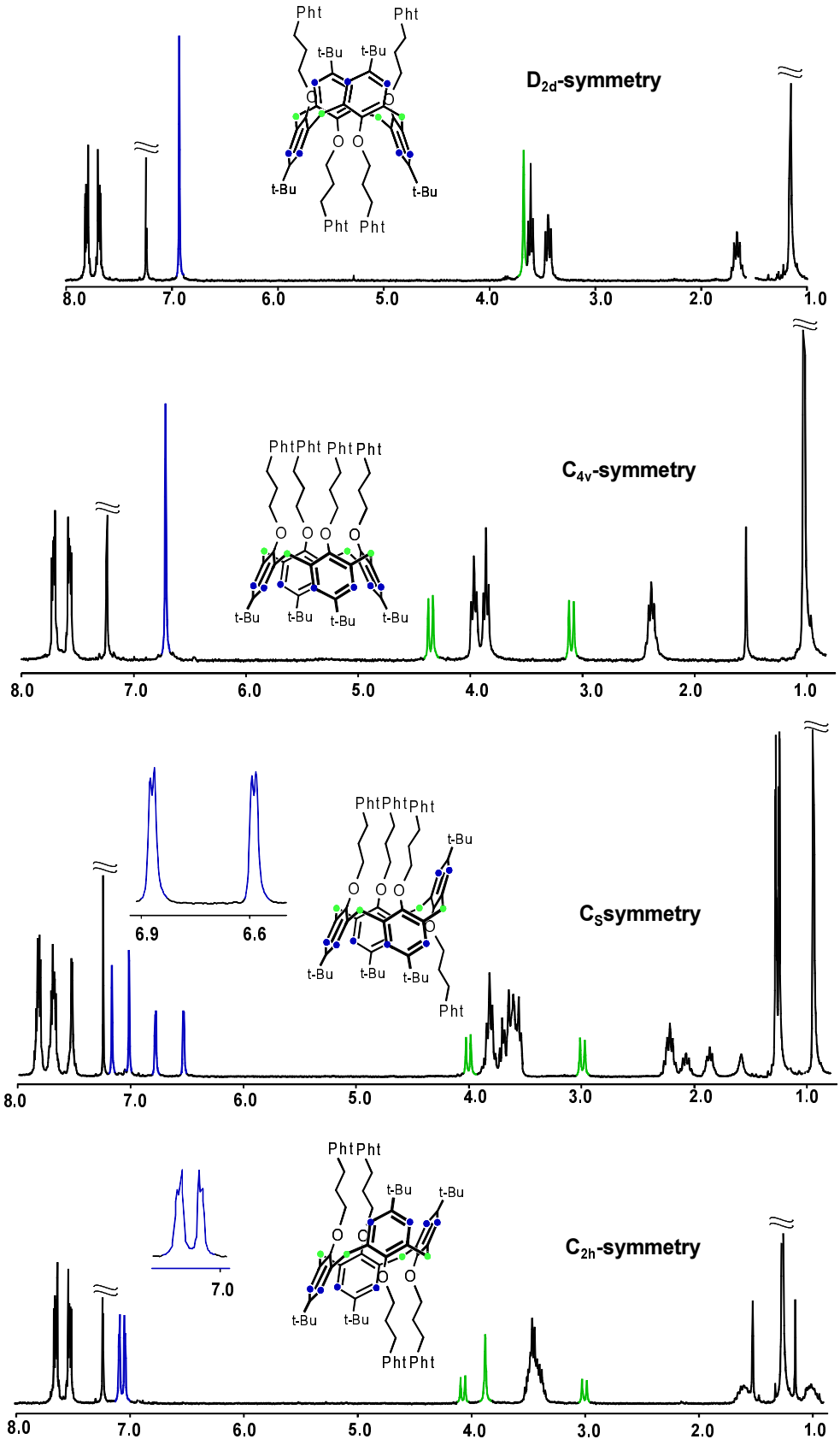


Figure 7. The [1]H-NMR spectra of **5 (n=m=3)** in all possible conformations.

When the length of alkyl chain in the residues positioned in pairwise in the *1,3-alternate* skeleton differs by one methylene groups as in **5 (n=3, m=4)**, the D_{2d}-symmetry of tetraether **5 (n=3)** is turns in C_{2v}-symmetry in tetraether **5 (n=3, m=4)**. Thus, the ^{1}H-NMR spectrum of **5 (n=3, m=4)** measured in C_6D_6 shows a well splitting for the methylene protons (AB-system, δ 3.87/3.92 ppm, 15.6 Hz) (Figure 8- green colour).

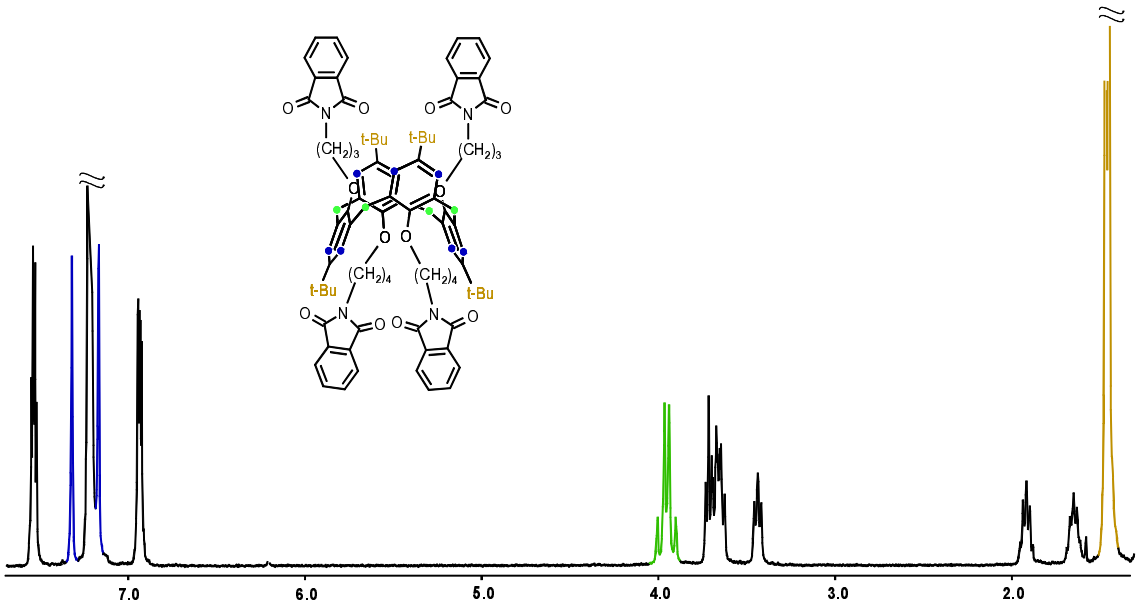


Figure 8. The ^{1}H-NMR spectra in C_6D_6 of **5 (n=3, m=4)**.

When the ether residues in 1,3 and 2,4 positions of the *1,3-alternate* skeleton are much more different than in previous case makes the difference in chemical shifts Δδ between the bridge doublets becomes larger (~ 0.1 ppm). Therefore, in case of **32** (**n=2, 3** and **4**) (Figure 9) a comparison of their ^{1}H-NMR spectra is shown. In this series of compounds small differences in the aromatic part is also observed. The signal of the aromatic proton of the NO_2-phenyl-unit is upfield shifted with the increase of the length of the alkyl chain (δ 8.29 ppm for n=2 to δ 7.99 ppm for n=4).

Since the *1,3-alternate*, *partial cone* and *cone* isomers of **32 (n=3)** are isolated their ^{1}H-NMR spectra measured in $CDCl_3$ are compared. They show distinct signals for the methylene bridge proton and for the aromatic part. The *1,3-alternate* and *cone* isomers of **32 (n=3)** have C_{2v}–symmetry (Figure 10). The difference in chemical shifts Δδ between the doublets corresponding to methylene bridges is about 0.12 ppm for the *1,3-alternate* (δ 3.69, 3.81 ppm) and 1.22 ppm for the cone isomer (δ 3.19, 4.41 ppm).

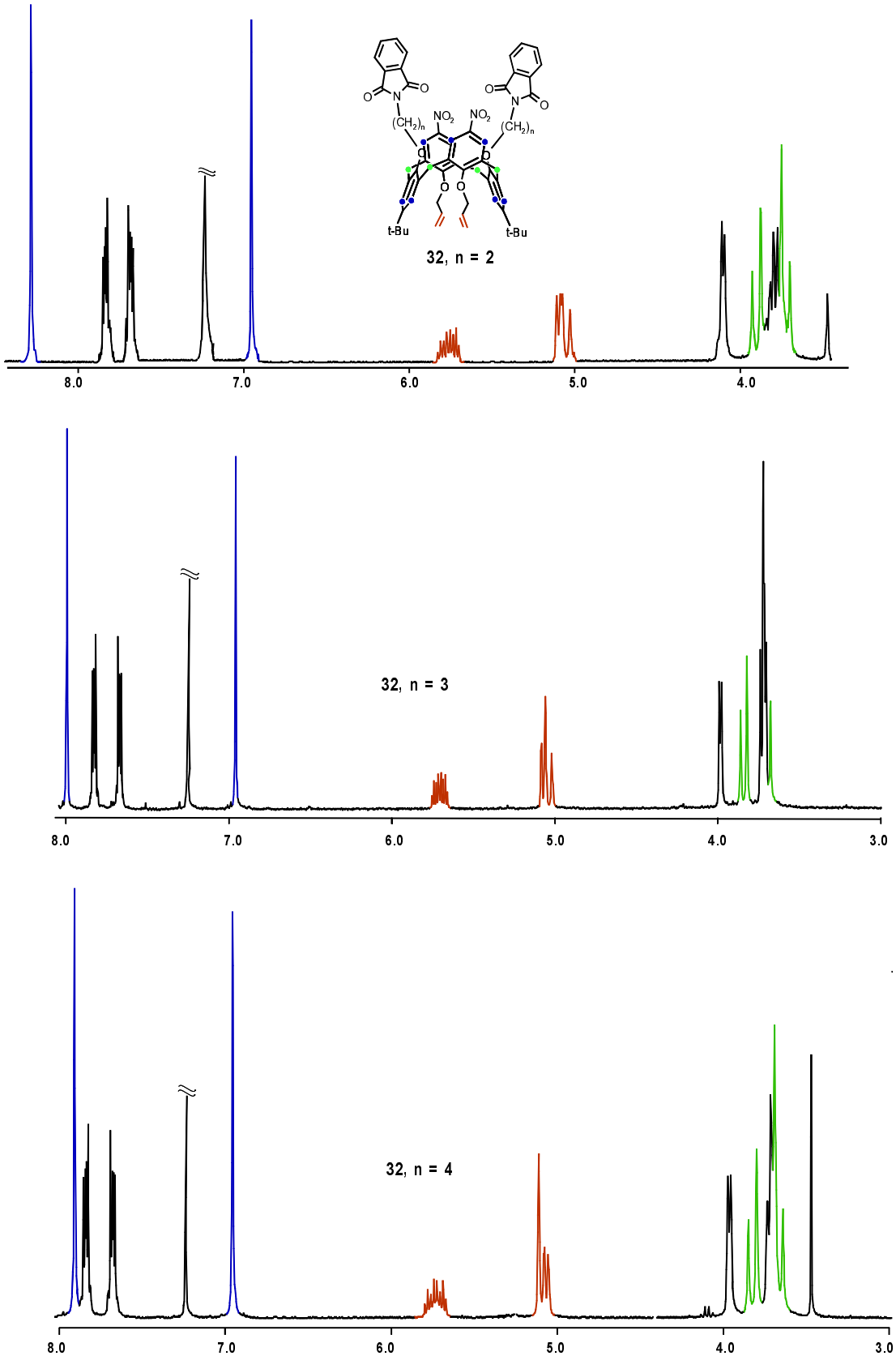


Figure 9. The ^{1}H-NMR spectra of the **32** (**n= 2**, **3** and **4**) in the *1,3-alternate* conformation.

Also, the aromatic part in the ^{1}H-NMR spectrum shows different chemical shifts for the *1,3-alternate* isomer (2s, δ 6.95, 7.99 ppm) and for the *cone* isomer (2s, δ 7.03, 7.12). Even the proton signal corresponding to the H_2C=C*H*- bond is up field shifted (5.70 ppm) for the *1,3-alternate* isomer versus down field shifted (6.13 ppm) in the *cone*.

In the case of the C_S-symmetrical *partial cone* **32 (n=3)** the ^{1}H-NMR spectrum measured in $CDCl_3$ shows four doublets for the methylene bridges. Thus, a difference in the chemical shifts Δδ around 1 ppm for the methylene bridges linked at alkylated phenol rings in a *syn* orientation (*J* 12.9 Hz; δ 3.19, 4.07 ppm) is observed. This corresponds to the similar difference Δδ of the analogous proton signals in the *cone* conformation. The value of difference Δδ of the bridge signals for *anti* disposition decreases to 0.22 ppm (*J* 13.4 Hz; δ 3.68, 3.90 ppm). This would correspond to the similar difference Δδ of the same proton signals in the *1,3-alternate* conformation. Thus, the *partial cone* isomer can be considered as intermediate between *cone* and *1,3-alternate* conformation.

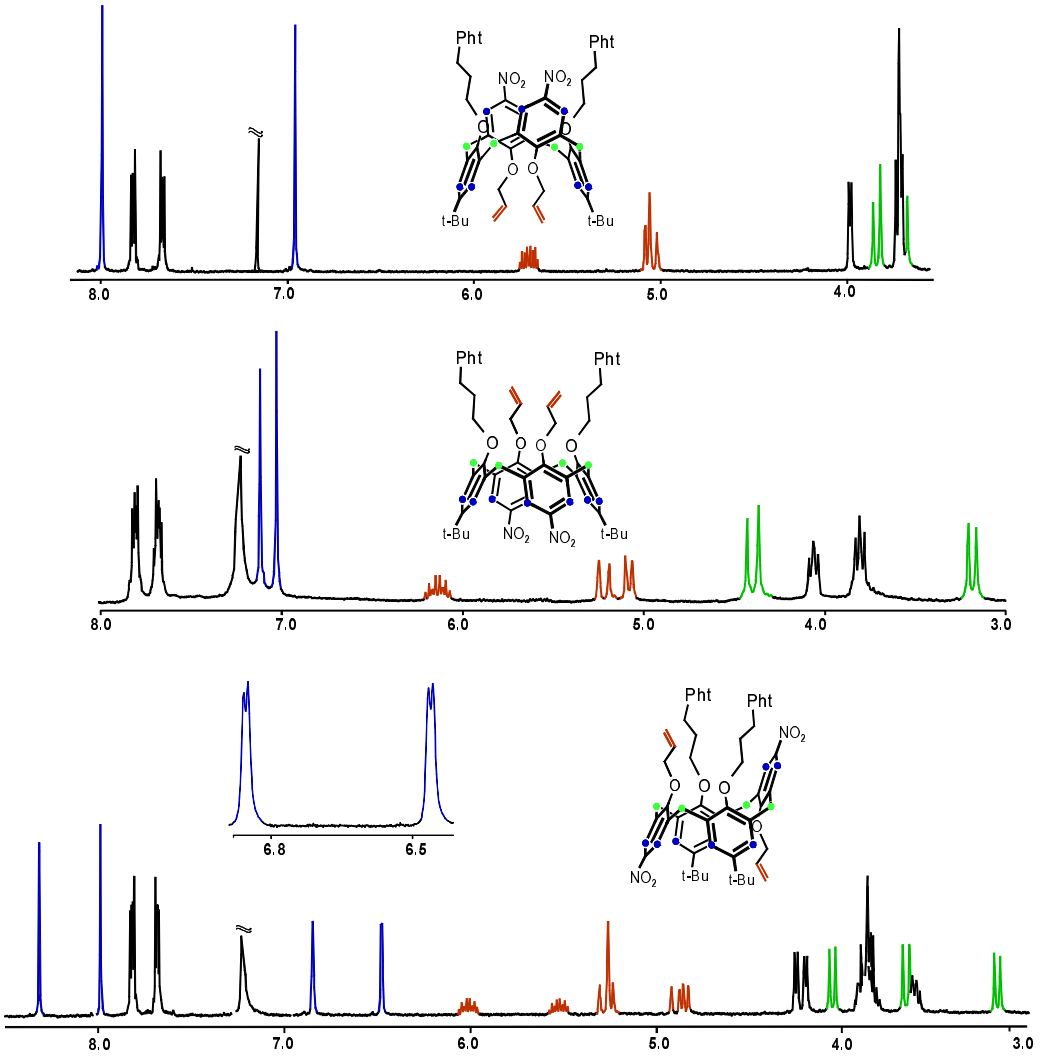


Figure 10. The ^{1}H-NMR spectra in $CDCl_3$ of the *1,3-alternate*, *cone partial* and *cone* isomers of **32 (n=3)**.

The aromatic part in the ^{1}H-NMR spectrum of **32 (n=3)** in *partial cone* conformation consists of two *m*-coupled doublets (*J* 1.9 Hz; δ 6.35, 6.87 ppm, corresponding to the *t*-butyl phenol ether unit) and two singlets (δ 8.05, 8.35 ppm, corresponding to the *p*-NO_2-phenol ether unit). In contrast to *1,3-alternate* and *cone* the ^{1}H-NMR spectrum of the *partial cone* isomer shows two kinds of proton signals for the H_2C=C*H*- double bond and for the methylene group next to the oxygen demonstrated that one of these phenol units is inverted.

An ^{1}H-NMR spectrum similar to the *partial cone* **32 (n=3)** shows the compound **16** in the same conformation (Figure 9).

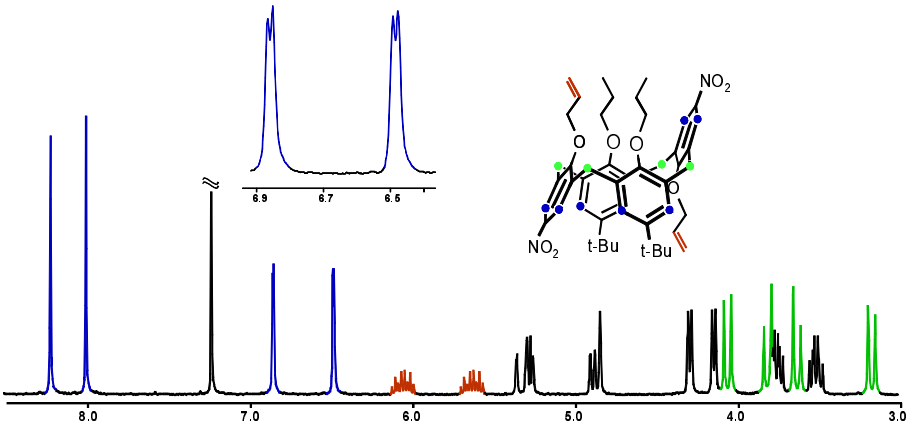


Figure 11. The ^{1}H-NMR spectra in $CDCl_3$ of **16** in the *partial cone* conformation.

A much more complicated ^{1}H-NMR spectrum reveal C_2-symmetrical compound **27** fixed in the *1,3-alternate* conformation. Thus, two ^{1}H-NMR spectra measured in $CDCl_3$ and C_6D_6 are required for the complete identification of the chiral **27** derivative, where a twofold axis intersects the carbon atoms of two opposite methylene bridges. Two singlets (3.28, 3.41 ppm) and a pair of doublets (3.32, 3.37 ppm) for the methylene protons are found in $CDCl_3$. Two AB-systems for the aromatic protons of **27** (doublets at 6.45/6.47 and 7.23/7.27 ppm, see Figure 12) are shown only in C_6D_6, while this clear splitting cannot be seen in $CDCl_3$. The compounds **29** and **30** show a similar pattern of signals reflecting the same C_2-symmetry in both cases.

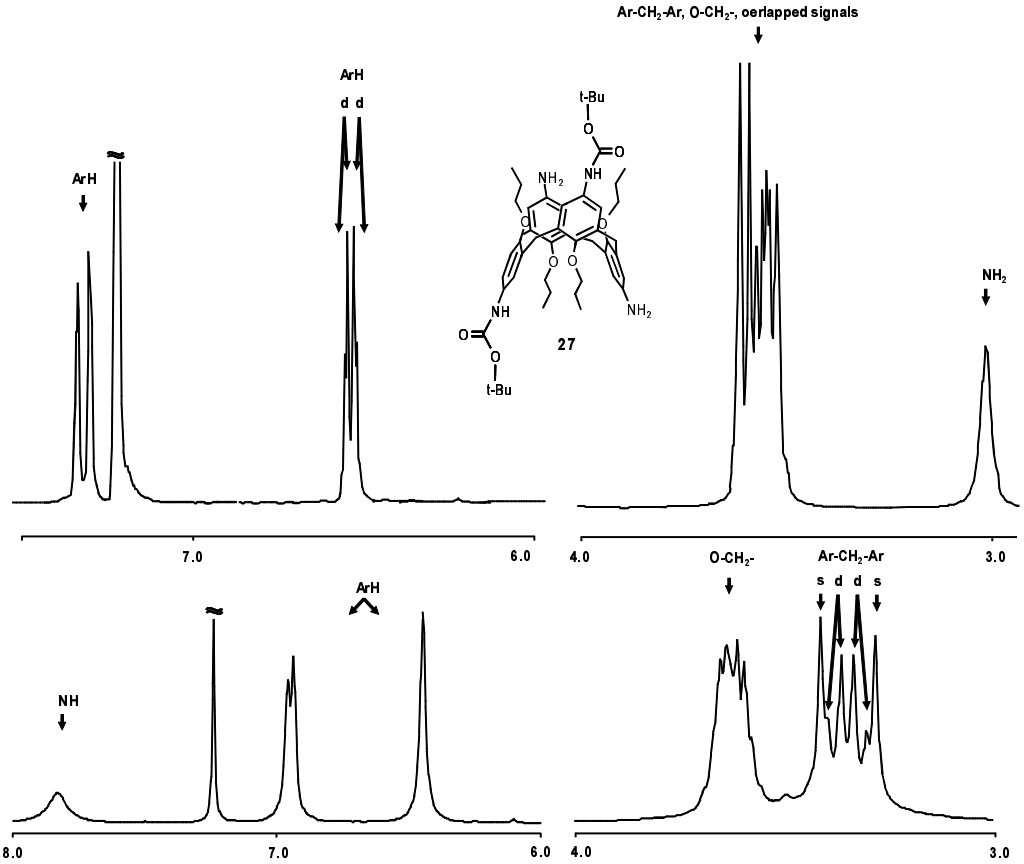


Figure 12. The ^{1}H-NMR spectra in C_6D_6 (above) and in $CDCl_3$ (below) of di-Boc **27**.

2.6. Single Crystal X-Ray Analyses

The topic of this thesis is around calix[4]arene fixed in the *1,3-alternate* conformation. But during the O-alkylation reaction when the calix[4]arene is fixed in the *1,3-alternate* conformation side products are also isolated being calix[4]arene derivatives fixed in other conformations as *partial cone*, *cone* or *1,2-alternate*. To prove the structure of such compounds fixed in different conformation the NMR spectroscopy is a special tool to identify them, but also single crystals would bring additional information about their solid state. Thus, we were able to grow up single crystals in many cases as **32 (n=3)** in *1,3-alternate* and in *cone* conformations, **2 (n=4)** *cone* isomer, **5 (n=3)** in *1,3-alternate* and *1,2-alternate* conformations, **32 (n=4), 37 (n=3), 21, 22** in *1,3-alternate* conformation, and **16** in *partial cone* conformation. Their structures were confirmed by X-ray analysis[*].

A general and unambiguous description of the conformation of calixarenes is possible, using the torsion angles[28] (see Figure 13) around the σ-bonds connecting the methylene bridges and the aromatic units (Table 3). The conformation of a given calix[4]arene is characterised by a typical sequence of the signs of these torsion angles, and these sequences are found for all compounds: (+,-)(+,-)(+,-)(+,-) for a

cone conformation, (-,-)(+,+)(-,-)(+,+) for *1,3-alternate*, (+,-)(+,-)(-,-)(+,+) for a *partial cone*, and (+,-)(+,+)(-,+)(-,-) for the *1,2-alternate*. Since starting point and direction are in principle arbitrary, the sequence (+,-)(+,-)(-,-)(+,+) is identical to (-,+) (+,+)(-,-)(-,+), listed in Table 3.

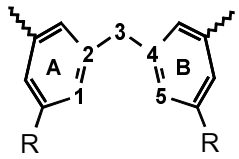


Figure 13. Schematic representation for the determination of the torsion angles around the methylene bridge in calixarenes. The torsion angles are: 1-2-3-4 (Cα6-Cα1-Cα-Cα3, α=1-4 as are presented in Table 4) and 2-3-4-5 (Cα1-Cα-Cα3-Cα4)

To visualize the consequences for the shape of the conformation of calix[4]arenes the inclination[29] (see Figure 14) of the single phenolic units with respect to a reference plane, the best plane through the four methylene carbon atoms (C1 – C4), may be used. These δ-values are included also in Table 4.

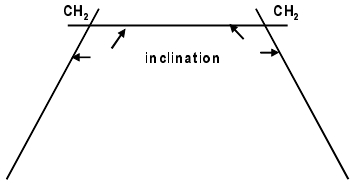


Figure 14. The inclination δ of the phenyl ring with respect to the best plane of methylene group.

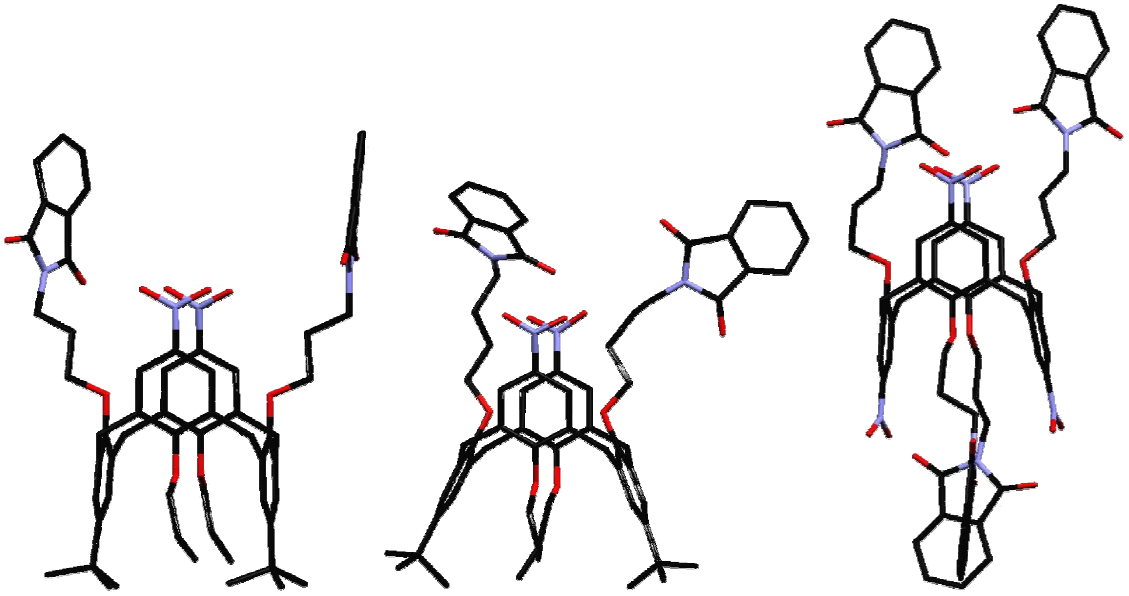
Table 3. Summary of crystal data

Compound	**32(*1,3-alt*, n=3)**	**32(*1,3-alt*, n=4)**	**37(*1,3-alt*)**	**32(*cone*, n=3)**	**2(*cone*, n=4)**	**5(*1,3-alt*, n=3)**	**5(*1,2-alt*, n=3)**	**16(*paco*)**	**19(*1,3-alt*)**	**4(*1,3-alt*)**
Formula	$C_{64}H_{64}N_4O_{12}$	$C_{67}H70Cl_2N_4O_{12}$	$C_{72}H_{56}N_8O_{20}$	$C_{64}H_{64}N_4O_{12}$	$C_{88}H_{92}N_4O_{12}$	$C_{68}H_{82}N_2O_{10}$	$C_{93}H_{108}C_{l4}N_4O_{15}$	$C_{48}H_{58}N_2O_8$	$C_{57}H_{53}C_{l3}N_4O_{12}$	$C_{67}H_{70}C_{l2}N_4O_{12}$
M_W	1081.19	1194.17	1353.25	1081.19	1397.66	1087.36	1663.63	790.96	1092.38	1194.17
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic	Triclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Triclinic
Space group	*C*2/*c* (No. 15)	*P*-1 (No. 2)	P-1	*P*-1 (No. 2)	P-1	P 21/c	P-1	*P*-1 (No. 2)	P-1	P-1
T/K	173	173	173(2)	173	173(2)	173(2)	173(2)	100	100(2)	173(2)
a/ Å	16.7651(15)	13.4904(6)	13.5443(11)	14.1953(7)	14.1131(15)	13.0264(9)	11.8240(9)	10.3423(7)	9.8020(7)	13.4904(6)
b/ Å	29.395(3)	14.1373(7)	13.6010(10)	14.6587(7)	14.5451(16)	24.5795(15)	16.9420(15)	13.1610(9)	15.6199(11)	14.1373(7)
c/ Å	24.507(2)	17.7409(8)	18.4301(15)	15.3671(7)	19.659(2)	19.9439(16)	22.3876(17)	16.5605(7)	17.9197(13)	17.7409(8)
αl°		83.459(4)	74.029(6)	111.121(4)	75.949(8)		85.013(7)	101.868(5)	72.276(6)	83.459(4)

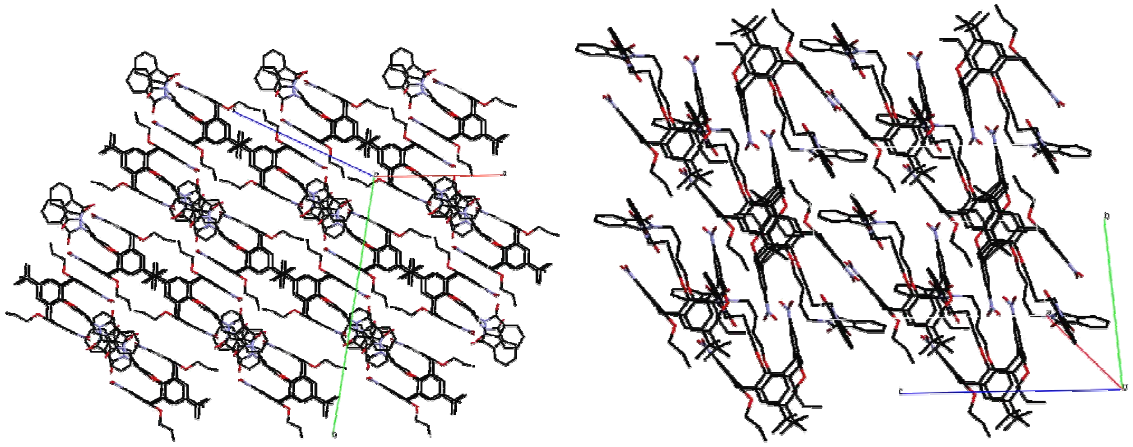
* The X-Ray analyses of compounds were done by Dr. Michael Bolte from Institut für Organische Chemie, Johann Wolfgang von Goethe Universität, Frankfurt/Main, Germany

βl°	95.993(7)	69.464(4)	81.116(7)	92.666(4)	81.634(9)	105.126(6)	84.962(6)	96.988(5)	88.546(6)	69.464(4)
γl°		76.454(4)	86.742(6)		82.159(9)		79.571(7)	91.968(5)	88.444(6)	76.454(4)
V/Å	12011.3(19)	3078.5(2)	3224.5(4)	2923.2(2)	3851.5(7)	6164.4(8)	4382.0(6)	2185.5(3)	2612.0(3)	3078.5(2)
Z	8	2	2	2	2	4	2	2	2	2
μ (mm^{-1})	0.083	0.171	0.104	0.085	0.080	0.078	0.201	0.081	0.244	0.171
Unique refins.	61211	83961	28245	62074	46955	64136	39617	31174	55297	83961
Measured Unique refins.[$I > 2\sigma(I)$]	11107	14584	0.0411	17077	0.0858	0.1027	0.0874	9295	0.0464	0.0896
$wR(F^2)$	0.3033	0.3124	0.0962	0.1492	0.1571	0.2671	0.2383	0.1077	0.1104	0.2944

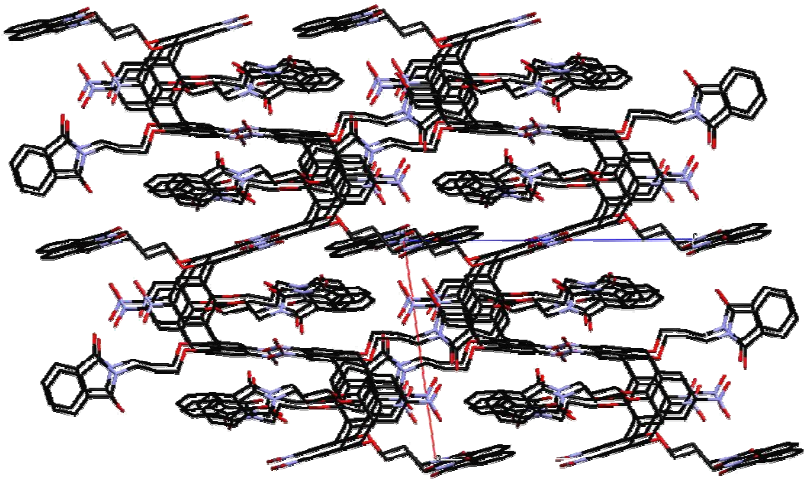
The molecular conformations of all ten compounds are shown in Figure 15.



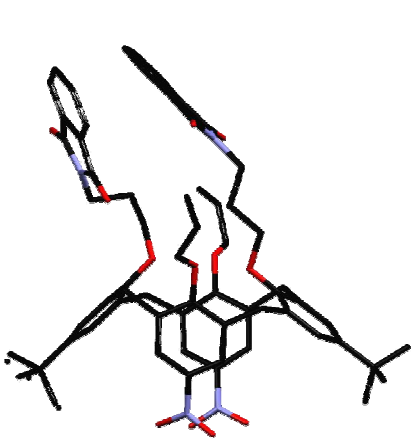
32 (n=3) **32 (n=4)** **37 (n=3)***1,3-alternate*



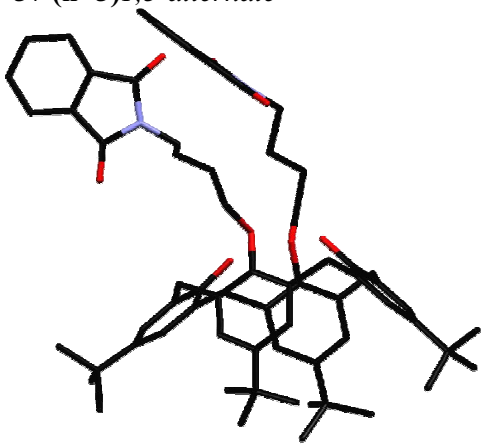
32(n=3), **32(n=4),** *1,3-alternate*



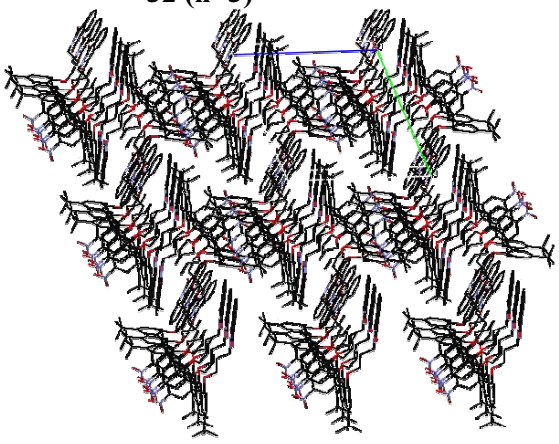
37 (n=3)*1,3-alternate*



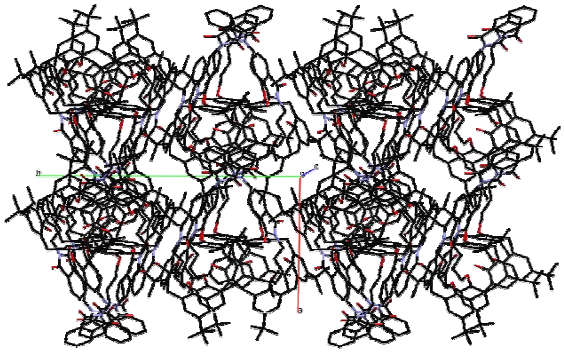
32 (n=3)



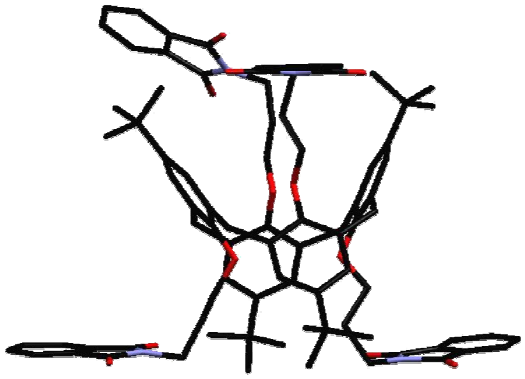
2 (n=4) *cone*



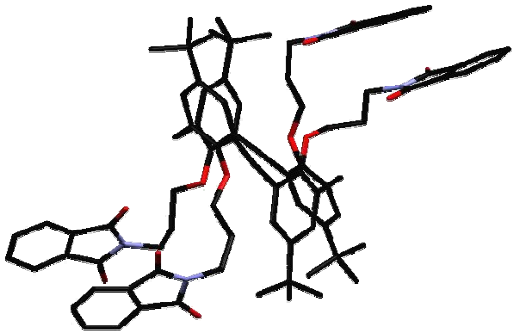
32(n=3)



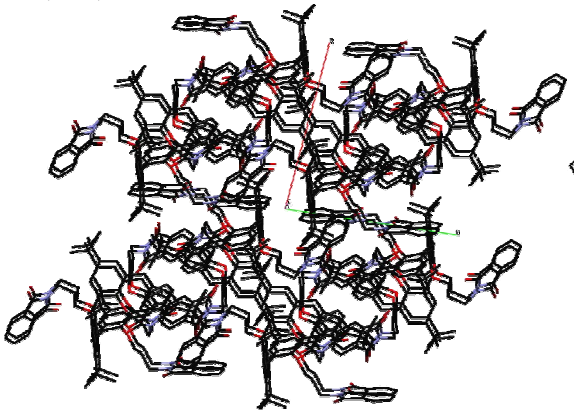
2 (n=4) *cone*



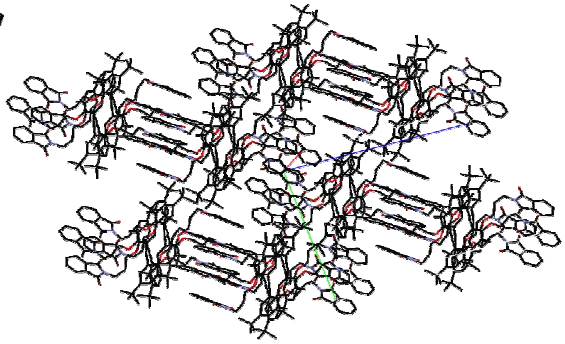
5 (n=3) *1,3-alternate*



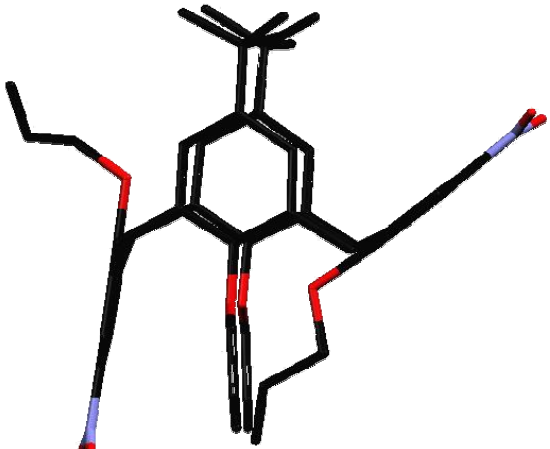
5 (n=3) *1,2-alternate*



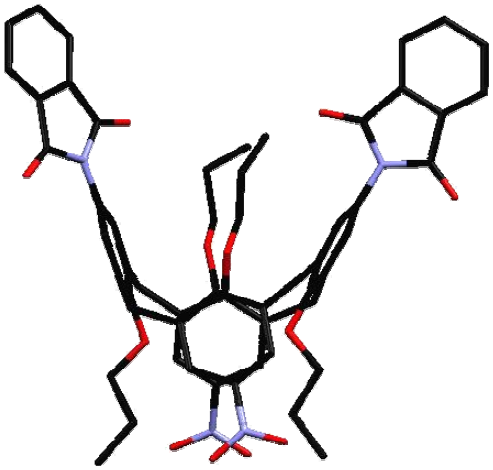
5 (n=3) *1,3-alternate*



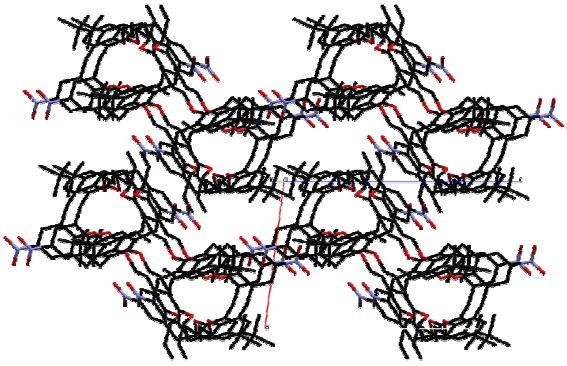
5 (n=3) *1,2-alternate*



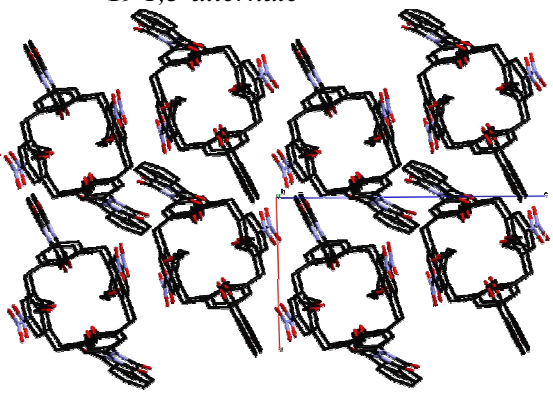
16 *partial cone*



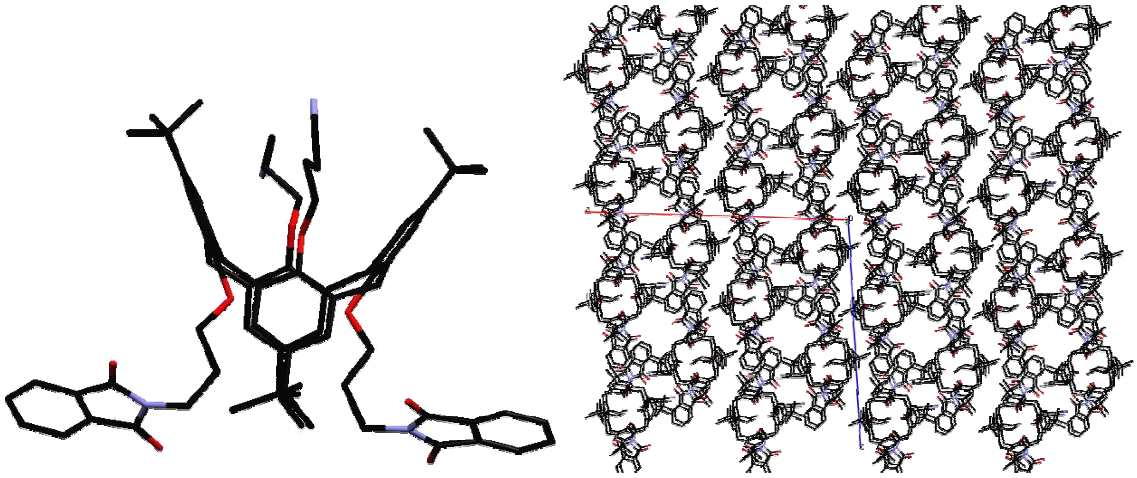
19 *1,3-alternate*



16 *partial cone*



19 *1,3-alternate*



4 **4** *1,3-alternate*

Figure 15. Molecular conformation of calix[4]arene derivatives in different conformation and their packing diagram.

Crystallographic data

Data were collected on a STOE-IPDS-II two-circle diffractometer employing graphite-monochromated MoKα radiation (0.71073 Å). Data reduction was performed with the X-Area software[30]. Table 3 lists the most important parameters of the X-ray analysis.

Table 4. Selected crystallographic data: **I)** Torsion angles (°) around the Ar-CH_2-bonds; **II)** Distances within the reference plane, the best plane through the carbon atoms of the methylene bridges (Å); **III)** Inclination δ (°) of the aromatic ring with respect to the reference plane.

	32(*1,3-alt*, n=3)	**32(*1,3-alt*, n=4)**	**37(*1,3-alt*)**	**32(*cone*, n=3)**	**2(*cone*, n=4)**	**5(*1,3-alt*, n=3)**	**5(*1,2-alt*, n=3)**	**16(*paco*)**	**19(*1,3-alt*)**	**4(*1,3-alt*)**
I. Torsion angles										
C16-C11-C1-C43	114.43	136.43	130.66	-102.78	-83.20	-124.42	91.66	-117.03	153.77	135.72
C11-C1-C43-C44	106.71	126.81	118.38	61.23	98.22	-152.64	-58.45	-121.8	102.66	130.34
C26-C21-C2-C13	-113.35	-115.86	-116.68	-40.41	-112.42	131.89	-147.40	104.56	-137.78	-132.67
C21-C2-C13-C14	-115.22	-141.38	-126.68	91.79	80.84	139.77	-142.56	119.95	-133.85	-141.83
C36-C31-C3-C23	116.17	132.34	118.82	-112.13	-79.04	-138.06	-59.83	103.49	135.90	135.69
C31-C3-C23-C24	112.20	122.01	115.60	60.62	116.16	-140.37	92.01	-54.23	119.15	141.74
C46-C41-C4-C33	-106.29	-122.85	-124.51	-43.47	-94.71	134.50	115.59	-66.14	-130.51	-119.84
C41-C4-C33-C34	-118.08	-134.80	-114.30	100.62	74.03	148.55	122.71	-101.56	-118.87	-146.84
II. Reference planes C1 – C4										
Distance C1 − C2)	5.060	5.129	5.038	4.962	5.119	5.142	5.128	5.077	5.145	5.102
Distance C2 − C3	5.097	5.109	5.093	5.122	5.106	5.184	5.103	5.111	5.134	5.120
Distance	5.059	5.112	5.075	4.988	5.130	5.162	5.096	5.061	5.109	5.122

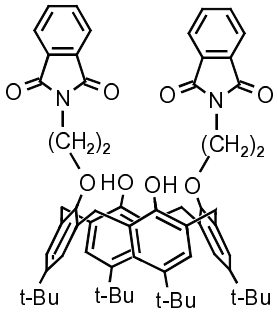
C3 − C4 Distance	5.090	5.121	5.116	5.117	5.104	5.155	5.066	5.042	5.123	5.101
C1 − C4 Distance	7.182	7.306	7.254	7.471	7.292	7.316	6.673	7.131	6.944	7.247
C1 − C3 Distance	7.177	7.164	7.145	6.729	7.173	7.238	7.709	7.215	7.412	7.191
C2 − C4										
III. Inclination of the aromatic units(δ)										
C11 − C16	91.4	116.3	105.12	134.4	114.69	116.32	128.92	99.0	121.13	117.49
C21 − C26	91.6	102.4	94.46	78.9	149.6	117.36	131.04	95.4	111.25	120.37
C31 − C36	94.3	110.9	94.48	142.4	108.57	123.29	97.37	84.4	105.81	106.21
C41 − C46	84.9	106.7	99.56	79.8	131.7	123.99	94.59	139.3	99.74	117.74

2.7. Experimental part.

Materials

Solvents and all other chemicals were purchased from Acros, Aldrich, Lancaster and used without further purification. Silica gel (Merck, 0.040-0.063 mm) was used for column chromatography. ^{1}H-NMR spectra were reordered on a Bruker AC200, AC300 and Brucker DRX400 Avance instruments. FD and ESI mass spectra were measured on a Finningan MAT 8230 spectrometer. Melting points are uncorrected.

5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-diphthalimidoethoxy-calix[4]arene 2 (n=2) (***cone***)

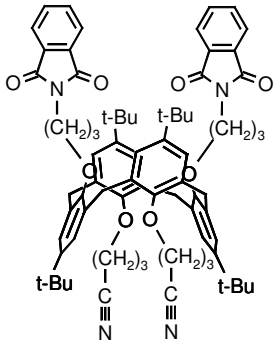


A solution of triphenylphosphine (6,0 g, 23 mmol) in THF (40 ml) was cooled down to 0-5°C (ice bath) and di-*iso*-propyl azodicarboxylate (DIAD) (23 mmol, 4.5 ml) was added dropwise under nitrogen. After 30 min a white precipitate was formed and a suspension of *t*-butyl calix[4]arene (5.0 g, 7.7 mmol) and *N*-(hydroxyethyl)-phthalimide (4.4 g, 23 mmol) in THF (100 ml) and DMF (15 ml) was slowly added. The reaction mixture was stirred 1 h at 0-5°C and after it was warmed to rt until the suspension became clear (5 h). Then the solvent was partially removed under reduced pressure until a pale yellow precipitate was formed. It was filtered off, washed with water (50 ml) and methanol (30 ml) to give the pure product as white powder (4.6 g, 60 %). mp 297-298°C (Found: C 77.21, H 7.17, N 12.80. $C_{64}H_{70}N_2O_8$ requires C 77.24, H 7.09, N 12.86)

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.86, 1.25 (2s, 18/18H, *t*-Bu), 3.25, 4.19 (2d, 4/4H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.24 (t, 4H, ^3J = 6.6 Hz, -CH_2- N), 4.42 (t, 4H, ^3J = 6.9 Hz, O-CH_2-), 6.69, 6.98 (2s, 4/4H, Ar*H*), 6.77 (s, 2H, O*H*), 7.67-7.92 (m, 8H, Phth-*H*)

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-phthalimidopropoxy-26,28 -*bis*-cyanopropoxy-calix[4] arene 4 (*1,3-alternate*)

a) by *O*-alkylation of **3**



A suspension of diether **3** (3.9 g, 5 mmol) and Cs_2CO_3 (16.25 g, 50 mmol) in dry DMF (40 ml) was heated to 50°C under argon for 1 h. A solution of *N*-(3-bromopropyl)-phthalimide (13.34 g, 50 mmol) in DMF (10 ml) was added and the heating was continued for 7 days under argon. The solvent was removed under reduced pressure and the yellow residue was dissolved in chloroform. The solution was washed with water (2x75ml), dried ($MgSO_4$), concentrated and the product was precipitated with methanol to give 3.3 g (60 %) of **4 (*1,3-alternate*)** as a white powder. From the filtrate 0.63 g (11 %) of a yellow powder separated after several days which consisted mainly of the *partial cone* isomer.

4 (*1,3-alternate*): mp 241-243 °C, (Found: C 74.55, H 7.16, N 4.48. $C_{74}H_{84}N_4O_8x2H_2O$ requires C 74.47, H 7.43, N 4.69)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20, 1.28 (2s, 18/18H, *t*-Bu), 1.32-1.42 (m, 8H, -CH_2-CH_2-CH_2-), 1.86 (t, 4H, ^3J = 7.5 Hz, -CH_2-CN), 3.38 (t, 4H, ^3J = 8.0 Hz, -CH_2-N), 3.46, 3.52 (2t, 4/4H, ^3J = 7.0, 6.63 Hz, O-CH_2-), 3.86, 3.78 (2d, 4/4H, ^2J = 13.8 Hz, Ar-CH_2-Ar), 6.97, 7.00 (2s, 4/4H, Ar*H*), 7.68-7.82 (m, 8H, Phth-*H*).

4 (*partial cone*): mp 233-235 °C after recrystallisation from chloroform/methanol (15 ml, 1:2)

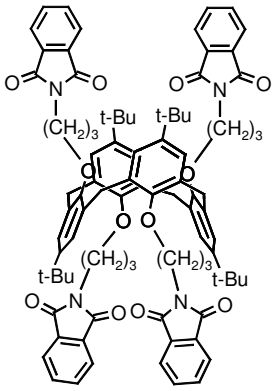
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01, 1.25, 1.27 (3s, 18/9/9H, *t*-Bu), 1.74 (m, 2H, -CH_2-CH_2-CH_2-), 1.89 (m, 2H, -CH_2-CH_2-CH_2-), 2.11 (m, 4H, -CH_2-CH_2-CH_2-), 2.57 (t, 4H, ^3J = 7.0 Hz, -CH_2-CN), 3.09 (d, 2H, ^2J = 12.5 Hz, Ar-CH_2-Ar), 3.30 (t, 4H, ^3J = 7.3 Hz, -CH_2-N), 3.55-3.88 (m, 12H, O-CH_2-, Ar-CH_2-Ar), 4.00 (d, 2H, ^2J = 12.1 Hz, Ar-CH_2-Ar), 6.67, 6.86 (2d, 2/2H, ^2J = 2.2 Hz Ar*H*), 7.01, 7.10 (2s, 2/2H, Ar*H*), 7.68-7.84 (m, 8H, Phth-*H*).

b) by *O*-alkylation of **2 (n=3)**

Diether **2** (1.0 g, 0.97 mmol), γ-bromo butyronitrile (0.97 ml, 9.7 mmol), and Cs_2CO_3 (3.16 g, 9.7 mmol) were suspended in DMF (15 ml) at 50 °C. The reaction was conducted as described above. The sticky mass formed after evaporation was treated twice with chloroform (50 ml) and slightly acidified water (75 ml). The organic phase was dried ($MgSO_4$) and the product was isolated and purified by precipitation from chloroform/methanol to give 0.45 g (40 %) of **4(*1,3-alternate*)** as white powder, identical in all aspects to the product described above. The filtrate contained the *partial cone* isomer (t.l.c.) which was not isolated in this case.

5,17,11,23-Tetra-*t*-butyl-25,27,26,28-tetra-phthalimidopropoxy-calix[4]arene 5 (n=m=3) *(1,3-alternate*), 5 (n=m=3, *1,2-alternate*) and 5 (n=m=3, *partial cone*).

a) starting from *t*-butyl-calix[4]arene **1**



A suspension of **1** (5 g, 7.7 mmol) in THF (400 ml) and Cs_2CO_3 (25 g, 77 mmol) was stirred at rt for 1 h under nitrogen. A solution of *N*-(3-bromopropyl)-phthalimide (20.6 g, 77 mmol) in THF (15 ml) was added and the mixture was refluxed under nitrogen for 7 days. The solvent was removed under reduced pressure and the dry residue was dissolved in chloroform (25 ml) and washed with water (3x100 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The pure *1,3-alternate* isomer was obtained as white crystals (3.45 g, 33 %) by two fold recrystallization from dichloromethane/methanol (30 ml, 1:5). The *1,2-alternate* isomer was found in the mother liquors and was isolated as white powder by precipitation with methanol (1.8 g, 22 %). The filtrate was evaporated to dryness and the white residue was dissolved in chloroform and methanol (40 ml, 1:1). The *partial cone* isomer of **5** precipitated as white powder upon slow evaporation of the solvents. (3.2 g, 31 %).

5 (n=m=3, *1,3-alternate*): mp 255-257 °C (Found: C 75.60, H 7.02, N 4.05. $C_{88}H_{92}N_4O_{12}$ requires C 75.60, H 6.63, N 4.01)

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 36H, *t*-Bu), 1.67 (m, 8H,-CH_2-CH_2-CH_2-), 3.44 (t, 8H, ^3J = 7.8 Hz, -CH_2-N),3.62 (t, 8H, ^3J = 6.8 Hz, -CH_2-O), 3.67 (s, 8H, Ar-CH_2-Ar), 6.92 (s, 8H, Ar*H*), 7.65-7.82 (m, 16H, Phth-*H*).

5 (n=m=3, *1,2-alternate*): mp 197-199°C

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.05 (m, 4H, -CH_2-CH_2-CH_2-) 1.26 (s, 36H, *t*-Bu), 1.60 (m, 4H, -CH_2-CH_2-CH_2-), 3.00, 4.07 (2d, 2/2H, ^2J = 12.1 Hz, Ar-CH_2-Ar), 3.54-3.87 (m, 16H, -CH_2-N, -CH_2-O), 3.88 (s, 4H, Ar-CH_2-Ar), 7.05, 7.09 (2d, 4/4H, ^2J = 2.2 Hz, Ar*H*), 7.51-7.66 (m, 16H, Phth-*H*).

5 (n=m=3, *partial cone*): mp 278-280 °C

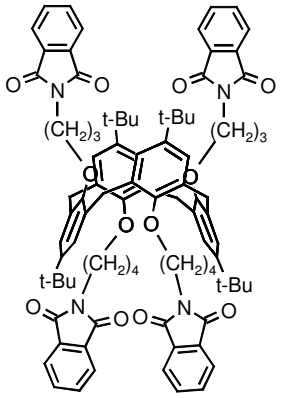
^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95, 1.25, 1.28 (3s, 18/9/9H, *t*-Bu), 1.87, 2.09, 2.22 (3m, 2/2/4H, -CH_2-CH_2-CH_2-), 2.99, 4.01 (2d, 2/2H, ^2J = 12.3 Hz, Ar-CH_2-Ar), 3.54-3.87(m, 20H, -CH_2-N, -CH_2-O, Ar-CH_2-Ar), 6.53, 6.78 (2d, 2/2H, ^4J = 1.4, 2.5 Hz, Ar*H*), 7.02, 7.17 (2s, 2/2H, Ar*H*), 7.52-7.71 (m, 16H, Phth-*H*).

b) starting from the *syn*-diether **2 (n=3)**

A suspension of **2 (n=3)** (4.0 g, 3.9 mmol) and Cs_2CO_3 (10 g, 31.2 mmol) in dry DMF (50 ml) was heated to 50°C under argon for 1 h. A solution of *N*-(3-bromopropyl)-phthalimide (8.3 g, 31.2 mmol) in DMF (10 ml) was added and the heating was continued for 5 days under argon. The solvent was removed under reduced pressure and the white residue was dissolved in chloroform. The solution was washed with water (2x75ml), dried ($MgSO_4$), concentrated and the product was precipitated with

methanol to give 2.0 g (36 %) of **5 (n=m=3, *1,3-alternate*)** as a white powder. The filtrate was contained mainly in the *partial cone* isomer of **5** (t.l.c) which was not isolated in this case.

5,17,11,23-Tetra-*t*-butyl-25,27-di-phthalimidobutyloxy-26,28-di-phthalimidopropoxy-calix[4] arene 5 (n=4, m=3) *(1,3-alternate*)

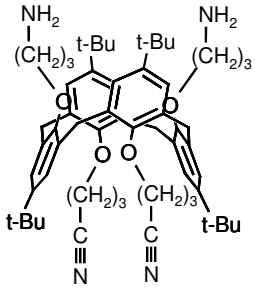


Compound **5 (n=4, m=3)** was obtained as described for **5 (n=m=3)**, starting from **2 (n=4)** (0.5 g, 0.47 mmol), *N*-(3-bromo-propyl)-phthalimide (1,0 g, 3.76 mmol) and Cs_2CO_3 (1.2 g, 3.76 mmol) in dry DMF (15 ml). The desired *1,3-alternate* isomer of **5 (n=4, m=3)** was isolated by crystallization from chloroform /methanol (20 ml, 1:4) as white powder (0.4 g, 60 %) mp 204°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.18, 1.19 (2s, 18/18H, *t*-Bu), 1.32, 1.71 (2m, 8/8H,-CH_2-CH_2-CH_2-), 3.38-3.66 (m, 20H, O-CH_2-, -CH_2-N Ar-CH_2-Ar), 3.70 (d, 4H, ^2J = 16.53 Hz Ar-CH_2-Ar), 6.91, 6.96 (2s, 4/4H, Ar*H*), 7.66-7.83 (m, 16H, Phth-*H*).

^{1}H-NMR (400 MHz, C_6D_6) δ 1.39, 1.41 (2s, 18/18H, *t*-Bu), 1.59, 1.86 (2m, 4/4H,-CH_2-CH_2-CH_2-), 3.38 (t, 4H ^3J = 7.4 Hz, -CH_2-N), 3.57-3.66 (m, 12H, O-CH_2-, -CH_2-N), 3.87, 3.92 (2d, 4/4H, ^2J = 15.6 Hz Ar-CH_2-Ar), 6.86-6.88 (m, 8H, Phth-*H*), 7.11, 7.26 (2s, 4/4H, Ar*H*), 7.46-7.49 (m, 8H, Phth-*H*).

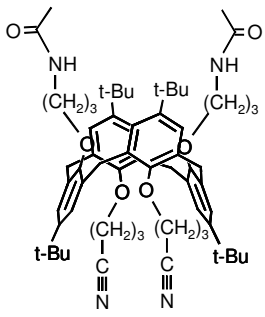
5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-aminopropoxy-26,28-*bis*-cyanopropoxycalix[4]arene 6 (*1,3-alternate*)



A suspension of **4** (0.60 g, 0.5 mmol) in ethanol (40 ml) was refluxed with hydrazine (12 ml) for 2 h after which a clear solution was formed. The solvent was evaporated, the organic residue was dissolved in $CHCl_3$ and washed several times with water. The organic solution was dried ($MgSO_4$) and the solvent evaporated again. The final product was purified by crystallization from $CHCl_3$ hexane (20 ml, 1:10) to give a yellow powder; yield 0.42 g, 88 %; mp 303 C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.37 (m, 8H, -CH_2-CH_2-CH_2-), 1.30, 1.31 (2s, 18/18H, *t*-Bu), 1.91 (t, 4H, ^3J = 7.7 Hz. CH_2-CN), 2.16 (bs, 4H, -NH_2), 2.50 (t, 4H, ^3J = 6.9 Hz, CH_2-NH_2), 3.45-3.50 (2t, 4/4H, -CH_2-O), 3.85, 3.86 (2d, 4/4H, ^2J = 17.3 Hz, Ar-CH_2-Ar), 7.01, 7.03 (2s, 4/4H, Ar*H*),

5,11,17,23-*Tetra-t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-cyanopropoxy-calix[4] arene 7 (*1,3 alternate*)



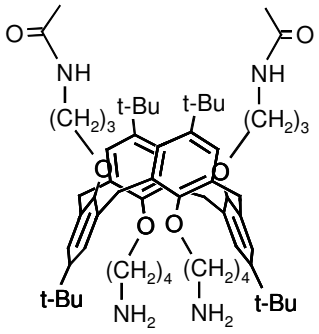
Diamine **5** (0.42 g, 0.46 mmol) was dissolved in acetanhydride (5 ml) containing a few drops of triethylamine. After 12 h stirring at room temperature a white precipitate had formed which was filtered off and washed

with water (30 ml). The desired diamide **7** was obtained as a white powder; (0.42 g, 93 %); mp 285-286 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13-1.41 (m, 8H, -CH_2-C*H*$_2$-CH_2-), 1.25, 1.30 (2s, 18/18H, *t*-Bu), 1.88 (t, 4H, ^3J = 7.3 Hz, C*H*$_2$-CN), 1.94 (s, 6H, -C*H*$_3$), 2.28-2.94 (m, 4H, -C*H*$_2$-NH), 3.26 (t, 4H, ^3J = 9.0 Hz, -C*H*$_2$-O), 3.49 (t, 4H, ^3J = 6.0 Hz, -C*H*$_2$-O), 3.84 (s, 8H, Ar-C*H*$_2$-Ar), 6.4 (bs, 2H, N*H*), 6.96, 7.01 (2s, 4/4H, Ar*H*)

5,11,17,23-*Tetra-t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-aminobutyloxy-calix[4]arene 8 (*1,3 alternate*)

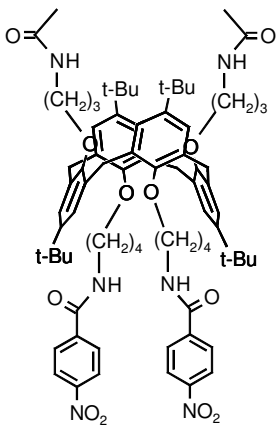
A suspension of **7** (0.25 g, 0.25 mmol) in ethanol/THF (1:4, 8 ml) and aqueous NaOH (6 %, 8 ml) was stirred with Raney-Ni under hydrogen atmosphere. After the hydrogen uptake was complete the catalyst was removed by filtration through sea sand and the solvent removed under reduced pressure. The white residue was extracted with chloroform, the solution washed several times with water, dried ($MgSO_4$) and evaporated. The residue was triturated with CH_2Cl_2/hexane (1:10, 10 ml) to give a yellow oil, yield 0.2 g , 50 %.



^{1}H NMR (300 MHz, $CDCl_3$) δ of **8** displays broad signals among which characteristically signals for aromatic protons , -NH, terminal methyl groups can be distinguished and also the ration of proton signals helps for the characterization of the diamines structure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (bm, 48H, -CH_2-C*H*$_2$-CH_2-, *t*-Bu), 1.91 (s, 6H, -C*H*$_3$), 2.50-3.81 (bm, 28H, -C*H*$_2$-NH_2, -N*H*$_2$, -C*H*$_2$-O, Ar-C*H*$_2$-Ar), 6.43 (bs, 2H, N*H*), 6.96 (bs, 8H, Ar*H*),

5,11,17,23-*Tetra-t*-butyl-25,27-*bis*-acetamidopropoxy-26,28-*bis*-(*p*-nitrobenzoylamino)-butyloxy-calix[4]arene 9 (*1,3-alternate*)

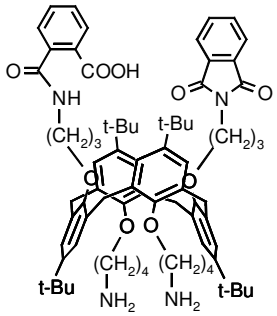


A solution of *p*-nitrobenzoylchloride (93 mg, 0.5 mmol) and triethylamine (0.07 ml, 0.5 mmol) were added to a stirred solution of **8** (0.247 g, 0.25 mmol) in chloroform (30 ml). After 12 h at room temperature the solvent was removed under reduced pressure, and the residue was purified by column chromatography (chloroform), to give a yellow powder; yield 0.15 g, 50 %; mp 123° C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13-1.41 (m, 8H, -CH_2-C*H*$_2$-CH_2-), 1.25, 1.30 (2s, 18/18H, *t*-Bu), 1.46 (m, 4H, -CH_2-C*H*$_2$-CH_2-), 1.92 (s, 6H, -C*H*$_3$), 2.28-2.94 (m, 4H, CH_2-C*H*$_2$-CH_2), 3.19-3.33 (m, 12H, -C*H*$_2$-O, -C*H*$_2$-N), 3.82 (s,

8H, Ar-CH_2-Ar), 6.2 (bs, 2H, N*H*), 6.89 (bs, 2H, N*H*), 6.94, 6.97 (2s, 4/4H, Ar*H*), 7.94, 8.23 (2d, 4/4H, ^4J=8.8 Hz, Ar*H*).

5,11,17,23-*Tetra-t*-butyl-25-phthalimidopropoxy-27-phthaloylaminopropoxy-26,28-*bis*-amino butyloxy-calix[4]arene, 10 (***1,3 alternate***)



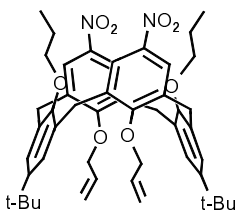
The dinitrile **4** (0.63 g, 0.54 mmol) was dissolved in ethanol/THF (1:4, 10 ml). A suspension of Pd/C (300 mg) in NaOH solution (10 ml, 6 %) was added, and the reaction mixture was stirred under hydrogen atmosphere at 50°C for 3 h. After the catalyst was filtered off, the solvents were removed under reduced pressure and the residue was treated with a mixture of CH_2Cl_2 (25 ml) and water (50 ml). The aqueous phase was extracted with CH_2Cl_2 (3x15 ml) and the combined organic phase was dried ($MgSO_4$) and evaporated. The diamine **9** was obtained as a white powder, yield 0.39 g, 62 %; mp 152-154 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13, 1.27 (2s+m, 48H, *t*-Bu, -CH_2-CH_2-CH_2-), 1.97 (t, 4H, ^3J = 7.3 Hz, -CH_2-NH_2), 3.05 (bs, 4H, N-CH_2-), 3.40 (bm, 12H, -O-CH_2-, -NH_2), 3.78, 3.95 (2d, 4/4H, ^2J = 16.5 Hz, Ar-CH_2-Ar), 7.03, 7.09 (2s, 4/4H, Ar*H*), 7.28-7.35 (m, 4H, Phth-*H*), 7.50, 7.62 (2d, 2/2H, ^2J = 7.0 Hz, $Phth_{COOH}$-*H*), 10.29 (bs, 1H, -COO*H*).

5,17-Di-*t*-butyl-11,23-dinitro-25,27-diallyloxy-26,28-dipropoxy-calix[4]arene 16 (*1,3-alternate*) and 16 (*partial cone*)

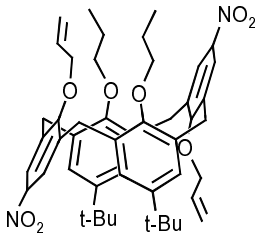
A stirred suspension of dinitro-calixarene **15** (2.0 g, 2.8 mmol) and Cs_2CO_3 (13.6 g, 42 mmol) in dry DMF (50 ml) was heated to 40 °C under nitrogen. After 1 h allylbromide (3.6 ml, 42 mmol) was added and the reaction was continued for 7 days. The DMF was removed under reduced pressure and the residue was treated with chloroform (25 ml) and water (75 ml). The organic phase was washed with water (2x75 ml), dried ($MgSO_4$) and the solvent was evaporated to give a yellow oil. Analysis by t.l.c showed the presence of two compounds, which were separated and purified by column chromatography (CH_2Cl_2/hexane 2:3) and identified by NMR as the *1,3-alternate* and the *partial cone* isomers.

16 (*1,3-alternate*): White-yellow powder, yield 1.4 g, 63 %; mp 278-279 °C; (Found: C 72.88, H 7.39, N 3.59 $C_{48}H_{58}N_2O_8$ requires C 72.89, H 7.39, N 3.54)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.79 (t, 6H, ^3J = 7.7 Hz, -CH_2-CH_3), 1.21 (s, 18H, *t*-Bu), 1.45 (m, 4H, -CH_2-CH_2-CH_3), 3.56 (t, 4H, ^3J = 7.7 Hz, O-CH_2), 3.68, 3.81 (2d, 4/4H, ^2J = 15.0 Hz, Ar-CH_2-Ar), 3.94 (d, 4H, ^4J = 5.1 Hz, CH_2=CH-CH_2-O-), 5.05 (m, 4H, CH_2=CH-), 5.70 (m, 2H, CH_2=C*H*-), 6.96, 7.95 (2s, 4/4H, Ar*H*).

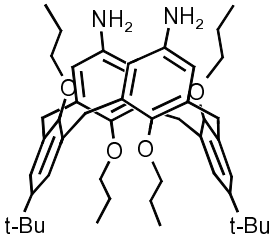
16 (*partial cone*): Colourless crystals, yield 0.38 g, 18 %; mp 248-249 °C;



^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 24H, *t*-Bu, -CH_2-CH_3), 1.89 (m, 4H, -CH_2-CH_3), 3.19 (d, 2H, ^2J = 12.9 Hz, Ar-CH_2-Ar), 3.52 (m, 2H, O-CH_2-), 3.64 (d, 2H, ^2J = 13.6 Hz, Ar-CH_2-Ar), 3.77 (m, 2H, O-CH_2), 3.83 (d, 2H, ^2J = 13.6 Hz, Ar-CH_2-Ar), 4.08 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.16, 4.31 (2d, 2/2H, ^4J = 5.9 Hz, -O-CH_2-CH=CH_2), 4.90, 5.29 (2m, 2/2H, -CH=CH_2), 5.65, 6.07 (2m, 1/1H, -C*H*=CH_2), 6.50, 6.87 (2d, 2/2H, ^4J = 2.2, 2.6 Hz, Ar*H*), 8.02, 8.23 (2s, 2/2H, Ar*H*)

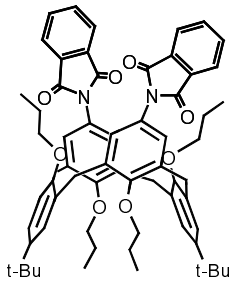
5,17-Di-*t*-butyl-11,23-diamino-25,26,27,28-tetrapropoxy calix[4]arene 17 (*1,3-alternate*)

Raney-Ni (0.5 g) was added to a solution of the dinitro compound **16** (0.7 g, 0.88 mmol) in THF (20 ml) and the suspension was stirred under hydrogen atmosphere at rt. After the hydrogen uptake was complete, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in chloroform (10 ml) and reprecipitated by hexane (25 ml) to give the pure diamine as a pink powder, yield 0.28 g, 45%; m.p 198°C



^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.68, 0.76 (2t, 6/6H, ^3J = 7.3, 7.7 Hz, -CH_2-CH_3), 1.13-1.38 (m, 26H, *t*-Bu, -CH_2-CH_3), 3.23-3.71 (m, 12H, O-CH_2-, -NH_2), 3.68, 3.80 (2d, 4/4H, ^2J = 15.4 Hz, Ar-CH_2-Ar), 6.64, 6.91 (2s, 4/4H, Ar*H*).

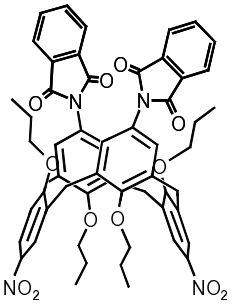
5,17-Di-*t*-butyl-11,23-diphthalimido-25,26,27,28-tetrapropo-xy-calix[4]arene 18 (*1,3-alternate*)



A solution of diamine **16** (0.7 g, 1.3 mmol), phthalic acid anhydride (0.45 g, 3 mmol) and triethylamine (1 ml) in toluene (25 ml) was refluxed for 12 h. The solvent was removed under reduced pressure to give a red sticky mass, which was dissolved in chloroform (5 ml) and passed through a silica column (chloroform) to remove the excess anhydride. **17** was isolated as a pink powder, yield 0.53 g, 42 %; mp 384-385°C; (Found: C 74.63, H 7.10, N 2.66 $C_{64}H_{70}N_2O_8$ requires C 77.24, H 7.09, N 2.81)

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.58-0.67 (m, 12H, -CH_2-CH_3), 1.04 (m, 4H, CH_3-CH_2-), 1.28 (m, 22H, *t*-Bu, -CH_2-CH_3), 3.39 (m, 8H, O-CH_2-), 3.84, 3.87 (2d, 4/4H, ^2J = 16.5 Hz**,** Ar-CH_2-Ar), 6.97, 7.12 (2s, 4/4H, Ar*H*), 7.70 (m, 8H, Phth-*H*).

5,17-Dinitro-11,23-diphthalimido-25,27,26,28-tetrapropoxy-calix[4]arene 19 (*1,3-alternate*)



Glacial acetic acid (0.32 ml) and fuming nitric acid (0.02 ml) were added to a vigorously stirred, clear solution of diphthalimide **18** (0.03 g, 0.03 mmol) in dry

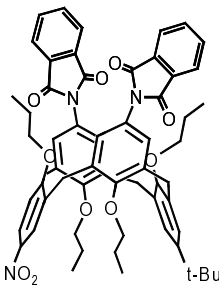
CH_2Cl_2 (6 ml) at rt. The reaction was monitored by t.l.c. After 5 h the colour of the solution had changed from black-indigo to yellow. Water (50 ml) was added and the reaction mixture was stirred for further 30 min. The organic solution was washed twice with water (2x10 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by precipitation from CH_2Cl_2/CH_3OH (20 ml, 1:1) to give the dinitro compound **19** as yellow powder, yield 0.013 g, 45 % (Found: C 69.10, H 5.87, N 5.41. $C_{56}H_{52}N_4O_{12}$ requires C 69.12, H 5.39, N 5.76). mp. 338-340 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89, 1.07 (2t, 12H, ^3J = 7.3 Hz,-CH_2-CH_3), 1.82 (m, 8H, -CH_2-CH_2-CH_3), 3.68 (s, 8H, Ar-CH_2-Ar), 3.74 (m, 8H, O-CH_2-), 7.19, 7.96 (2s, 4/4H, Ar*H*), 7.47-7.57 (m, 8H, Phth-*H*).

Dinitro compound **19** was obtained also from the mononitro compound **24** using similar conditions. Glacial acetic acid (1.97 ml) and fuming nitric acid (0.11 ml) were added to a stirred solution of **24** (0.37 g, 0.375 mmol) in CH_2Cl_2 (25 ml). The reaction was followed by t.l.c and stopped (the colour of the solution had changed from black to yellow) by adding water (50 ml). The organic solution was washed several times with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Precipitation from CH_2Cl_2/CH_3OH (20 ml, 1:1) gave **19** as yellow powder (0.3 g, 83 %).

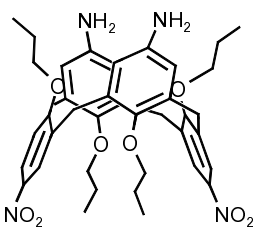
5-Nitro-17-*t*-butyl-11,23-diphthalimido-25,27,26,28-tetrapro-poxy-calix[4]arene 24 (***1,3-alternate***)

Glacial acetic acid (3 ml) and fuming nitric acid (0.22 ml) were added to a vigorously stirred, clear solution of diphthalimido **18** (0.5 g, 0.5 mmol) in dry CH_2Cl_2 (50 ml) at rt. After a certain time (around 7-15 min.) when the color of the solution had changed from black-indigo to yellow, water (50 ml) was added and the reaction mixture was stirred for further 30 min. The organic solution was washed several times with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by precipitation from CH_2Cl_2/CH_3OH (20 ml, 1:1) to give a yellow powder, yield 0.38 g, 78 %; mp 313-315 °C;



^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, 1.03 (2t, 3/3H, ^3J = 7.3 Hz,-CH_2-CH_3), 1.03 (t, 6H, ^3J = 7.3 Hz,-CH_2-CH_3), 1.17 (s, 9H, t-Bu), 1.66-1.91 (m, 8H, -CH_2-CH_2-CH_3), 3.55 (d, 2H, ^2J = 14.0 Hz, Ar-CH_2-Ar), 3.61-3.83 (m, 12H, Ar-CH_2-Ar, O-CH_2-), 3.81 (t, 2H, ^3J = 7.7 Hz, O-CH_2-), 6.98, 7.94 (2s, 2/2H, Ar*H*), 7.15, 7.20 (2d, 2/2H, ^4J = 2.6 Hz, Ar*H*), 7.47-7.57 (m, 8H, Phth-*H*).

5,17-Dinitro-11,23-diamino-25,27,26,28-tetrapropoxy-calix[4]arene 20 (***1,3-alternate***)



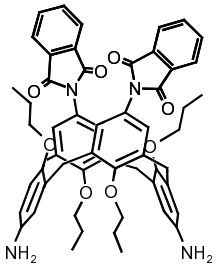
A solution of **19** (0.2 g, 0.2 mmol) in EtOH (10 ml) was refluxed with hydrazine (3 ml). After 2 h the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (10 ml), washed with water (2x25 ml), dried ($MgSO_4$) and the solvent was evaporated. The formed powder was dissolved in

chloroform (5 ml) and precipitated with hexane (15 ml) to give the pure diamine **20** as a yellow powder, yield 0.11 g, 79 %; mp 216°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69, 0.78 (2t, 6/6H, ^3J = 7.3 Hz,-CH_2-CH_3), 1.30-1.43 (m, 8H, -CH_2-CH_2-CH_3), 2.69 (bs, 4H, -NH_2), 3.27, 3.35 (2t, 4/4H, ^3J = 7.3 Hz, O-CH_2), 3.65, 3.66 (2d, 4/4H, ^2J = 15.4 Hz, Ar-CH_2-Ar), 6.4, 6.93 (2s, 4/4H, Ar*H*).

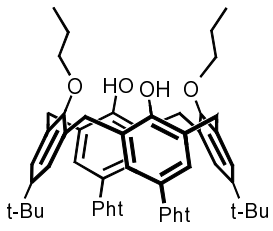
5,17-Diamino-11,23-diphthalimido-25,27,26,28-tetrapropoxy-calix[4]arene 21 (***1,3-alternate***)

The dinitro compound **19** (0.11 g, 0.11 mmol) was dissolved in toluene (2 ml) and THF (8 ml) and hydrogenated under atmospheric pressure in the presence of Ra-Ni at rt. After the hydrogen uptake was complete, the catalyst was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (5 ml) and reprecipitated with hexane (15 ml) to give the pure diamine **21** as a yellow powder, yield; 0.05 g, 50%; mp. 278-280°C. FD-MS, (M^++H) m/z = 914.4.



^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.52, 0.71 (2t, 6/6H, ^3J = 7.4 Hz, -CH_2-C*H3*), 1.17-1.24 (m, 8H, -CH_2-CH_2-CH_3), 3.12 (bt, 4H, O-CH_2-), 3.20 (bs, 4H, O-CH_2-), *3*.64, 3.72 (2d, 4/4H, ^2J = 15.6 Hz, Ar-CH_2-Ar), 4.33 (bs, 4H, -NH_2), 6.28, 7.07 (2s, 4/4H, Ar*H*), 7.88, 7.91 (2bs, 8H, Phth-*H*).

5,17-Di-*t*-butyl-11,23-diphthalimido-26,28-dipropoxy-calix[4]arene 23 (***cone***)



A clear solution of the dinitrocompound **15** (1.86 g, 2.6 mmol) in THF (50 ml) was hydrogenated under atmospheric pressure in the presence of Ra-Ni at rt. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in toluene (25 ml) and phthalic acid anhydride (0.7 g, 5 mmol) and triethylamine (1 ml) were added. The reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure to give a red sticky mass, which was dissolved in chloroform (5 ml) and passed through a silica column (chloroform) to remove the excess anhydride. **23** was isolated as a pink powder, yield 1.1 g, 43 %

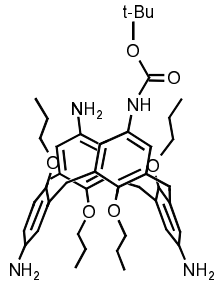
^{1}H-NMR (300MHz, $CDCl_3$) δ, 1.03 (m, 18H, *t*-Bu), 1.04 (m, 6H, CH_3-CH_2-), 2.05 (m, 4H, -CH_2-CH_3), 3.38, 4.32 (2d, 4/4H, ^2J = 12.8 Hz**,** Ar-CH_2-Ar), 3.96 (m, 4H, ^3J = 6.8 Hz, O-CH_2-), 6.90, 7.15 (2s, 4/4H, Ar*H*), 7.69-7.91 (m, 8H, Phth-*H*), 8.22 (s, 2H, O*H*).

Mono and di-protection by Boc; calix[4]arenes 26 and 27 (*1,3-alternate*)

A solution of Boc-anhydride (0.59 g, 2.7 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of the tetraamine **25** (1.0 g, 1.5 mmol) in dichloromethane (100 ml). After 24 h of

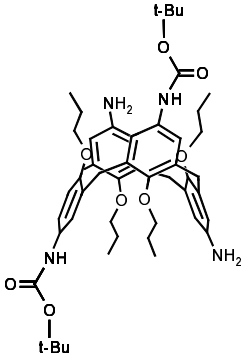
stirring at ambient temperature the solvent was evaporated. The mono- and di-Boc protected compounds **26** and **27** were isolated by column chromatography (EtOAc/hexane = 1:1) in 23 % (0.25 g), 58 % (0.65 g) respectively.

Mono-Boc derivative 26: pink powder, mp 138-140°C(Found: C 71.34, H 7.90, N 6.53 $C_{44}H_{58}N_4O_6$ requires C 71.52, H 7.91, N 7.58)



^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-1.24 (m, 12H, -CH_2-C*H*$_3$), 1.50 (s, 9H, *t*-Bu), 1.86 (m, 8H, -CH_2-C*H*$_2$-CH_3), 3.11-3.6 (m, 22H, Ar-C*H*$_2$-Ar, O-C*H*$_2$-, Ar-N*H*$_2$), 6.34, 6.44 (2s, 2/2H, Ar*H*), 6.98 (bs, 2/2H, Ar*H*).

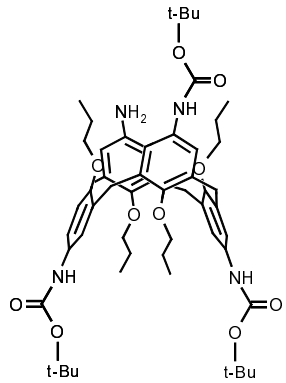
Di-Boc derivative 27: yellow powder, mp 251°C(Found: C 70.21, H 7.71, N 6.56 $C_{49}H_{66}N_4O_8$ requires C 70.14, H 7.93, N 6.68)



^{1}H NMR (400 MHz, C_6D_6) δ 0.99 (t, 12H, ^3J = 7.3 Hz,-CH_2-C*H*$_3$), 1.66 (s, 18H, *t*-Bu), 1.71 (m, 8H, -CH_2-C*H*$_2$-CH_3), 2.94 (bs, 4H, -N*H*$_2$), 3.42-3.55 (m, 16H, Ar-C*H*$_2$-Ar, O-C*H*$_2$-), 6.45, 6.47 (2d, 2/2H, ^4J = 2.9 Hz, Ar*H*), 7.23, 7.27 (2d, 2/2H, ^4J = 2.4 Hz, Ar*H*), 7.5 (bs, 2H, -N*H*)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.29 (bm, 12H, ,-CH_2-C*H*$_3$), 1.48 (s,18H, *t*-Bu), 1.87 (m, 8H, -CH_2-C*H*$_2$-CH_3), 3.28 (s, 2H, Ar-C*H*$_2$-Ar), 3.32 (d, 2H, ^2J = 12.5 Hz, Ar-C*H*$_2$-Ar), 3.37 (d, 2H, ^2J = 13.0 Hz, Ar-C*H*$_2$-Ar), 3.41 (s, 2H, Ar-C*H*$_2$-Ar), 3.57-3.65 (m, 12H, O-C*H*$_2$-, -N*H*$_2$), 6.44, 6.93, 6.95 (3s, 4/2/2H, Ar*H*), 7.82 (bs, 2H, -N*H*).

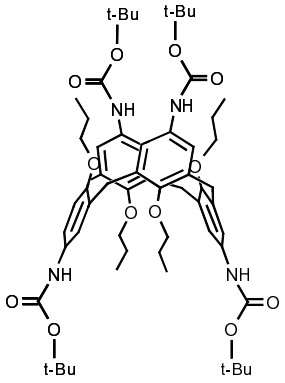
Tri-and tetra protection by Boc; calix[4]arenes 31 and 32 (***1,3-alternate***)



The **tri-Boc compound** was prepared in the same way, starting from a solution of tetraamino-calixarene **25** (1.0 g, 1.5 mmol) in CH_2Cl_2 (100 ml) and Boc-anhydride (0.948 g, 4.35 mmol). Isolation and purification by column chromatography (EtOAc /hexane = 1:1) gave pure tri-Boc derivative **31** (0.8 g, 60 %). mp. 242-244°C (Found: C 66.90, H 7.68, N 5.05 $C_{54}H_{74}N_4O_{10}$x0.5 CH_2Cl_2 requires C 66.68, H 7.70, N 5.71)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98, 1.12 (2t, 12H, ^3J =7.3 Hz. -CH_2-C*H*$_3$), 1.50, 1.52 (2s, 18/9H, *t*-Bu), 1.59, 1.73 (2m, 4H, -CH_2-C*H*$_2$-CH_3), 1.91 (m, 4H, -CH_2-C*H*$_2$-CH_3), 3.33-3.69 (m, 18H, O-C*H*$_2$**,** Ar-C*H*$_2$-Ar, N*H*$_2$), 6.14, 6.56 (2s, 1/2H, N*H*), 6.95, 6.98 (2s, 6/2H, Ar*H*).

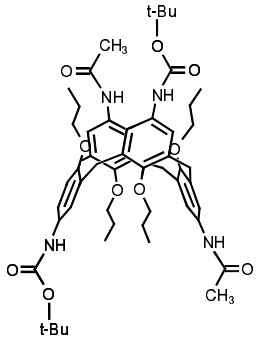
The **tetra-Boc derivative 32** is formed as side product, but can be obtained in nearly quantitative yield, using 20-30% excess of Boc-anhydride. E.g. starting from a solution of tetraamino-calixarene **25** (1.0 g, 1.5 mmol) in CH_2Cl_2 (100 ml), pure tetra-Boc compound **32** (1.35 g, 90 %) was obtained after purification by reprecipitation from $CHCl_3$/hexane (1:5) as white powder. mp. 268-270°C.



^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, 12H, ^3J =7.3 Hz, -CH_2-CH_3), 1.44-1.53 (m, 8H, -CH_2-CH_2-CH_3), 1.50 (s, 36H, *t*-Bu) 3.41 (t, 8H, ^3J =7.3 Hz, -CH_2-CH_2-CH_3), 3.60 (s, 8H, Ar-CH_2-Ar), 6.18 (s, 4H, -N*H*), 6.99 (s, 8H, Ar*H*)

5,11-Bis-t-butyloxycarbonylamino-17,23-bis-acetamido-25,26,27,28-tetrapropoxy-calix[4]arene 29 (*1,3-alternate*)

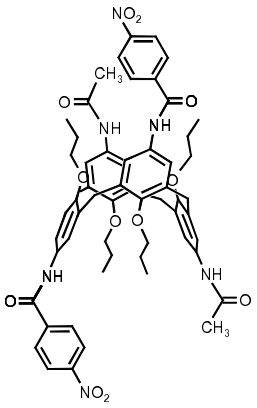
Di-Boc compound **27** (70 mg, 0.084 mmol) was stirred in acetic anhydride (5 ml) with a few drops of triethylamine at rt. After 12h the reaction mixture was poured on ice and the desired diacetamide precipitated as white solid to give 79 mg of pure **29** (85 % yield). mp 262-263°C. (Found: C 68.58, H 7.86, N 5.71. $C_{54}H_{72}N_4O_{10}$ x 0.5H_2O requires C 68.55, H 7.78, N 5.92)



^{1}H NMR (300 MHz, DMSO) δ 0.62 (bs, 12H,-CH_2-CH_3), 1.26 (bm, 26H, *t*-Bu, -CH_2-CH_2-CH_3), 1.97 (s, 6H, -CO-CH_3), 3.06 (bt, 8H, O-CH_2-), 3.58 (bs, 8H, Ar-CH_2-Ar), 7.16, 7.25 (2s, 4/4H, Ar*H*), 8.93, 9.51 (2s, 2/2H, -N*H*-)

5,11-Bis-*p*-nitrobenzoylamino-17,23-bis-acetamido-25,26,27,28-tetrapropoxy-calix[4]arene 30 (*1,3-alternate*)

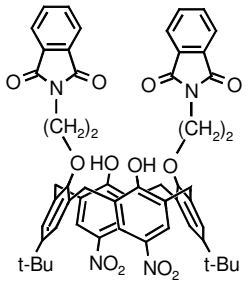
To a stirred solution of **29** (67 mg, 0.07 mmol) in CH_2Cl_2 (7 ml) was added TFA (7 ml). The reaction mixture was stirred at rt for 2 h, then diluted with toluene (15 ml). The solvents were evaporated, the remaining yellow oil was dissolved in chloro-form (15 ml) and triethylamine (0.05 ml, 0.35 mmol) and *p*-nitro-benzoyl chloride (27 mg, 0.15 mmol) were added with stirring. After 12 h the solvent was removed under reduced pressure. The dry residue was purified by column chromatography (chloroform) to obtain **30** as an orange powder (50 mg, 70 % yield). mp 223°C. FD-MS, (M^++H) m/z = 1036.3.



^{1}H NMR (300 MHz, DMSO) δ 0.64 (m, 12H, -CH_2-CH_3), 1.31 (bm, 8H, -CH_2-CH_2-CH_3), 1.95 (s, 6H, -CO-CH_3), 3.2 (bt, 8H, O-CH_2-), 3.67, 3.65 (2d, 4/4H, ^2J=15.4 Hz, Ar-CH_2-

Ar), 7.37, 7.57 (2d, 4/4H, ^4J = 3.7, 3.3 Hz, Ar*H*), 8.11, 8.37 (2d, 4/4H, ^4J = 8.8, 8.4 Hz, Ar*H*), 9.55, 10.26 (2s, 2/2H, -N*H*-)

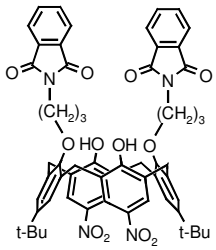
5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidoethoxy-calix[4]arene 31 (n=2)



Nitric acid (65 %, 7.5 ml) was added with stirring to a cold (0 °C) solution of **2 (n=2)** (2.5 g, 2.5 mmol) in dry CH_2Cl_2 (75 ml). After 10 min the color changed from black-indigo to yellow and the reaction was complete. Water was added (100 ml) and the mixture was stirred for 30 min. After phase separation the organic phase was washed with water (3x100 ml) until a neutral pH was reached, dried ($MgSO_4$) and the solvent was evaporated. The residue was dissolved in chloroform (10 ml) and the pure product was precipitated with methanol (25 ml) as yellow powder (1.6 g, 67 %). m.p 298-300°C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.9 (s, 18H, *t*-Bu), 3.41, 4.15 (2d, 4/4H, ^2J = 13.2 Hz, Ar-C*H*$_2$-Ar), 4.29 (t, 4H, ^3J = 6.2 Hz, -C*H*$_2$-N), 4.47 (t, 4H, ^3J = 6.3 Hz, O-C*H*$_2$-), 6.73, 7.98 (2s, 4/4H, Ar*H*), 7.69-7.93 (m, 8H, Phth-*H*), 8.20 (s, 2H, O*H*).

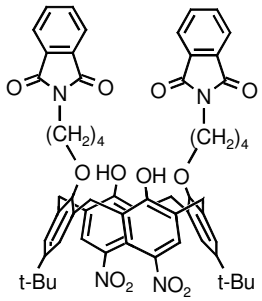
5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidoproxy-calix[4]arene 31 (n=3)



Reaction and work up as described above. 2.0 g (1.95 mmol) **2 (n=3)** finally gave 1.5 g, (75 %) of pure product as yellow powder; m.p 253.5-254°C

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H, t-Bu), 2.45 (m, 4H, -CH_2-C*H*$_2$-CH_2), 3.48 (d, 4H ^2J = 13.8 Hz, Ar-C*H*$_2$-Ar), 4.11 (m, 8H, O-C*H*$_2$-, -C*H*$_2$-N), 4.30 (d, 4H, ^2J = 13.8 Hz, Ar-C*H*$_2$-Ar), 6.88, 8.04 (2s, 4/4H, Ar*H*), 7.62-7.78 (m, 8H, Phth-*H*), 8.94 (s, 2H, -O*H*)

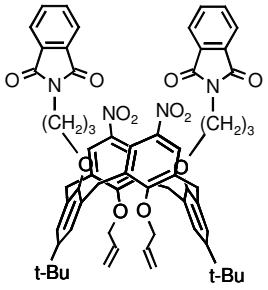
5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidobutoxy-calix[4]arene 31 (n=4)



Reaction and work up as described above. 3.0 g (2.85 mmol) **2 (n=4)** finally gave 2.0 g, (70 %) of pure product as yellow powder; m.p 229-231°C; (Found: C 68.82, H 6.30, N 5.35 $C_{60}H_{60}N_4O_{10}$ x H_2O requires C 68.82, H 5.97, N 5.35)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 18H, t-Bu), 2.10 (bs, 8H, -CH_2-C*H*$_2$-CH_2), 3.44 (d, 4H ^2J = 13.2 Hz, Ar-*CH*$_2$-Ar), 3.89 (bt, 4H, -C*H*$_2$-N), 4.06 (bt, 4H, O-C*H*$_2$-) 4.21 (d, 4H, ^2J = 13.2 Hz, Ar-*CH*$_2$-Ar), 6.88, 8.00 (2s, 4/4H, Ar*H*), 7.66-7.82 (m, 8H, Phth-*H*), 9.07 (s, 2H, O*H*)

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidopropoxy-25,27-diallyloxy-calix[4]arene 32 (n=3) (***1,3-alternate, partial cone, cone)***



A stirred suspension of dinitro calixarene **31 (n=3)** (0.5 g, 0.5 mmol) and Cs_2CO_3 (1.3 g, 4 mmol) in dry DMF (12.5 ml) was heated to 40°C under nitrogen. After 1 h allylbromide (0.34 ml, 4 mmol) was added and the reaction mixture was kept under these conditions for 7 days. The DMF was removed at reduced pressure and the residue was treated with chloroform (15 ml) and water (50 ml). The organic phase was washed twice with water (2x50 ml), dried ($MgSO_4$) and evaporated. T.l.c, analysis of the residue showed the presence of two isomers (*1,3-alternate* and *partial cone*). After column chromatography (dichloromethane/ethylacetate, 95:5) three different fractions were isolated which were identified as *1,3-alternate, partial cone* and *cone* conformers. Recrystallization from chloroform/methanol (10 ml, 1:4) gave **32 (n=3, *1,3-alternate*)** as colorless crystals (0.1 g, 19 %), **32 (n=3, *partial cone*)** as yellow powder (0.1 g, 19 %) and **32 (n=3, *cone*)** as colorless crystals (10 mg, 2 %).

32 (n=3, *1,3-alternate*): mp 230-232°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 18H, *t*-Bu), 1.88 (m, 4H,-CH_2-CH_2-CH_2-), 3.69 (m, 8H, O-CH_2-, -CH_2-N), 3.69, 3.81 (2d, 4/4H, ^2J = 15.6 Hz, Ar-CH_2-Ar), 3.97 (d, 4H, ^2J = 9.7 Hz, CH_2=CH-CH_2-O-), 5.03 (m, 4H, CH_2=CH-), 5.70 (m, 2H, CH_2=C*H*-), 6.95, 7.99 (2s, 4/4H, Ar*H*), 7.74 (m, 8H, Phth-*H*).

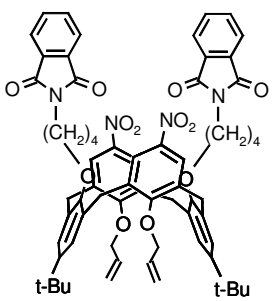
32 (n=3, *partial cone*): mp 191-192°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.00, (s, 18H, *t*-Bu), 2.21 (m, 4H, -CH_2-CH_2-CH_2-), 3.19, 3.68 (2d, 2/2H, ^2J = 12.9, 13.7 Hz, Ar-CH_2-Ar), 3.88 (m, 8H, O-CH_2-, **-**CH_2-N), 3.90, 4.07 (2d, 2/2H, ^2J = 13.3, 12.9 Hz, Ar-CH_2-Ar), 4.19, 4.24 (2d, 2/2H, ^2J = 6.3 Hz, -O-CH_2-CH=CH_2), 4.89, 5.28 (2m, 2/2H, CH_2=CH-), 5.54, 6.02 (2m, 1/1H, CH_2=C*H*-), 6.35, 6.87 (2d, 2/2H, ^4J=1.9 Hz, Ar*H*), 7.83 (m, 8H, Phth-*H*), 8.05, 8.35 (2s, 2/2H, Ar*H*)

32 (n=3, *cone*): mp 270-272°C

^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 18H, *t*-Bu), 2.28 (m, 4H, -CH_2-CH_2-CH_2-), 3.19, 4.41 (2d, 4/4H, ^2J = 13.6 Hz, Ar-CH_2-Ar), 3.81 (t, 4H, ^3J = 7.3 Hz, -CH_2-N), 4.07 (t, 4H, ^3J = 7.5 Hz, -CH_2-O-), 4.38 (d, 4H, ^2J = 5.9 Hz, -O-CH_2-CH=CH_2), 5.11 (m, 4H, CH_2=CH-), 6.13 (m, 2H, CH_2=C*H*-), 7.03, 7.12 (2s, 4/4H, Ar*H*), 7.78 (m, 8H, Phth-*H*)

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidobutyloxy-25,27-di-allyloxy-calix[4]arene 32 (n=4) (*1,3-alternate*)



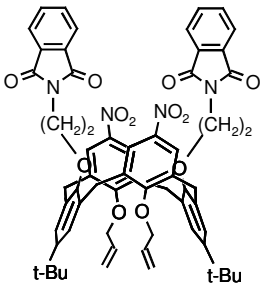
Compound **32 (n=4)** was obtained in an analogous way starting from the dinitro compound **31 (n=4)** (1.6 g, 1.55 mmol) in dry DMF (40 ml) and Cs_2CO_3 (5 g, 15.5 mmol). The desired *1,3-alternate* isomer of **32 (n=4)** was isolated by crystallization from chloroform/methanol (25 ml, 1:4) as colorless

crystals (0.9 g, 53%). mp 199°C (Found: C 71.30, H 6.41, N 4.96. $C_{66}H_{68}N_4O_{12}$ requires C 71.46, H 6.18, N 5.05)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 18H, *t*-Bu), 1.55, 1.72 (2m, 4/4H,-CH_2-C*H*$_2$-CH_2-), 3.69 (m, 8H, O-C*H*$_2$-, -C*H*$_2$-N), 3.62, 3.66 (2d, 4/4H, *J* = 15.6 Hz, Ar-C*H*$_2$-Ar), 3.97 (d, 4H, *J* = 5.1 Hz, CH_2=CH-C*H*$_2$-O-), 5.12 (m, 4H, C*H*$_2$=CH-), 5.74 (m, 2H, CH_2=C*H*-), 6.95, 7.99 (2s, 4/4H, Ar*H*), 7.67 (m, 8H, Phth-*H*).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diphthalimidoethyloxy-25,27-di-allyloxy-calix[4]arene 32 (n=2) (***1,3-alternate***)

Compound **32 (n=2)** was obtained in an analogous way starting from the dinitro compound **31 (n=2)** (2.9 g, 2.98 mmol) in dry DMF (40 ml) and Cs_2CO_3 (7.8 g, 23 mmol). The reaction mixture was stirred under nitrogen at 50 °C for 6 days. Water (50 ml) was added to stop the reaction and after several washing (3x50 ml water) the organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The desired *1,3-alternate* isomer of **32 (n=2)** was isolated by column chromatography (chloroform/hexane = 1:2) as colorless crystals (0.05 g, 2%) together with the *partial cone* isomer (0.27 g, 9 %).



32 (n=2, *1,3-alternate*): mp 251-253 °C

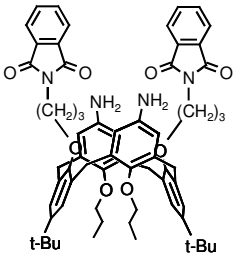
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 18H, *t*-Bu), 3.72, 3.86 (2d, 4/4H, ^2J = 15.6 Hz, Ar-C*H*$_2$-Ar), 3.79 (m, 8H, O-C*H*$_2$-, -C*H*$_2$-N), 4.10 (d, 4H, ^2J = 5.16 Hz, CH_2=CH-C*H*$_2$-O-), 5.08 (m, 4H, C*H*$_2$=CH-), 5.75 (m, 2H, CH_2=C*H*-), 6.95, 8.28 (2s, 4/4H, Ar*H*), 7.66-7.85 (m, 8H, Phth-*H*).

32 (n=2, *partial cone*): mp 215-217 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 18H, *t*-Bu), 3.24 (d, 2H, ^2J = 13.2 Hz, Ar-C*H*$_2$-Ar), 3.70-4.25 (m, 18H, O-C*H*$_2$-, -C*H*$_2$-N, Ar-C*H*$_2$-Ar, -O-C*H*$_2$-CH=CH_2), 4.85, 5.22 (2m, 2/2H, C*H*$_2$=CH-), 5.56, 5.88 (2m, 1/1H, CH_2=C*H*-), 6.57, 6.88 (2d, 2/2H, ^4J=2.2 Hz, Ar*H*), 7.82 (m, 8H, Phth-*H*), 8.00, 8.42 (2s, 2/2H, Ar*H*).

5,17-Di-*t*-butyl-11,23-diamino-26,28-diphthalimidopropoxy-25,27-dipropoxy-calix[4]arene 33 (n=3) (***1,3-alternate***)

A clear solution of the dinitrocompound **32 (n=3)** (0.6 g, 0.55 mmol) in THF (20 ml) was hydrogenated under atmospheric pressure in the presence of Ra-Ni at rt. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (5 ml) and

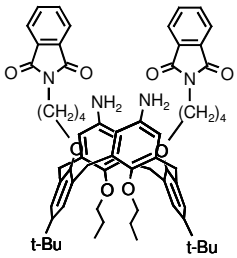


the diamine was reprecipitated with hexane (10 ml) as yellow powder (0.4 g, 80 %). mp 133°C. FD-MS, (M^++H) m/z = 1026.3.

^{1}H-NMR (200MHz, $CDCl_3$) δ 0.58 (t, 6H, ^3J = 7.3 Hz, C*H*$_3$-CH$_2$-), 1.04-1.18 (m, 22H, CH$_3$-C*H*$_2$-CH$_2$-, *t*-Bu), 1.55 (m, 4H, -CH$_2$-C*H*$_2$-CH$_2$-), 3.18 (bt, 4H, ^3J = 6.8 Hz , -C*H*$_2$-N), 3.33-3.3.45 (bm, 12H, O-C*H*$_2$-, -N*H*$_2$), 3.57, 3.68 (2d, 4/4H, ^2J = 15.5 Hz, Ar-C*H*$_2$-Ar), 6.38, 6.88 (2s, 4/4H, Ar*H*), 7.59-7.76 (bm, 8H, Phth-*H*)

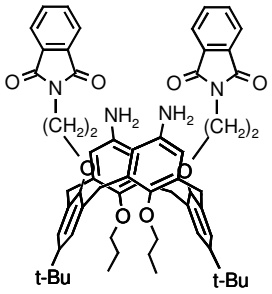
5,17-Di-*t*-butyl-11,23-diamino-26,28-diphthalimidobutoxy-25,27-dipropoxy-calix[4]arene 33 (n=4) (***1,3-alternate***)

The diamine **33 (n=4)** was obtained as described above for the analogous compound **33 (n=3)** starting from a clear solution of **32 (n=4)** (0.2 g, 0.18 mmol) in THF (15 ml) Analogous work up gave a beige powder (0.16 g, 90 %). mp 129°C.



^{1}H-NMR (300MHz, $CDCl_3$) δ 0.65 (t, 6H, ^3J = 7.7 Hz, C*H*$_3$-CH$_2$-), 1.03-1.46 (m, 26H, -C*H*$_2$-, *t*-Bu), 1.81 (m, 4H, -C*H*$_2$-), 3.18-3.69 (m, 24H, -C*H*$_2$-N, O-C*H*$_2$-, -N*H*$_2$, Ar-C*H*$_2$-Ar), 6.40, 6.92 (2s, 4/4H, Ar*H*), 7.67-7.80 (bm, 8H, Phth-*H*)

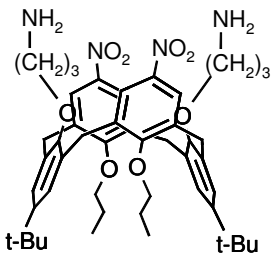
5,17-Di-*t*-butyl-11,23-diamino-26,28-diphthalimidoethoxy-25,27-dipropoxy-calix[4]arene 33 (n=2) (***1,3-alternate***)



The diamine **33 (n=2)** was obtained as described above for the analogous compound **33 (n=3)** starting from a clear solution of **32 (n=2)** (0.05 g, 0.04 mmol) in THF (15 ml) Analogous work up gave a yellow powder (0.03 g, 64 %). mp 315°C.

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.57 (t, 6H, ^3J = 7.16 Hz, C*H*$_3$-CH$_2$-), 1.23 (s, 18H, *t*-Bu), 3.17 (bt, 4H, -N*H*$_2$), 3.45-3.60 (2bt, 4/4H, -C*H*$_2$-N, O-C*H*$_2$-) 3.74, 3.84 (2d, 4/4H, ^2J = 12.2 Hz, Ar-C*H*$_2$-Ar), 6.88, 6.95 (2s, 4/4H, Ar*H*), 7.68-7.79 (2m, 8H, Phth-*H*).

5,17-Di-*t*-butyl-11,23-dinitro-26,28-diaminopropoxy-25,27-dipropoxy-calix[4]arene 34 (n=3) (***1,3-alternate***)



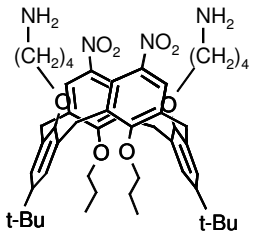
A solution of **32 (n=3)** (0.58 g, 0.53 mmol) in EtOH (60 ml) was refluxed with hydrazine hydrate (4.5 ml) for 3 h. Then solvent was evaporated till dryness and the residue was dissolved in CH_2Cl_2 (10 ml) and washed with water (2x20 ml). The organic phase was dried ($MgSO_4$) and evaporated again. The

resulting powder was dissolved in CH_2Cl_2 (5 ml) and the desired diamine was reprecipitated with hexane (10 ml) as yellow powder (0.25 g, 57 %). mp 155°-157°C. (Found: C 67.99, H 7.48, N 6.29. $C_{48}H_{66}N_4O_8x0.25CHCl_3$ requires C 67.63, H 7.79, N 6.54) FD-MS, (M^+) m/z = 825.05.

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.79 (t, 6H, ^3J = 7.3 Hz, -CH_2-CH_3), 1.23 (s, 18H, *t*-Bu,) 1.39-1.58 (m, 8H, -CH_2-), 2.64 (t, 4H, ^3J = 7.0 Hz -CH_2-NH_2), 3.50 (t, 4H, ^3J = 7.3 Hz, O-CH_2-) 3.66-3.73 (m, 8H, O-CH_2-, Ar-CH_2-Ar), 3.84 (d, 4H, ^2J = 15.0 Hz Ar-CH_2-Ar), 6.89, 7.98 (2s, 4/4H, Ar*H*).

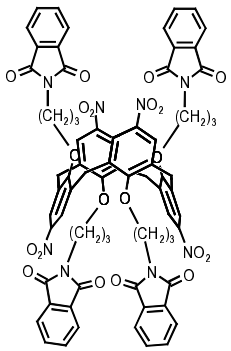
5,17-Di-*t*-butyl-11,23-dinitro-26,28-diaminopropoxy-25,27-dibutyloxy-calix[4]arene 34 (n=4) (***1,3-alternate***)

The diamino compound **34 (n=4)** is obtained in similar way as **34 (n=3)** starting from dinitro **32 (n=4)** (0.45 g, 0.43 mmol) dissolved in EtOH (30 ml). Hydrazine (3 ml) is added to the reaction mixture which is refluxed for 2 h. After working up of reaction, the diamine **34 (n=4)** is obtained as yellow oil (0.3 g, 81 %).



^{1}H-NMR (400MHz, $CDCl_3$) δ 0.80 (t, 6H, ^3J = 7.4 Hz, -CH_2-CH_3), 1.23 (m, 22H, *t*-Bu, -CH_2-), 1.47 (m, 4H, -CH_2-), 2.28 (bs, 4H, -NH_2), 2.69 (bt, 4H, -CH_2-), 3.51 (t, 4H, ^3J = 7.4 Hz, N-CH_2-) 3.59 (bt, 4H, O-CH_2-), 3.63, 3.71 (2d, 4/4H, ^2J = 15.2 Hz, Ar-CH_2-Ar), 6. 98, 7.94 (2s, 4/4H, Ar*H*).

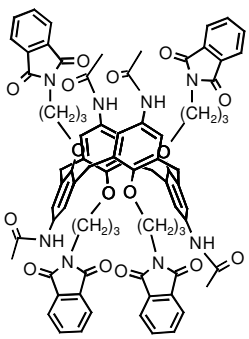
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-phthalimidopropoxy-calix[4]arene 37 (***1,3-alternate***)



Glacial acetic acid (13.5 ml) and fuming nitric acid (8 ml) were added to a vigorously stirred suspension of tetraphthalimido compound **5 (n=m=3)** in dry CH_2Cl_2 (50 ml) at rt. The reaction was complete when the color of the solution had changed from black-indigo to yellow (about 12 h). Then water (100 ml) was added and the mixture was stirred for 30 min. The organic phase was washed several times with water (3x100 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by slow crystallization from CH_2Cl_2/CH_3OH (40 ml, 1:2) which gave yellow crystals (1.12 g, 71 %). mp. 387-389 °C (Found: C 62.85, H 4.29, N 8.16. $C_{72}H_{56}N_8O_{20}xH_2O$ requires C 63.06, H 4.26, N 8.17)

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.26 (m, 8H, -CH_2-CH_2-CH_2-), 3.84 (s, 8H, Ar-CH_2-Ar), 3.95 (m, 16H, -CH_2-N, O-CH_2-), 7.68-7.86 (m, ,16H, Phth-*H*), 8.06 (s, 8H, Ar*H*).

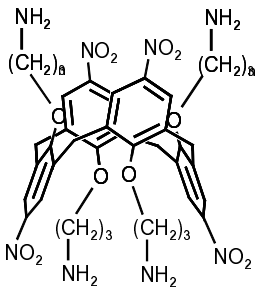
5,11,17,23-Tetra-acetamido-25,26,27,28-tetra-phthalimido-propoxy-calix[4]arene 38 (***1,3-alternate)***



A clear solution of the tetranitro compound **37 (n=m=3)** (0.75 g, 0.55 mmol) in THF/DMF (50 ml, 1:1) at 50°C was hydrogenated under atmospheric pressure in the presence of Ra-Ni. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (10 ml) and the tetraamine **40** (R=H) was reprecipitated with hexane (20 ml) as pale yellow powder (0.53 g, 85 %) which shows a broad ^{1}H NMR-spectrum in $CDCl_3$ as well as in DMSO. Therefore it was characterized as tetraacetamide **38** (R=$COCH_3$).The solution of the tetra amine (0.2 g, 0.16 mmol) in acetic anhydride (5ml) and few drops of triethylamine was stirred for 12 h at rt. The reaction mixture was poured in ice to form a sticky brown mass which was dissolved in chloroform (10 ml). After separation the organic phase was dried and the solvent was evaporated. The tetra-acetamide **38** (R=$COCH_3$) was obtained after column chromatography using ($CHCl_3$/MeOH; 9.8:0.2) as eluent as a yellow powder (0.14 g, 64 %). m.p 335°C. FD-MS, (M^++H) m/z = 1403.5.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (bm, 20H, CH_2-C*H*$_2$-CH_2-, -C*H*$_3$), 3.45 (s, 8H, Ar-C*H*$_2$-Ar), 3.79 (t, 8H, ^3J = 4.7 Hz, O-C*H*$_2$-), 4.24 (t, 8H, ^3J = 7.8 Hz, -C*H*$_2$-N), 7.36 (s, 8H, Ar*H*), 7.70-7.81 (m, 16H, Phth-*H*), 8.09 (s, 4H, N*H*)

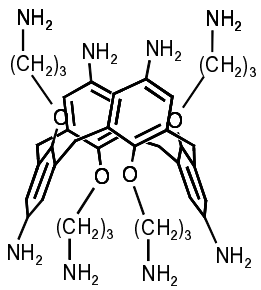
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-aminopropoxy-calix[4]arene 39 (***1,3-alternate***)



A suspension of **37 (*1,3-alternate*)** (1.12 g, 0.83 mmol) in EtOH (60 ml) was refluxed with hydrazine hydrate (20 ml) for 4h (the solution became clear). After the solvent was evaporated in *vacuo* till dryness the residue was dissolved in CH_2Cl_2 (15 ml) and washed twice with water (2x30 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed in *vacuo.* The residue was dissolved in chloroform (10 ml) and the tetraamine **39 (*1,3-alternate*)** was reprecipitated with hexane to give a yellow powder (0.39 g, 57 %). mp. 249-251 °C. (Found: C 56.34, H 6.30, N 12.41 $C_{40}H_{50}N_8O_{12}xH_2O$requires C 56.33, H 6.15, N 13.14). FD-MS, (M^++H) m/z = 835.2

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (m, 16H, -N*H*$_2$, -CH_2-C*H*$_2$-CH_2-), 2.79 (t, 8H, ^3J = 6.3 Hz, -C*H*$_2$-N), 3.53 (s, 8H, Ar-C*H*$_2$-Ar), 3.78 (t, 8H, ^3J = 6.5 Hz, O-C*H*$_2$-), 7.78 (s, 8H, Ar*H*).

5,11,17,23-Tetra-amino-25,26,27,28-tetra-aminopropoxy-calix[4]arene 40 (***1,3-alternate***)



A suspension of **37** (0.4 g, 0.4 mmol) and Pd/C (100 mg) in EtOH (30 ml) was refluxed with hydrazine hydrate (8 ml) for 4h. Then, the solvent was evaporated under reduced pressure the residue was dissolved in $CHCl_3$ (10 ml) and washed twice with water (2x25 ml). The organic solution was dried ($MgSO_4$) and the solvent was removed in *vacuo.* The formed powder was

dissolved in chloroform (5 ml) and the octaamine was obtained as bright yellow powder by reprecipitation with hexane (0.39 g, 57 %). m.p. 259°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98-2.06 (m, 8H, -CH_2-CH_2-CH_2-), 3.00 (t, 8H, ^3J = 6.6 Hz, -CH_2-N), 3.73 (s, 8H, Ar-CH_2-Ar), 3.98 (t, 8H, ^3J = 6.6 Hz, O-CH_2-), 8.00 (s, 8H, Ar*H*).

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Chapter 3

3. Ligands for Lanthanides and Actinides.

3. Introduction.

The processing of nuclear waste is a current topic of great importance. A successful process usually is based on the separation of its components. The elements present differ remarkably in their toxicity, the type and energy of the emitted radiation, life-times and, of course, in the reprocessing methods required. One of the generally used chemical separation processes in fuel treatment is based on liquid-liquid extraction by specific molecules. The industrially used PUREX[1] (Plutonium-Uranium Recovery by Extraction) process effectively removes plutonium and uranium from nuclear fuel. Lanthanides and actinides are extracted in the next step using the so-called TRUEX[2] (Trans-Uranium-Extraction) process. The extractant used is [(*N*,*N*-diisobutylcarbamoyl) methyl] octyl (phenyl) phosphine oxide (figure 1) which powerfully extracts the cations from acidic solution (HNO_3) into the organic phase. The disadvantage of CMPO is that it discriminates only slightly between actinides and lanthanides. The actinides are the minor but more toxic component in the nuclear waste compared with lanthanides. Ideally extractants with high actinides/ lanthanides selectivity are required.

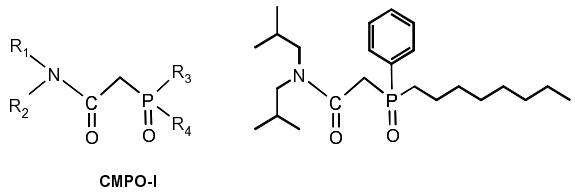


Figure 1. General formula of the carbamoylmethylphosphine oxides and the specific example used [(*N*,*N*-diisobutylcarbamoyl) methyl] octyl (phenyl) phosphine oxide.

In the carbamoylmethylphosphine oxides (CMPO-I) the C=O and P=O act as the ligating functions. During the last decades the general structure of CMPO-I was modified in many ways and compounds bearing numerous residues at the nitrogen (R_1, R_2) and phosphorus (R_3, R_4) in various combinations have been checked[3].

Horwitz *et al*. studied the solution structure of the americium (III) complex formed with CMPO-I under the technical conditions of the TRUEX process. Their results show that three molecules of CMPO-I coordinate one americium (III) ion and three nitrate anions in an overall neutral complex as indicated in figure 2. A further molecule of HNO_3 is loosely bonded via hydrogen bonds to each of carbamoyl oxygen[4].

It seems reasonable to construct molecules, in which several CMPO functions are combined in a suitable mutual arrangement. This may not only lead to new ligands which show in general improved extraction properties on the basis of chelate effects, but also to ligands which show selectivity in extraction due to the different stoichiometry of complexes and to differences in the steric requirements.

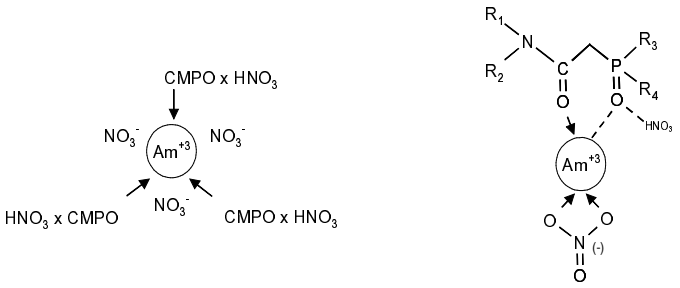


Figure 2. Possible solution structure (schematic) of the americium (III) nitrato-CMPO complex at high HNO_3 concentration.

The easily available calix[4]arenes can be used as a platform for the attachment of a varied number of CMPO-like ligating functions to rich the high coordination numbers of the *f*-block elements. In addition, the calix[4]arenes in the *cone* conformation offer a preorganizated coordination environment, while aliphatic ether groups bring enough lipophilicity to facilitate the passage of the cation into the organic phase as complex. A large number of cation extractants derived from calixarenes has been developed in the last decade, in which the preorganization of ligating functions adds favorably to their specificity[5]. The ligating functions have been attached at either the wide rim[6,7] or narrow rim[8] of the calix[4]arenes in the *cone* conformation and the extraction ability and the selectivity[9] for actinides (or light lanthanides) from heavy lanthanides are reported.

Three series of calix[4]arene derivatives (CI, CII, CIII, figure 3) bearing four carbamoylmethylphosphine oxide groups were synthesized as extractants for lanthanides and actinides. Among them the CI series are powerful extractants showing high ability of extraction towards lanthanides and actinides, combined with a pronounced selectivity within the groups of trivalent lanthanides[6,7,10] and between trivalent lanthanides and actinides. Less efficient are the narrow rim tetra-CMPO derivatives CIII where the CMPO ligating functions are linked via alkoxy groups. A series of compounds having spacers with two to four methylene groups were synthesized in order to investigate their extraction efficiency and selectivity[11]. In this series a strong increase in extractability with increasing length of the spacer is shown. The wide rim tetra-CMPO CII derivative has a rigidified skeleton due to the short crown-ether bridges[12] and shows an enhanced extractability by a factor of ten compared with CI, but no change of the selectivity[11]. In comparison with CMPO-II, the compounds CI-III show excellent extraction results but not much is known about the exact composition and structure of the extracted species.

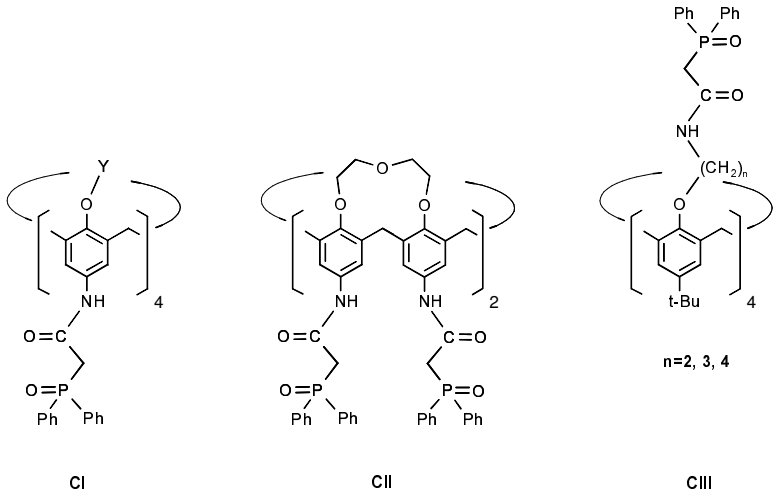


Figure 3. Series of calix[4]arene derivatives bearing CMPOs to the a) wide rim CI (different alkyl chain), b) wide rim CII (rigidified skeleton by using a shortness bridge) and c) narrow rim CIII (different spacer).

MD (Molecular dynamics)-simulations[13] suggested a 1:1 complex of the tetrapentylether calix[4]arene from the CI series with trivalent cations such as Eu^{+3} or Am^{+3}. The complex of the narrow rim tetra-CMPO CIII with cations has a monomeric structure. The complex of CI or CII formed in the presence of 20-50 % excess of the metal cation (Th^{4+}, La^{3+}, Yb^{3+}) shows only under these conditions well resolved NMR spectra[9a]. Relaxivity measurements suggest the formation of oligomeric to polymeric structures.

The combination of four CMPO-like ligating functions is not the only factor which influences the complexation, but also their mutual arrangement and the flexibility of their linkage. We proposed to built molecules where the CMPO-like ligating functions are attached to calix[4]arenes fixed in the *1,3-alternate* conformation. This offers the possibility to combine narrow and wide rim CMPO linkages orientated to the same side. Two CMPO-like ligating functions are attached to the narrow rim via alkoxy linkages (C_2 to C_4 similar to the *cone* isomer derivatives of CIII) and the other two CMPOs are directly attached to the wide rim (similar to CI). The synthesis and the extraction studies of tetra-CMPO calix[4]arene derivatives in the *1,3-alternate* conformation are described in the next subchapter named *tetra-CMPO derivatives*.

In order to increase the selectivity An/Ln softer sulphur or nitrogen – bearing extractants are used in the so called SANEX[14,15] (Selective ActiNides EXtraction) separation process. It is based on the affinity of these ligands to An(III). Different pyridine derivatives such as terpyridines and 2,6-bis(triazinyl)pyridines[16,17,18,19,20], or dithiophosphinic acids[21,22,23] show quite remarkable separation factors. Among these ligands the N-alkylpicolinamides have also been proposed as ligands for the selective extraction of actinides from radioactive waste[24,25,26] showing quite promising separation factor ($S_{Am/Eu}$ ~ 9) under optimum conditions. They can act as bidentate ligands as the X-ray analysis proved for the complex of the Cu^{II} salt[27]. The molecular modelling[28] show that the carbonyl group and

the softer pyridin nitrogen are the coordinating parts for the metal ion. Alternatively, they can act also as monodentate ligands through the pyridine nitrogen[29] or, under basic conditions, as bidentate ligands through the deprotonated amide NH rather than the carbonyl group[30].

Besides of the synthesized series of the CMPO calix[4]arene derivatives in the *1,3-alternate* conformation, we synthesized compounds using the same conformer as platform, where the CMPOs are combined with the picolinamide ligating functions in order to investigate the extraction efficiency and selectivity for actinides and lanthanides (see subchapter 3.2).

3.1. Tetra-CMPO derivatives

If four CMPO functions attached to the *1,3-alternate* platform are orientated in the same direction two of them must be linked to the narrow rim via alkoxy spacers and two directly to the wide rim (see figure 4).

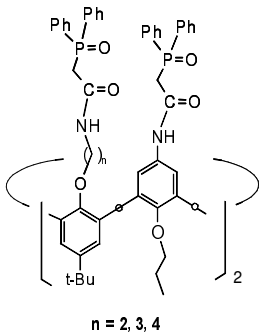
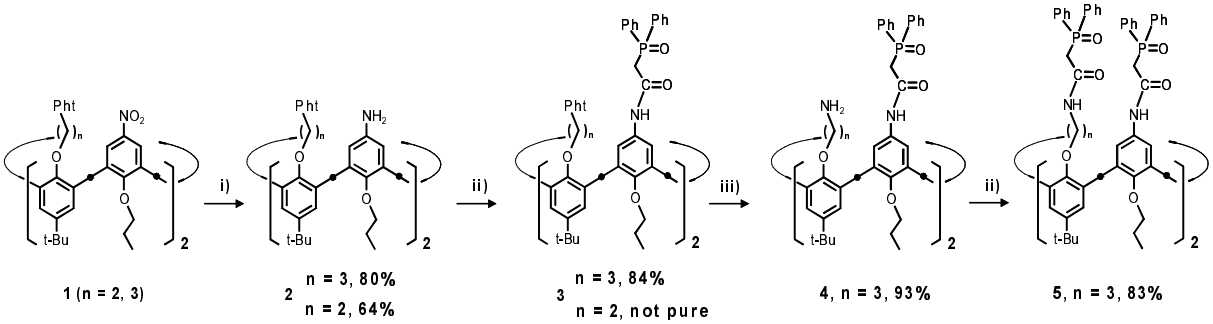


Figure 4. The general formula of a tetra-CMPO calixarene in the *1,3-alternate* conformation; 2, 3 and 4 methylene groups are used to link the CMPO groups to the narrow rim.

The synthesis of tetraCMPO calix[4]arene derivatives starts from the precursor **1** (**32**, from chapter 2). In principle three pathways are possible:

A. Reduction of the nitro groups, followed by a first N-acylation with N-AE leads to diCMPO derivatives. Then the cleavage of the phthalimido groups liberates the narrow rim amines, which are further N-acylated with N-AE [*p*-nitrophenyl (diphenyl phosphoryl)-acetate][6] to achieve the target compound (Scheme 1).

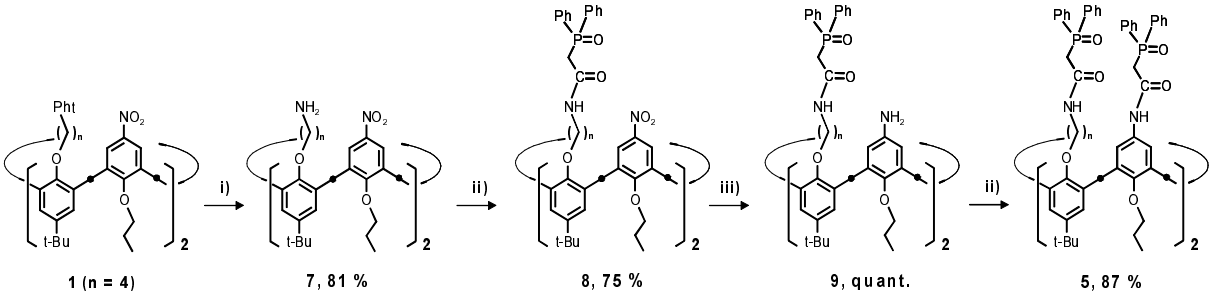
This reaction sequence was tried for **1 (n=3, 4)**. In case of n=3 the synthesis occurred without difficulties and with high yields. Since the yield of precursor **1(n=2)** the amount of **1** was not sufficient to continue the synthesis. Although in case of n=3 the synthesis occurred without difficulties and with high yields, for n=4, a mixture of compounds was obtained after a first attempt (after several attempts the desired compound was obtained) therefore another way was applied in this case.



Scheme 1. The synthesis of the tetra-CMPO derivative **5 (n=3)**.

i) H_2, Raney-Ni, THF, rt, ii) N-AE, CH_2Cl_2, rt, iii) hydrazine, EtOH, reflux.

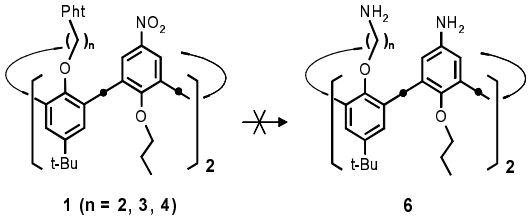
B. The other pathway starts with the cleavage of phthalimido groups followed by acylation with N-AE for the introduction of CMPO groups. DiCMPO derivative is further subjected to reduction of nitro groups and the formed wide rim diamine is acylated with N-AE to achieve the target compound (Scheme 2). In this way the target tetraCMPO derivative **5(n=4)** was obtained without difficulties.



Scheme 2. The synthesis of the tetra-CMPO derivative **5 (n=4)**.

i) hydrazine, EtOH, reflux H_2, ii) N-AE, CH_2Cl_2, iii) rt, Raney-Ni, THF, rt.

C. A direct conversion from tetraether **1** into narrow/wide rim tetraamine calix[4]arene derivative in *1,3-alternate* conformation was also followed (see below). In the case of n=3, an inseparable mixture of compounds was obtained, while in the case of n=4 a mixture of only two compounds mainly the target one and minority with unconverted allyl groups is observed (see chapter 2). This mixture can be easily converted into pure tetraCMPO derivative **5** by treating it with hydrazine in boiling ethanol.



Based on our experience, to obtain tetra-CMPO derivatives in the *1,3-alternate* conformation it is preferable to follow four step synthesis.

A comparison of ^{1}H-NMR spectra of **5** (**n=3)** with **5 (n=4)** is depicted in Figure 6. The homologues proton signals show close values of their chemical shifts.

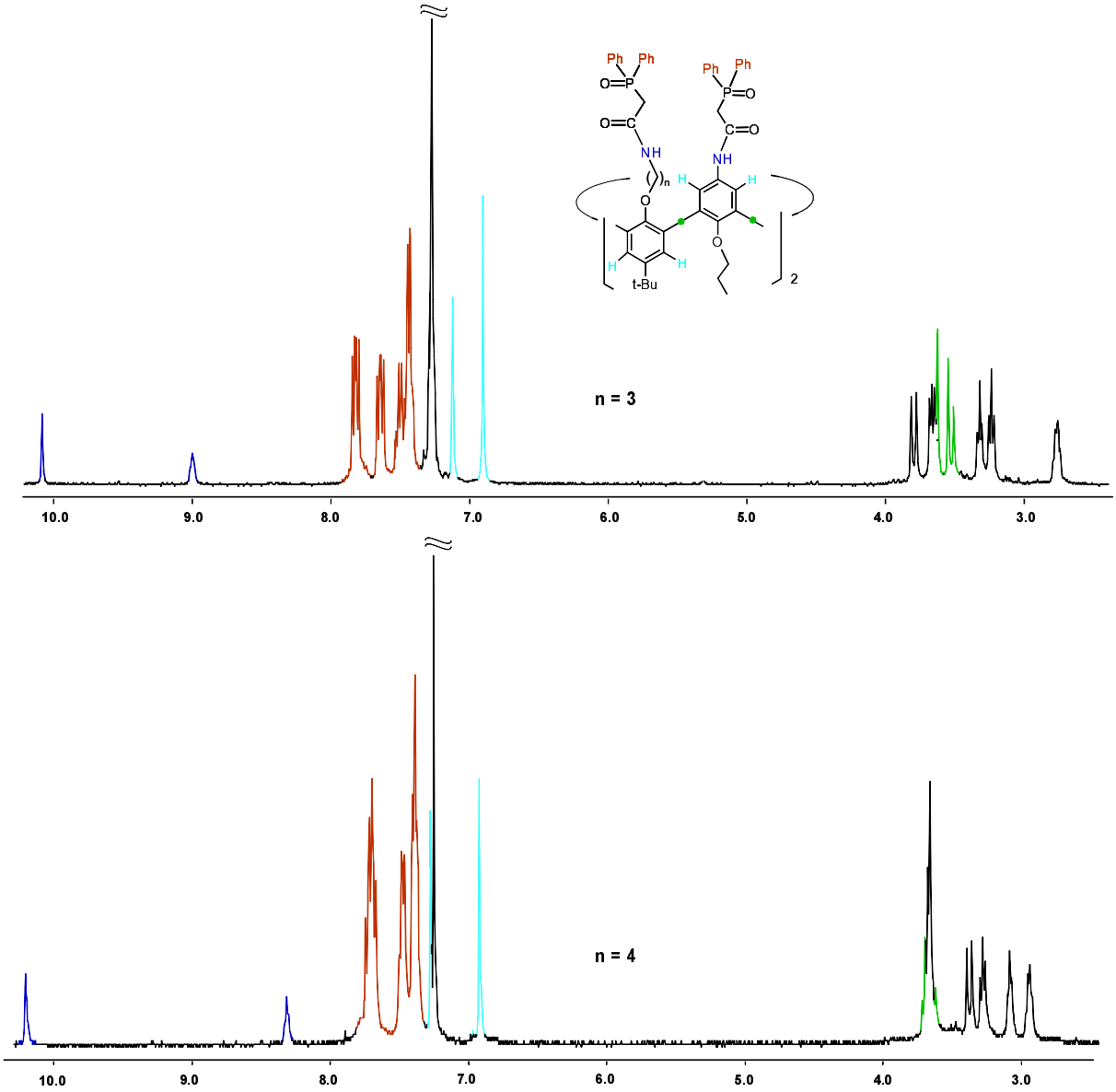
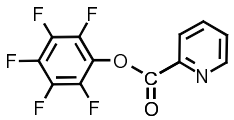


Figure 6. Comparison of the ^{1}H-NMR spectra in $CDCl_3$ corresponding to tetra-CMPO derivative **5 (n=3)** and **5 (n=4)**

Two signals in range of 8 up to 10 ppm, which consist of a singlet and a broad triplet (1:1 ratio) characterize the amidic protons (aromatic and aliphatic respectively) in the both cases (blue colour). The aromatic and aliphatic part are almost similar for the both cases. In case of **5 (n=4)** the methylene bridge signals are not clearly seen due to the overlapping with the signal of the methylene group protons coupled with phosphorus.

3.2. Two CMPO combined with two picolinamide functions in the same side of the *1,3-alternate* conformation.

The picolinamide function can be attached to the calix[4]arenes scaffold by simple N-acylation of the amino calix[4]arenes with picolinic acid derivative. Casnati et al[31] tested the acylation of primary amine (e.g butyl amine) with picolinic acid chloride, but the desired amide was obtained with low yield. When the same reaction was applied to the tetraamines tetraether calix[4]arenes a mixture of compounds was obtained beside the desired tetrapicolinamide. Finally, a pentafluorophenyl[32,33] ester of picolinic acid (F-AE) was found as acylation agent.

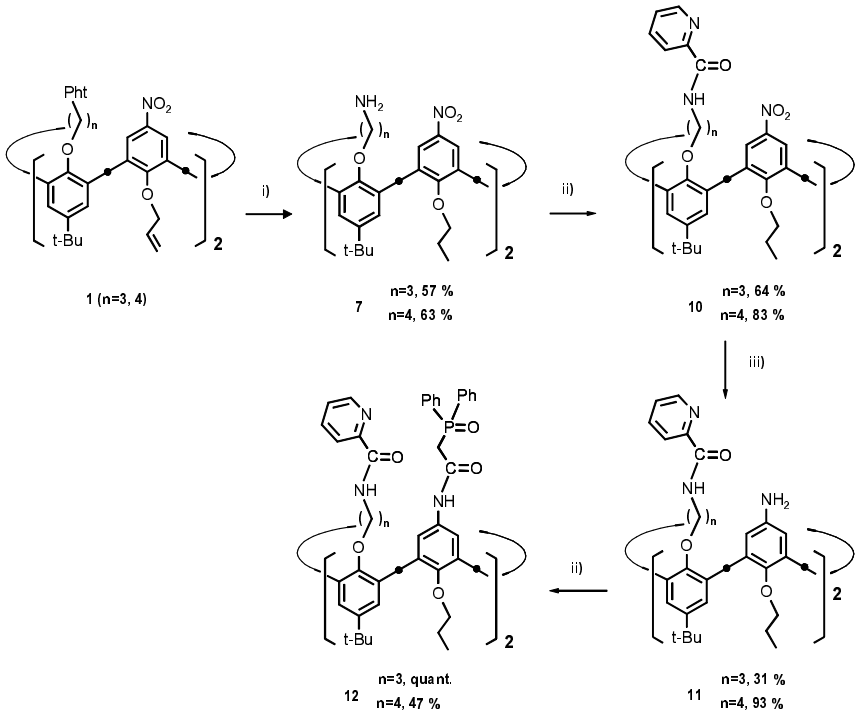


Reaction of the active ester with butylamine doubled the yield of the desired compound and in the case of amine calix[4]arenes it is allowed to isolate the calix[4]arene ligands in reasonable yields.

To obtain the dipicolinamide diCMPO derivatives in the *1,3-alternate* conformation a four step synthesis is needed starting from the precursor **1 (n=3, 4)** (see scheme 3). After cleavage of the phthalimido groups the picolinamide groups are first introduced by acylation with F-AE (the desired compound **12** is easier isolated when the CMPO ligatig function is introduced after the picolinamide is already incorporated). The narrow rim dipicolinamide derivative **10** bears wide rim nitro groups which are reduced and the formed diamine **11** is further acylated with the N-AE to obtain the desired wide rim di CMPO narrow rim dipicolinamide derivative **12**. Both ligatig functions are attached at the same side of the *1,3-alternate* platform.

No difficulties were encountered in the preparation of the diCMPO dipicolinamide **12 (n=3)**.

Regarding the synthesis of **12 (n=4)**, in step of cleavage of the phthalimido groups from the precursor **1 (n=4)** the desired di-amine **7** was accompanied by a trace of di-amine which contain allyl groups (**7a**-Figure 7). According to our experience under this conditions the phthalimide groups are always entirely cleaved, the nitro groups remain intact, but the allyl groups can be either converted into propyl groups or not. Since in one of the next steps the reduction of the nitro groups occurs under suitable conditions for the hydrogenation of the double bond, the conversion of the by products (**7a**, **10a**) in the target one (**11**) can be done later. So, the synthesis was continued with the mixture of the diamines **7** and **7a**, which is



Scheme 3. The synthesis of the di-picolinamide di-CMPO calix[4]arenes derivatives in *1,3-alternate* conformation, in which all ligands are pointing in the same direction.

i) hydrazine, EtOH, reflux, ii) AE or F-AE CH_2Cl_2, rt, iii) Ra/Ni, THF, rt.

further N-acylated with the F-AE and isolated again the mixture **10** and **10a**. After reduction of the nitro groups the mixture is converted almost quantitatively to the diamines **11**.

The sequence **7**-to-**11** via **10** of the synthesis is followed by NMR spectroscopy and the ^{1}H-NMR spectra of intermediates are depicted in Figure 7. A second N-acylation of amino groups with N-AE gives the desired compound **12 (n=4)** in 47 % yield.

3.3. Octa-CMPO derivatives of calix[4]arenes in all possible conformations.

We also tried to attach eight CMPO groups to both sides of the *1,3-alternate* skeleton. In these octa CMPOs four CMPOs are bond to the narrow rim via alkoxy linkage and four CMPOs are directly attached to the wide rim. Because reasonable amounts of *partial cone* and *1,2-alternate* isomers of tetraether **13** (**5** from chapter 2) are obtained as side products near the target one, they can also be used as skeleton for octa-CMPO derivatives.

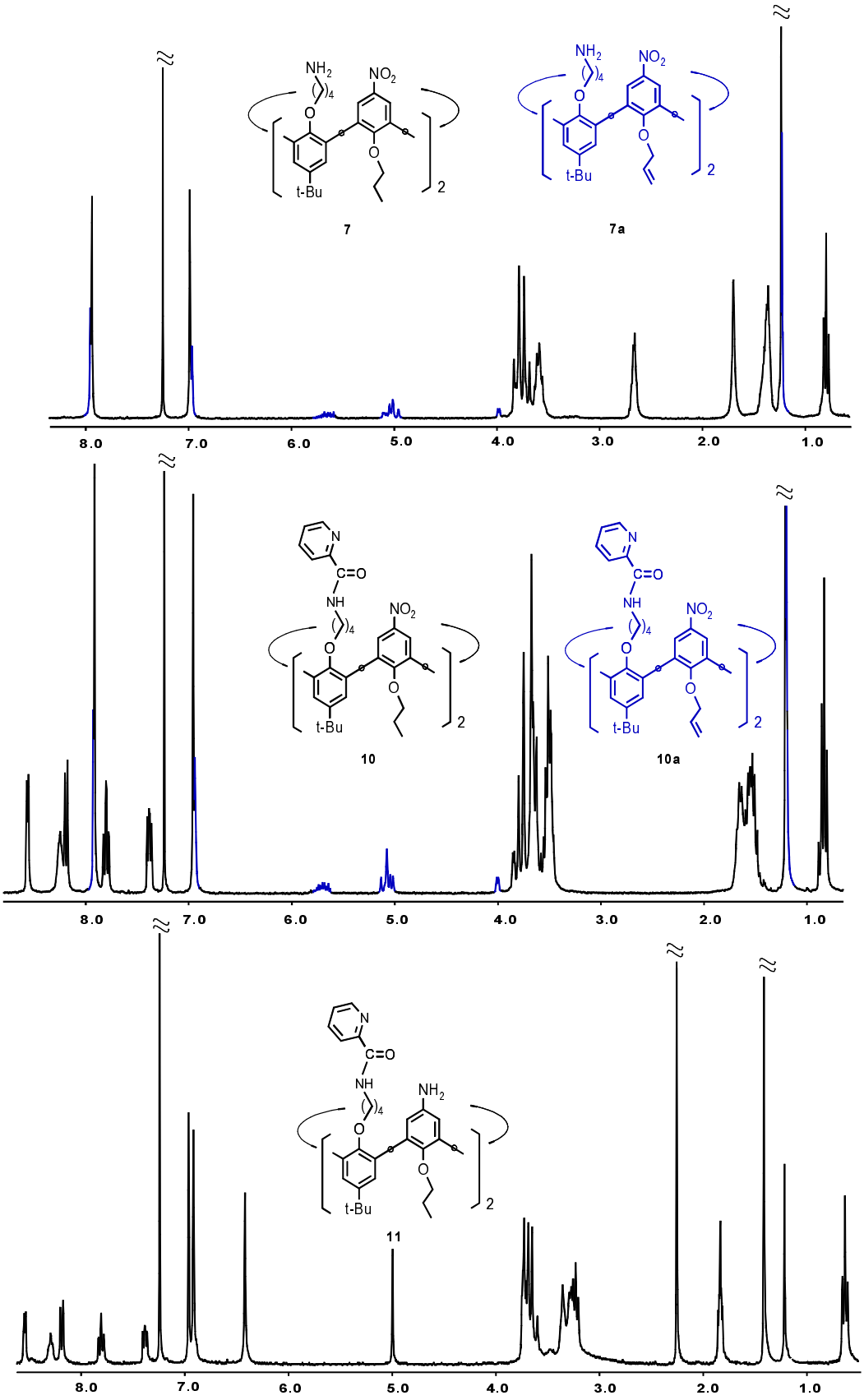
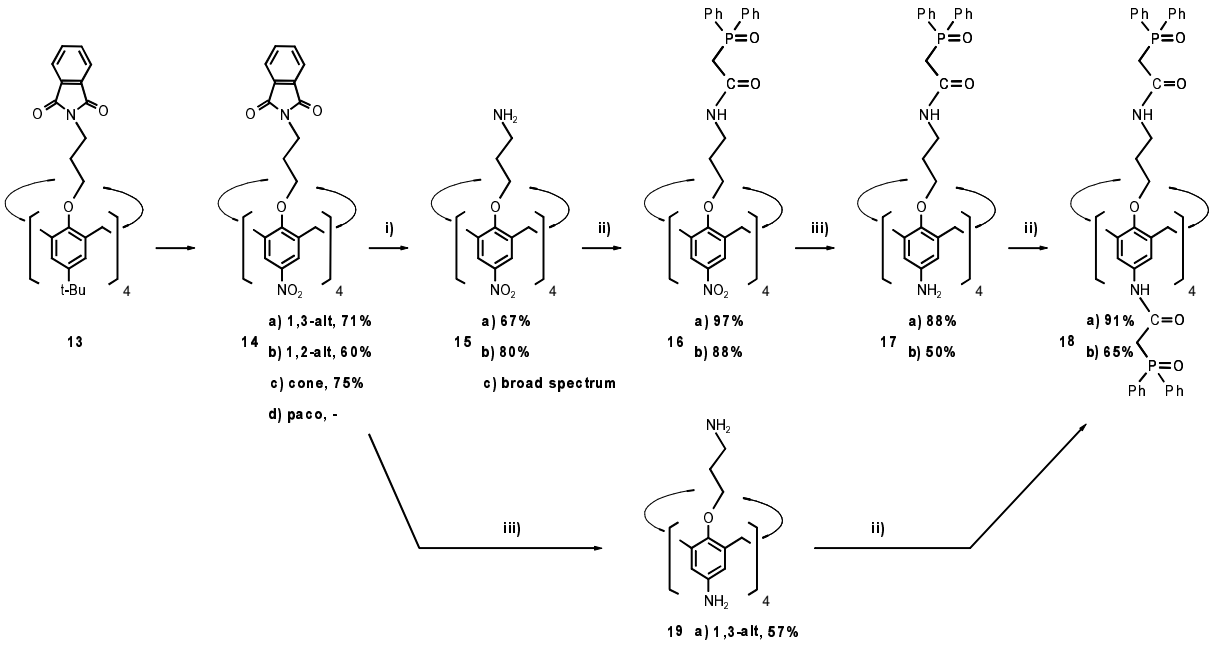


Figure 7. The ^{1}H-NMR spectra in $CDCl_3$ of **7**, **10**, **11**. Few drops a DMSO-d_6 was added in the sample of **7** to avoid the broad peaks which appear in the ^{1}H-NMR spectrum measured in $CDCl_3$.

The strategy of obtaining the octa-CMPO derivatives is identical for all four cases and include five steps (Scheme 4). *Ipso*-nitration of tetraether **13**, followed by cleavage of phthalimido groups leads to narrow rim tetraamine **15**. A first N-acylation with N-AE achieve tetraCMPO **16**. Reduction of nitro groups, subsequent the second N-acylation with N-AE leads to octaCMPO derivative **18**. It is worth to be mentioned that the synthesis can start either with the cleavage of phthalimido groups or with reduction of the nitro groups, but in the last case a high solubility of the compound is required. Due to low solubility of the **14** (all isomers) in usual solvents, the cleavage of phthalimido groups is taken as first step in this synthesis.

a) *1,3-alternate*

All the steps occurred without difficulties and the intermediates and the target compound are obtained in high yields. The octa-CMPO calix[4]arenes fixed in the *1,3-alternate* conformation and the intermediates posses a high D_{2d}-symmetry.



Scheme 4. The synthesis of the octa-CMPO derivatives in all possible conformers. i) hydrazine, EtOH, reflux, ii) AE, CH_2Cl_2, rt iii) Ra-Ni, hydrazine, boiling EtOH

b) *1,2-alternate*

All the steps of the synthesizing the octa-CMPO **18** in *1,2-alternate* occurred without difficulties and with good yields.

c) *partial cone*

Several attempts for the *ipso*-nitration of the tetraether **13** were tried and in all cases a mixture of compounds can be distinguished by TLC, Mass-spectra or ^{1}H-NMR spectra. The mixture can not be separated neither by crystallization nor by chromatography. A reasonable explanation could be that the *t*-butyl group attached to the inverted aromatic ring is surrounded by three phthalimido groups which

could influence the *ipso*-attack. Due to these difficulties encountered in the *ipso*-nitration step another strategy was envisaged. This starts with the tri-O-alkylation of the *t*-butylcalix[4]arene with N-(3-Bromopropyl) phthalimide, followed by exhaustive *ipso*-nitration. In the next step the tri-O-alkylated compound should be fixed in the *partial cone* conformation by O-alkylation with bromopropylphthalimide in the presence of K^+ or Cs^+ cation.

The tri-O-alkylated compound was obtained as by product of the tetra-ether **13** in *cone* conformation (see below). However, the *ipso*-nitration of the ethers gave only a mixture of compounds; as the tlc shows. Since this mixture was inseparable the synthesis remains for the moment at this stage.

d) *cone*

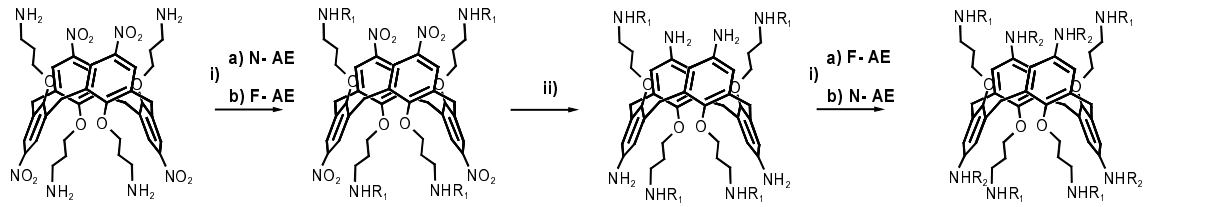
The direct tetra-O-alkylation of **1** leads selectively to the *cone* conformation when the reaction is performed in the presence of NaH in DMF at room temperature in 4-5 days. When the alkylating agent is N-(3-bromopropyl)-phthalimide the tri-O-alkylated compound is formed as by-product in up to 20 % yield. The cleavage of the phthalimido groups was not possible in a clean fashion. The ^{1}H-NMR spectrum shows broad proton signals of the obtained narrow rim tetraamine **15**. If instead of this step the reduction of the nitro groups is tried, a mixture of compounds is formed. One of them being the unreacted material (as tlc shows, after 1 day) due to low solubility of tetranitro in usual solvents as we mentioned before.

A direct conversion of tetranitro **14** into octamines **19** was also tried for all conformers, but only in case of 1,3-alternate isomer worked (see chapter 2).

3.4. Tetra CMPO, tetra picolinamides in the *1,3-alternate* conformation.

In order to combine CMPO with picolyl functions on the both sides of the *1,3-alternate* skeleton, we envisaged two possibilities namely wide rim CMPOs, narrow rim picolinamides and inversely narrow rim CMPOs, wide rim picolinamides.

A four step synthesis is required here: deprotection of the phthalimido groups, acylation with N-AE/F-AE, followed by reduction of the nitro groups and final acylation with F-AE/N-AE.



Scheme 5. The synthesis of tetra-CMPO tetrapicolinamides of calix[4]arene in the *1,3-alternate*.

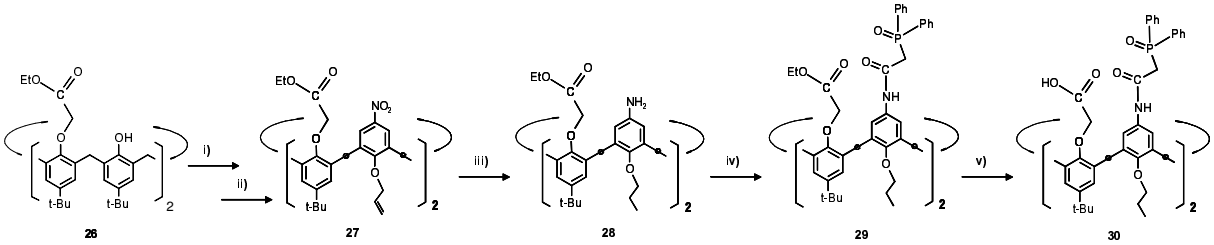
i) N-AE or F-AE, CH_2Cl_2, rt, ii) H_2, Ra-Ni, THF or EtOH.

The synthesis of tetra-CMPO tetrapicolinamide derivatives **24** and **25** and the yields of each step are presented in Scheme 5. As can be observed the N-acylation by the F-AE occurs with lower yield than the N-acylation with the N-AE.

3.5. Two CMPO combined with acidic functions at the same side of the *1,3-alternate* conformation.

It is reported that calix[4]arenas substituted by acetamide, acetate or acetic acid groups at the narrow rim, or analogous compounds with mixed functionalities, are effective and selective receptors for sodium[34], calcium[35], lanthanides[36], actinium[37], uranium (VI) and thorium (IV)[38].

In order to obtain selective extractants for lanthanides and actinides the calix[4]arene in the *1,3-alternate* conformation is used as a platform on which such ligating functions as CMPOs and acidic groups are placed on the same side of the skeleton.



Scheme 6. i) 65 % HNO_3, 0-5 °C, CH_2Cl_2 ii) allybromide, Cs_2CO_3, DMF, 50 °C, iii) THF, H_2, Ra-Ni, iv) N-AE, CH_2Cl_2, rt, v) LiOH, THF/MeOH, rt.

The synthesis starts with the di-O-alkylation[39] of the *t*-butyl-calix[4]arene with bromoethylacetate, followed by selective *ipso*-nitration which leads to compounds known from literature[40]. In the next step the calix[4]arene is fixed in the *1,3-alternate* conformation by O-alkylation in the presence of Cs^+ cation by again the reactive allylbromide. The nitro groups are reduced to diamine **28** which is further N-acylated with N-AE to achieve the di-CMPO derivative **29** in high yield. The next step consists in the cleavage of the ester to obtain quantitative the acidic functions to the desired compound **30**.

In our hands, only 21 % of the *1,3-alternate* isomer **27** is obtained together with up to 40 % *partial cone* isomer **27** (a comparison of their ^{1}H-NMR spectra is shown in Figure 8). The wide rim diamine was not isolated, but was further subjected to N-acylated with N-AE when desired di-CMPO was isolated after column chromatography in up to 92 % yield. The quantitative hydrolysis of the ester functions takes place under basic condition (aq.LiOH) in THF/MeOH solution.

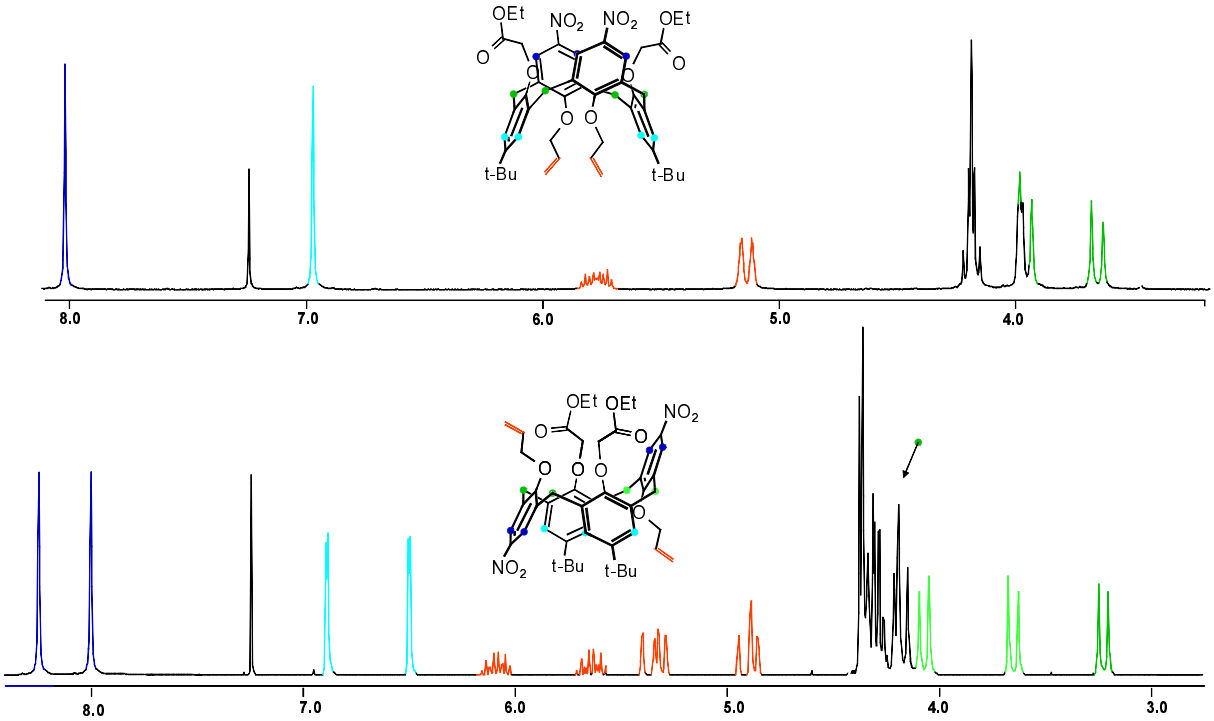


Figure 8. The ^{1}H-NMR spectra of compound **27** in *1,3-alternate* (above) and *partial cone* (below) conformation.

3.6. Extraction results.

The extraction of a series of non-radioactive elements was investigated. Thus, La^{+3}, Eu^{+3}, Yb^{+3}, and Th^{+4} cations were extracted by tetraCMPO- **5**(n=3, 4) and octaCMPO calix[4]arene **18** in *1,2-* and *1,3-alternate* conformations (c_L=10^{-3} - 10^{-4} M) from their nitrates (c_M=10^{-4} M) in 1 M nitric acid aqueous solution into dichloromethane. The extraction results are shown in Table 1.

Extractants	C_L (M)	**La^{3+}**	**Eu^{3+}**	**Yb^{3+}**	**Th^{4+}**
5(n=3)	10^{-3}	11±2	11±1	9±2	
	10^{-4}				17±2
5(n=4)	10^{-3}	12	10	11	48
	10^{-4}				12
18(1,2-alt)	10^{-4}	61±3	43±1	20±3	95±1
18(1,3-alt)	10^{-4}	14±1	12±3	7±2	83±1

Table 1. Extraction percentages (%E) of lanthanides and thorium nitrates by ligands **5(n=3, 4)** and octaCMPO **18** (***1,2-, 1,3-alt***) from 1 M nitric acid aqueous solution into dichloromethane (t = 20 °C).

Compounds octaCMPO in the *1,2-* and *1,3-alternate* conformation are highly efficient extractans for thorium, even high selectivity toward thorium over lanthanides is shown by octaCMPO in *1,3-alternate* conformation. Concerning the extraction of lanthanides, only octaCMPO **18(1,2-alt)** proved good extraction results which are comparable in extraction efficiency with the tetraCMPO wide rim[8].

The complexation experiment follows these conditions: UV absorption spectropho-tometric titrations in methanol, where $(Et_4N)NO_3$ (0.01 M)-ligand concentrations ranging between 5 10^{-5} and 10^{-4} M is used as supporting electrolyte. The ratios between metal and ligand concentrations at the end of the titration in up to 19 according to the stability constants. A plot of stability constant for complexes with cations of calixarene derivatives is illustrated in Figure 9.

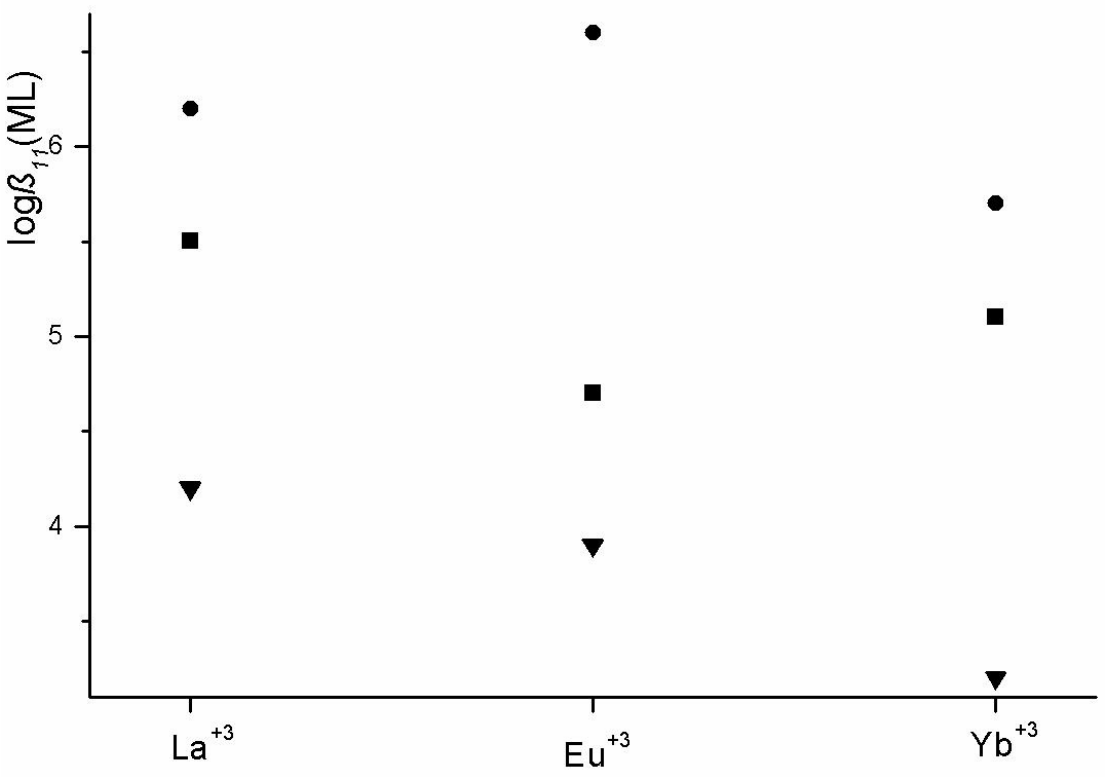
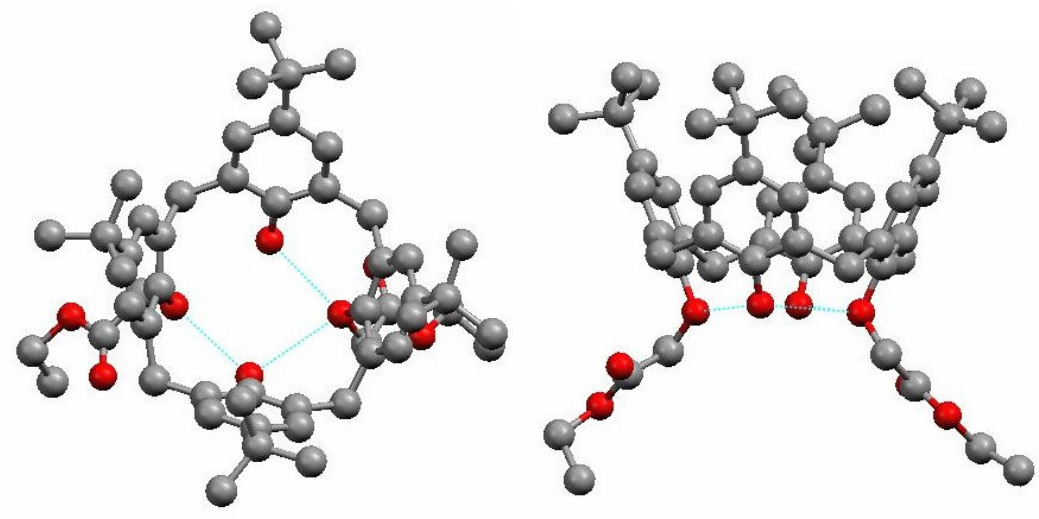


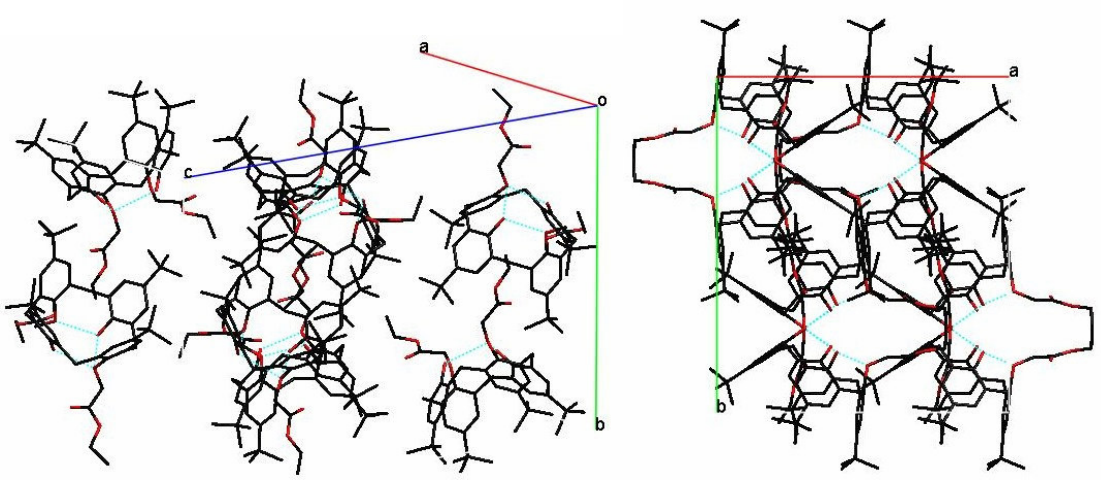
Figure 9 . The plot of stability constant (logβ) for complexes of La, Eu, Yb cations with CMPO calix[4]arenes [▼-**5(n=4)**, ■-**5(n=3)**, ●-**18(*1,3-alt*)**] derivatives in MeOH.

3.7. X-ray analysis.

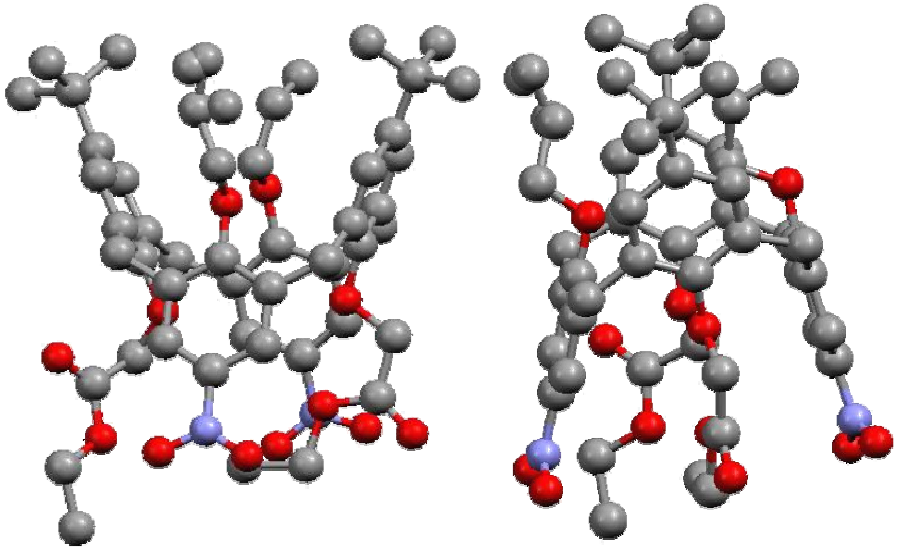
The molecule of **26**[41] still assumes *cone* conformation stabilize by two intramolecular hydrogen bonds (distances between adjacent oxygen atoms are about 2.72 Å and 2.77 Å respectively).



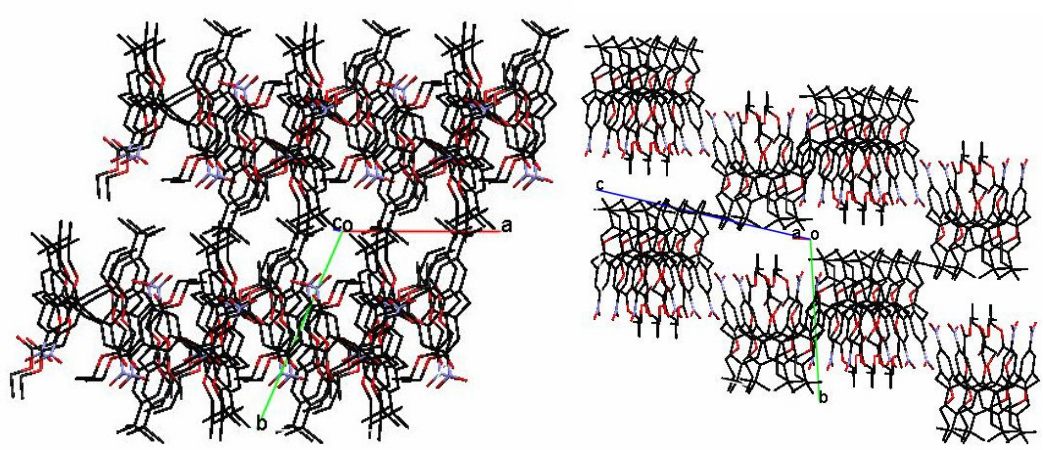
View on top (left) and at side (above and right) of the crystal **26**.



The packing diagram of **26**.



View at side of crystal **27**.



The packing diagram of **27**, view along *c* (left) axis and along *a* (right) axis.

Figure 9. Molecular conformation of **26** and **27** and their packing diagram.

In the packing diagram of the **26** one can observe that one ester residue is orientated into the cavity of the neighboring molecule. The same single crystal was analyzed by Ferguson et all[39], but the results of the present structure determination are of significantly higher precision.

The structure of **27** confirms that tetraether is fixed in *1,3-alternate* conformation. In this case one of the phenol unit which bears the ester residue is most titled toward the inner of the cavity. In the packing of the crystal each molecule is rotated clockwise in the plan of paper with 180 ° to each other.

For the both crystals their crystallographic data and geometrical parameters are gathered in table 1 and 2 respectively.

Table 1. Summary of crystal data.

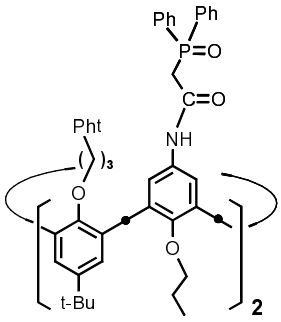
Compound	**26 (*cone*)**	**27 (*1,3-alt*)**
Formula	$C_{54}H_{70}Cl_6O_8$	$C_{51}H_{59}Cl_3N_2O_{12}$
M_W	1059.80	998.35
Crystal system	Orthorhombic	triclinic
Space group	*Pbca*	*P*-1
T/K	173(2)	173(2)
a/ Å	17.7766(2)	10.4879(6)
b/ Å	20.41080(10)	14.0724(8)
c/ Å	32.0452(2)	19.2015(11)
α^o	90	96.336(4)
β^o	90	104.191(4)
γ^o	90	111.084(4)
V/Å	11627.11(16)	2501.0(2)
Z	8	2
μ (mm^{-1})	0.344	0.247
Unique refins. Measured	52500	66572
Unique refins.[$I > 2\sigma(I)$]	0.0945	0.0479
$wR(F^2)$	0.2619	0.1229

Table 2. Selected crystallographic data: **I)** Torsion angles (°) around the Ar-CH_2-bonds [1-2-3-4, Cα6-Cα1-Cα-Cα3, α=1-4) and 2-3-4-5 (Cα1-Cα-Cα3-Cα4), the same representation as was described before]; **II)** Distances within the reference plane, the best plane through the carbon atoms of the methylene bridges(Å); **III)** Inclination δ (°) of the aromatic with respect to the reference plane.

	26 (*cone*)	**27 (*1,3-alt*)**
I. Torsion angles		
C16-C11-C1-C43	-83.96	-146.74
C11-C1-C43-C44	95.72	-107.17
C26-C21-C2-C13	-84.37	132.93
C21-C2-C13-C14	76.56	128.11
C36-C31-C3-C23	-82.02	-138.67
C31-C3-C23-C24	95.05	-117.46
C46-C41-C4-C33	-88.08	123.23
C41-C4-C33-C34	72.32	128.45
II. Reference planes C1 – C4		
Distance C1 − C2	5.143	5.108
Distance C2 − C3	5.132	5.137
Distance C3 − C4	5.145	5.130
Distance C1 − C4	5.104	5.125
Distance C1 − C3	7.404	7.062
Distance C2 − C4	7.085	7.366
III. Inclination of the aromatic units(δ)		
C11 − C16	115.55	113.1
C21 − C26	122.19	107.4
C31 − C36	112.91	109.5
C41 − C46	126.69	99.9

3.8. Experimental part.

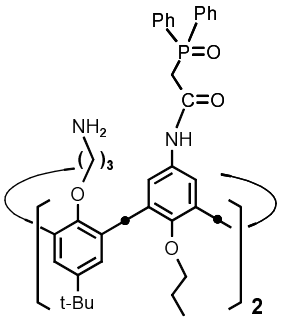
5,17-Di-*t*-butyl-11,23-diCMPOamido-26,28-diphthalimidopropoxy-25,27-dipropoxy-calix[4] arene 3 (n=3) (*1,3-alternate*)



To a clear solution of diamine **2 (n=3)** (0.28 g, 0.27 mmol) in dichlormethane (30 ml) was added the *p*-nitro phenyl carbamoylmethyl di-phenyl phosphine oxide (N-AE, 0.25 g, 0.65 mmol) as powder and few drops of NEt_3, which were kept under stirring at ambiance temperature over night. The *p*-nitro phenol which is released in the reaction is extracted with a solution of NaOH 5 % (3 x 100 ml) by several washing of the organic phase. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was dissolved in dichlormethane (5 ml) while the desired compound was obtained as white powder by repricipitation from hexane. (0.4 g, 84 %). mp 194-196 °C, FD-MS, (M^++H) m/z = 1508.9.

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.65 (t, 6H, ^3J = 7.3 Hz, -CH_2-CH_3), 1.20 (m, 22H, t-Bu, -CH_2-), 1.51 (m, 4H, -CH_2-), 3.26-3.69 (m, 24H, Ar-CH_2-Ar, O-CH_2-, -CH_2-P, -CH_2-N), 6.90, 6.95 (2s, 8H, Ar*H*), 7.40-7.75 (m, 28H, *m*, *p*-Ph_2*H*, *o*-Ph_2*H*, Pht-*H*), 8.84 (bs, 2H, N*H*).

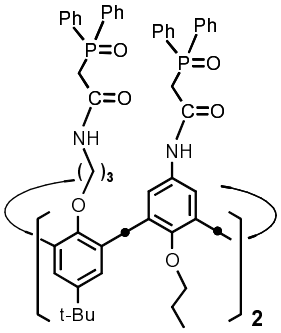
5,17-Di-*t*-butyl-11,23-diCMPOamido-26,28-diaminopropoxy-25,27-dipropoxy-calix[4]arene 4 (n=3) (***1,3-alternate***)



The same procedure of cleavage of the phthalimido groups by hydrazine is followed. Starting from the solution of the compound **3** (0.33 g, 0.2 mmol) in ethanol (15 ml) using hydrazine (1.6 ml), after 2 h and working up of the reaction mixture the desired diamines is obtained as white powder in 93 % yield. mp 212-214 °C. FD-MS, (M^++H) m/z = 1250.7.

^{1}H NMR (200 MHz, DMSO-d_6) δ 0.60 (t, 6H, ^3J = 6.8 Hz, -CH_2-CH_3), 1.00 (m, 4H, -CH_2-), 1.19 (s, 18H, t-Bu) 1.46 (m, 4H, -CH_2-), 3.22-4.03 (m, 28H, NH_2, Ar-CH_2-Ar, O-CH_2-, -CH_2-P, -CH_2-N), 6.98, 7.23 (2s, 8H, Ar*H*), 7.55-7.92 (m, 20H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*), 10.24 (bs, 2H, N*H*).

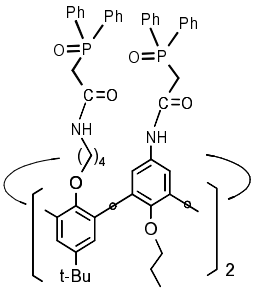
5,17-Di-*t*-butyl-11,23-diCMPOamido-26,28-diCMPOamidopropoxy-25,27-dipropoxy-calix[4] arene 5 (n=3) (***1,3-alternate***)



The desired compound **5(n=3)** is obtained following the same procedure to achieve the compound **3**. Starting from a solution of diamine **4** (0.22 g, 0.14 mmol) in dichlormethane (30 ml) and N-AE (0.16 g, 0.42 mmol) the tetra-CMPO compound is obtained as white powder in 83 % (0.2 g). mp 152 °C, FD-MS, (M^++H) m/z = 1732.5.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (t, 6H, ^3J = 7.7 Hz, -CH_2-CH_3), 1.20 (m, 22H, t-Bu, -CH_2-), 2.75 (m, 4H, -CH_2-), 2.72 (t, 4H, ^3J = 7.0 Hz, -CH_2-N), 3.20 (t, 4H, ^3J = 7.3 Hz, O-CH_2-), 3.50, 3.56 (2d, 8H, ^2J = 15.8 Hz, Ar-CH_2-Ar), 3.61 (m, 8H, O-CH_2-, -CH_2-P), 3.76 (d, 4H, ^2J = 10.3 Hz, -CH_2-P), 6.87, 7.09 (2s, 8H, Ar*H*), 7.38-7.81 (m, 40H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*), 8.96, 10.05 (2bs, 2/2H, N*H*).

5,17-Di-*t*-butyl-11,23-diCMPOamido-26,28-diCMPOamidobutyloxy-25,27-dipropoxy-calix[4] arene 5 (n=4) (***1,3-alternate***)

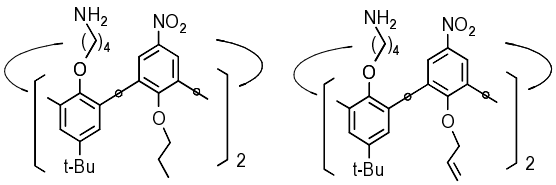


The desired compound **5(n=4)** is obtained following the same procedure to achieve the compound **3**. Starting from a solution of diamine **9** (100 g, 0.078 mmol) in dichlormethane (10 ml) and N-AE (72 mg, 0.18 mmol) the tetra-CMPO compound is obtained after purification by column chromatography (CHCl3 : MeOH = 9.8:0.5) as pink powder in 87 % (0.138 g). mp 142 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (t, 6H, ^3J = 7.7 Hz, -CH_2-CH_3), 1.01-1.23 (m,

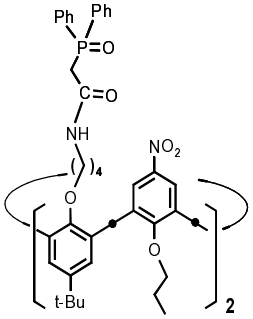
26H, t-Bu, 3x-CH_2-), 2.93 (t, 4H, ^3J = 7.0 Hz, -CH_2-N), 3.08, 3.27 (2t, 8H, ^3J = 7.3 Hz, 2xO-CH_2-), 3.37, 3.67 (2d, 4H, ^2J = 14.3 Hz, CH_2-P), 3.65, 3.69 (2d, 8H, ^2J = 15.5 Hz, Ar-CH_2-Ar), 6.92, 7.27 (2s, 8H, Ar*H*), 7.38-7.74 (m, 40H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*), 8.31, 10.20 (2bs, 2/2H, N*H*).

Mixture 7 and 7a.



This mixture is obtained under the same procedure which was applied for the obtaining of **2(n=3)**.

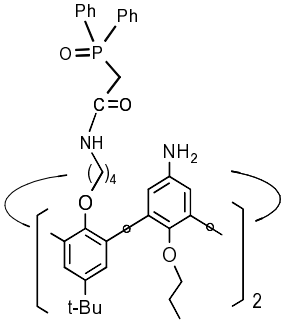
5,17-Di-*t*-butyl-11,23-dinitro-26,28-diCMPOamidobutyloxy-25,27-dipropoxy-calix[4]arene 8 (n=4) (***1,3-alternate***)



The same procedure of acylation with N-AE (CMPO) like in the case of **5 (n=3)** is followed also. Starting from the clear solution of diamine **8 (n=4)** (0.3 g, 0.35 mmol) in dichloromethane (15 ml) and N-AE (0.32 g, 0.84 mmol). The desired diCMPOamide **8 (n=4)** is obtained as white powder in 75 % yield (0.35 g). mp.142 °C

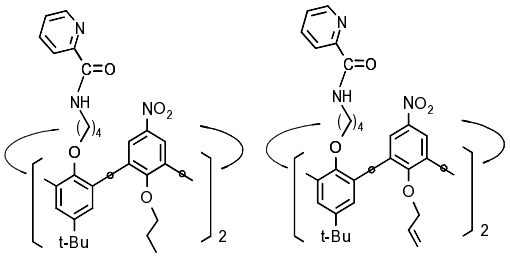
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, 6H, ^3J = 7.4 Hz, -CH_2-CH_3), 1.22 (m, 26H, t-Bu, 2x-CH_2-), 3.13 (m, 4H, -CH_2-), 3.07 (bt, 4H, -CH_2-N), 3.48 (2t, 4/4H, 2x O-CH_2-), 3.66 (d, 4H, ^2J = 13.7 Hz, -CH_2-P), 3.66, 3.75 (2d, 8H, ^2J = 15.2 Hz, Ar-CH_2-Ar), 6.96, 7.88 (2s, 4/4H, Ar*H*), 7.38-7.81 (m, 22H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*, N*H*).

5,17-Di-*t*-butyl-11,23-diamino-26,28-diCMPOamidobutyloxy-25,27-dipropoxy-calix[4] arene 9 (n=4) (***1,3-alternate***)



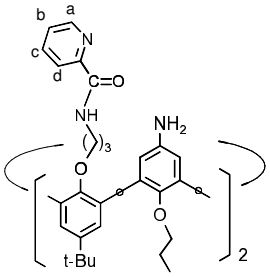
To a solution of **8(n=4)** (110 mg, 0.082 mmol) in ethanol (15 ml) was added hydrazine (1 ml) and Ra/Ni as catalyst. The reaction was refluxed for 2 h. The solvent was evaporated under reduced pressure and the formed residue was dissolved in chloroform (10 ml) and was washed three times with water. After phase separation, the organic one was dried over $MgSO_4$, the solvent was evaporated under reduced pressure when an yellow oil was obtained. Thus, the formed diamine was used in the next step without further purification.

Mixture 10 and 10a.



This mixture is obtained under the same procedure which was applied for the obtaining of **10(n=3)**.

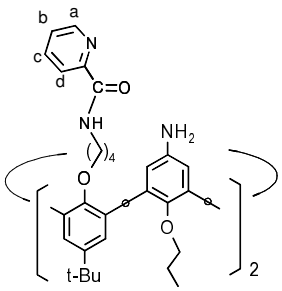
5,17-Di-*t*-butyl-11,23-diamino-26,28-dipicolinamidopropyloxy-25,27-dipropoxy-calix[4] arene 11 (n=3) (***1,3-alternate***)



To a clear solution of **10(n=3)** (740 mg, 0.70 mmol) in THF (20 ml) was added Ra/Ni. The reaction mixture was subjected to hydrogenated atmosphere during 4 days. When the hydrogen was complete undertaken the catalyst was filtered off and the solvent evaporated under reduced pressure. The formed residue was dissolved in chloroform (10 ml) and the desired amine was reprecipitated with hexane (15 ml) as white powder (200 mg, 31 %). mp 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (t, 6H, ^3J = 7.7 Hz, -CH_2-CH_3), 1.01-1.08 (m, 4H, -CH_2-), 1.22 (s, 18H, t-Bu), 1.55-1.59 (m, 4H, -CH_2-), 2.89 (bs, 4H, -NH_2), 3.17-3.22 (m, 8H, -CH_2-N, -CH_2-O), 3.51 (t, 4H, ^3J = 7.3 Hz, O-CH_2-), 3.65, 3.74 (2d, 4/4H, ^2J = 15.8 Hz, Ar-CH_2-Ar), 6.48, 6.92 (2s, 4/4H, Ar*H*), 7.38 (m, 2H, H_b), 7.80 (m, 2H, H_c), 8.13 (m, 2H, H_d), 8.26 (bt, 2H, -N*H*), 8.51 (m, 2H, H_a).

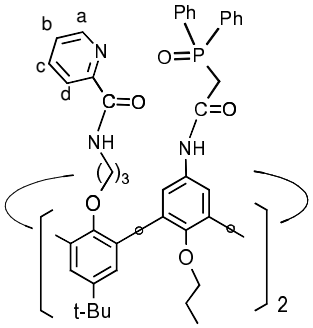
5,17-Di-*t*-butyl-11,23-diamino-26,28-dipicolinamidobutyloxy-25,27-dipropoxy-calix[4] arene 11 (n=4) (***1,3-alternate***)



Compound **11(n=4)** was obtained in the same manner as its inferior homologous, with the exception of reaction time. In this case 30 h was need to complete the reaction. The diamine was reprecipitated from chloroform/hexane (~20 ml, 1:3) as white powder (220 mg, 93 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (t, 6H, ^3J = 7.7 Hz, -CH_2-CH_3), 1.09-1.22 (m, 26H, 2x-CH_2-, t-Bu), 1.82-1.86 (m, 4H, -CH_2-), 3.21-3.73 (m, 20H, -CH_2-N, -CH_2-O, Ar-CH_2-Ar), 6.42 (s, 4H, -NH_2), 6.92, 6.97 (2s, 4/4H, Ar*H*), 7.38 (m, 2H, H_b), 7.81 (m, 2H, H_c), 8.18 (m, 2H, H_d), 8.30 (bt, 2H, -N*H*), 8.54 (m, 2H, H_a).

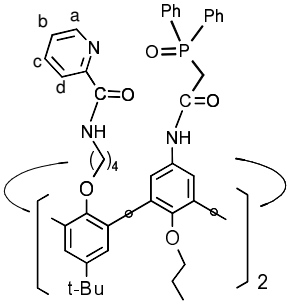
5,17-Di-*t*-butyl-11,23-diCMPO-26,28-dipicolinamidopropyloxy-25,27-dipropoxy-calix[4]arene 12 (n=3) (***1,3-alternate***)



The same procedure of acylation with N-AE (CMPO) like in the case of **5 (n=3)** is also here followed. Starting from the clear solution of diamine **11(n=3)** (200 mg, 0.20 mmol) in dichloromethane (30 ml) and N-AE (490 mg, 2.4 mmol). The desired diCMPOamide **12(n=3)** is obtained as white powder in 65 % yield (170 mg).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 0.93 (t, 6H, ^3J = 7.2 Hz, -CH$_2$-CH_3), 1.18 (s, 18H, t-Bu), 1.44 (m, 4H, -CH_2-), 3.05-3.78 (m, 24H, -CH_2-N, -CH_2-O, Ar-CH_2-Ar, -CH_2-P), 6.32 (s, 2H, -N*H*), 6.95, 7.12 (2s, 4/4H, Ar*H*), 7.49-7.99 (m, 22H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*, H_b), 8.34 (m, 2H, H_c), 8.50 (m, 2H, H_d), 8.73 (bt, 2H, -N*H*,), 9.77 (m, 2H, H_a).

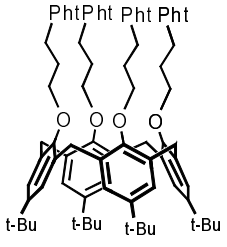
5,17-Di-*t*-butyl-11,23-diCMPO-26,28-dipicolinamidopropyloxy-25,27-dipropoxy-calix[4]arene 11 (n=4) (***1,3-alternate***)



The same procedure of acylation with N-AE (CMPO) like in the case of **5 (n=3)** is also here followed. Starting from the clear solution of diamine **11(n=4)** (220 mg, 0.23 mmol) in dichloromethane (30 ml) and N-AE (325 mg, 0.55 mmol). The desired diCMPOamide **12(n=4)** is obtained as white powder in 47 % yield (160 mg).

^{1}H NMR (200 MHz, DMSO-d$_6$) δ 0.60 (t, 6H, ^3J = 7.2 Hz, -CH$_2$-CH_3), 1.21 (m, 30H, t-Bu, -CH_2-), 3.06-3.72 (m, 24H, -CH_2-N, -CH_2-O, Ar-CH_2-Ar, -CH_2-P), 6.90, 7.06 (2s, 4/4H, Ar*H*), 7.40-7.80 (m, 22H, *m*, *p*-Ph$_2$*H*, *o*-Ph$_2$*H*, H_b), 8.11 (m, 2H, H_c), 8.34-8.50 (m, 6H, H_d,-N*H*, H_a), 9.45 (s, 2H, N*H*).

5,17,11,23-Tetra-*t*-butyl-25,27,26,28-tetra-phthalimidopropoxy-calix[4]arene 13 ***(cone)***

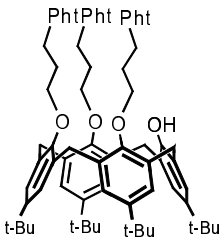


A suspension of **1** (2 g, 1.9 mmol) in DMF (40 ml) and NaH (0.19 g, 7.8 mmol) was stirred at rt for 1 h under nitrogen. A solution of *N*-(3-bromopropyl)-phthalimide (2.0 g, 7.8 mmol) in DMF (5 ml) was added. The mixture was stirred under nitrogen at room temperature for 6 days. The solvent was removed under reduced pressure and a dry residue was obtained which contained two compounds (shown in t.l.c). The mixture was chromatographically separated (ethyl acetate : hexane =1:2) and the *cone* isomer **5** (1.35 g, 35 %) and tri-O-alkylated compound (0.9 g, 24 %) were isolated.

13 (*cone*): mp 213-215°C

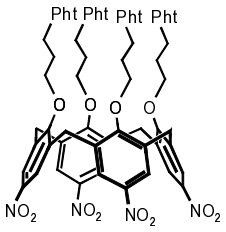
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 36H, *t*-Bu), 2.39 (m, 8H,-CH_2-CH_2-CH_2-), 3.10 (d, 4H, ^2J = 12.5 Hz, Ar-CH_2-Ar), 3.87 (t, 8H, ^3J = 7.8 Hz, -CH_2-N), 3.97 (t, 8H, ^3J = 6.8 Hz, -CH_2-O), 4.36 (d, 4H, ^2J = 12.5 Hz, Ar-CH_2-Ar), 6.72 (s, 8H, Ar*H*), 7.56-7.72 (m, 16H, Phth-*H*).

tri-O-alkylated compound: mp 214-216 °C



^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.78, 1.28, 1.31 (3s, 18/9/9H, *t*-Bu), 1.87, 2.30, 2.65 (2m, 4/2H, -CH_2-CH_2-CH_2-), 3.16, 3.21 (2d, 2/2H, ^2J = 12.87, 13.24 Hz, Ar-CH_2-Ar), 3.79-4.02 (m, 12H, -CH_2-N, -CH_2-O), 4.23, 4.33 (2d, 2/2H, ^2J = 12.87, 13.24 Hz, Ar-CH_2-Ar), 5.37 (s, 1H, O*H*), 6.46, 6.47 (2d, 4H, ^4J = 2.21, 2.21 Hz, Ar*H*), 7.00, 7.10 (2s, 4H, Ar*H*), 7.53-7.81 (m, 12H, Phth-*H*).

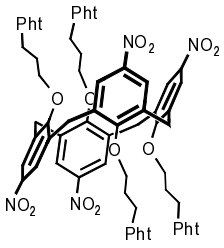
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-phthalimidopropoxy-calix[4]arene 14 (***cone***)



This compound was obtained under similar procedure according to **14 (*1,3-alternate*)** which yielded the tetranitro derivative in *cone* conformation as yellow powder in 75 %. mp .191 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30 (t, 8H, ^3J = 6.7 Hz, -CH_2-CH_2-CH_2-), 3.40 (d, 4H, ^2J = 14.1 Hz, Ar-CH_2-Ar), 3.88 (t, 8H, ^3J = 7.0 Hz, -CH_2-N), 4.18 (t, 8H, ^3J = 6.6 Hz, -CH_2-O), 4.58 (d, 4H, ^2J = 14.1 Hz, Ar-CH_2-Ar), 7.52 (s, 8H, Ar*H*), 7.60-7.73 (m, 16H, Phth-*H*).

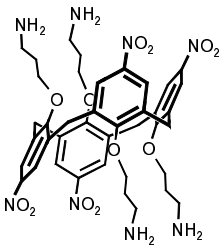
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-phthalimidopropoxy-calix[4]arene 14 (***1,2-alternate***)



This compound was obtained under similar procedure according to **14 (*1,3-alternate*)** which yielded the tetranitro derivative in *1,2-alternate* conformation as yellow powder in 60 %.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.27, 1.58-1.68 (2m, 8H, -CH_2-CH_2-CH_2-), 3.53-3.70 (m, 18H, -CH_2-N, O-CH_2-, Ar-CH_2-Ar), 4.12 (s, 4H, Ar-CH_2-Ar), 4.27 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 7.62-7.75 (m, 16H, Phth-*H*), 8.01, 8.10 (2d, 8H, ^4J = 2.5 Hz, Ar*H*).

5,11,17,23-Tetra-nitro-25,26,27,28-tetra-aminopropoxy-calix[4]arene 15 (***1,2-alternate***).

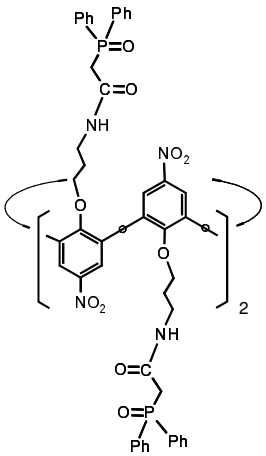


Compound **15 (*1,2-alternate*)** was obtained in an analogous way starting from the tetra-nitro compound **14 (*1,2-alternate*)** (0.85 g, 0.6 mmol) in boiling ethanol (45 ml) and excess of hydrazine (14 ml). The desired tetraamine **15 (*1,2-alternate*)** was reprecipitated with hexane to give a white powder (0.4 g, 80 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.43 (m, 16H, -NH_2 , -CH_2-CH_2-CH_2-), 2.15-

2.50 (m, 8H, -C*H*$_2$-NH$_2$), 3.40 (d, 2H, ^2J = 13.2 Hz, Ar-C*H*$_2$-Ar), 3.53-3.72 (m, 8H, O-C*H*$_2$-), 4.07 (s, 4H, Ar-C*H*$_2$-Ar), 4.20 (d, 2H, ^2J = 13.2 Hz, Ar-C*H*$_2$-Ar), 8.01 (d, 4H, ^4J = 2.2 Hz, Ar*H*), 8.09 (d, 4H, ^4J = 2.2 Hz, Ar*H*).

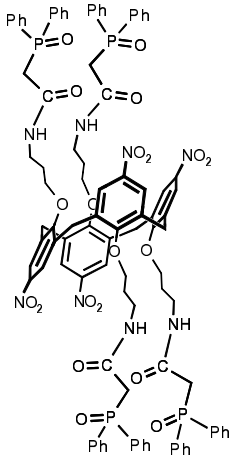
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 16 (or 20) (***1,3-alternate***).



In a suspension of tetraamine **15 (*1,3-alternate*)** (0.4 g, 0.47 mmol) in dichlormethane (50 ml) was added the *p*-nitro phenyl carbamoylmethyl di-phenyl phosphine oxide (N-AE, 0.85 g, 2.25 mmol) as powder and few drops of NEt_3, which were kept under stirring at ambiance temperature over night, when the reaction mixture became clear. The *p*-nitro phenol which is released in the reaction is extracted with a solution of NaOH 5 % (3 x 100 ml) by several washing of the organic phase. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was dissolved in dichlormethane (5 ml) while the desired compound was obtained as white powder by repricipitation from hexane. (0.85 g, 97 %).

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74 (bt, 8H, -CH_2-C*H*$_2$-CH_2-), 3.36-3.40 (m, 16H, -C*H*$_2$-P, -C*H*$_2$-N), 3.60 (bt, 8H, O-C*H*$_2$-), 3.68 (s, 8H, Ar-C*H*$_2$-Ar), 7.41-7.45 (m, 24H, *m*, *p*-Ph_2*H*), 7.66-7.75 (m, 16H, *o*-Ph_2*H*), 7.94 (s, 8H, Ar*H*). The proton signal corresponding to NH is missing in the ^{1}H-NMR spectrum.

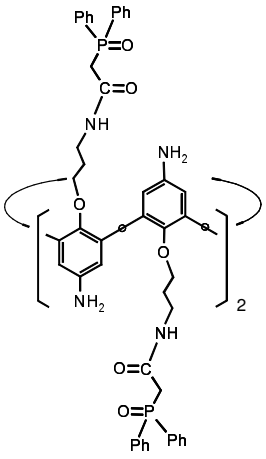
5,11,17,23-Tetra-nitro-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 16 (***1,2-alternate***)



This compound was obtained under similar procedure according to **16 (*1,3-alternate*)** which yielded the tetra-CMPO as white powder in 88 %. mp .275-277 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94-1.30 (m, 8H, -CH_2-C*H*$_2$-CH_2-), 2.85-3.40 (m, 30H, -C*H*$_2$-P, -C*H*$_2$-N, O-C*H*$_2$-, Ar-C*H*$_2$-Ar), 3.96 (d, 2H, ^2J = 11.02 Hz, Ar-C*H*$_2$-Ar), 7.36-7.69 (m, 44H, *m*, *p*-Ph_2*H*, *o*-Ph_2*H*, N*H*), 7.91, 8.07 (2d, 8H, ^4J = 2.2 Hz, Ar*H*).

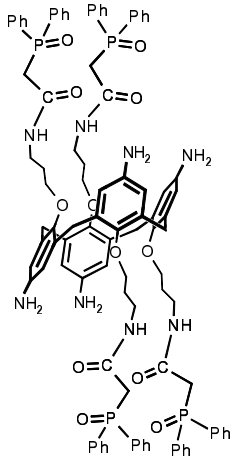
5,11,17,23-Tetra-amino-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 17 (or 22) (***1,3-alternate***).



To a suspension of tetranitrocompound **16 (*1,3-alternate*)** (0.95 g, 0.52 mmol) in EtOH (100 ml) with Ra-Ni as catalyst were boiled with hydrazine (6 ml) for 3.5 h. When the tlc shows just one spot corresponding to the formed amines with high polarity, the catalyst and the formed precipitate were filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (5 ml) and the tetraamine was reprecipitated with hexane (20 ml) as white powder (0.65 g, 74 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (m, 8H, -CH_2-CH_2-CH_2-), 3.08-3.55 (m, 40H, -CH_2-P, -CH_2-N, O-CH_2-,-NH_2, Ar-CH_2-Ar), 6.37 (s, 8H, Ar*H*), 7.40-7.47 (m, 24H, *m*, *p*-Ph_2*H*), 7.49-7.76 (m, 16H, *o*-Ph_2*H*), 8.33 (bs, 4H, -N*H*).

5,11,17,23-Tetra-amino-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 17 (***1,2-alternate***)

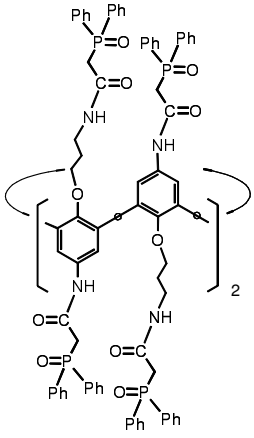


Compound **17 (*1,2-alternate*)** was obtained in an analogous way starting from the tetra-nitro compound **16 (*1,2-alternate*)** (0.74 g, 0.5 mmol) as a suspension with Ra-Ni as catalyst in boiling ethanol (75 ml) and excess of hydrazine (6 ml). The desired tetraamine **17 (*1,2-alternate*)** was yielded as white powder in 50 % (0.34 g). mp 243-245 °C

The ^{1}H NMR spectrum reveals quite broad proton signals but few signals can be solved as:

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82-3.90 (m, 40H, -NH_2, -CH_2-NH_2, O-CH_2-, Ar-CH_2-Ar), 6.52, 6.61 (2bd, 8H, Ar*H*), 7.37-7.89 (m, 40H, Ph_2-*H*), 8.03, 8.07 (2bs, 4H, -N*H*).

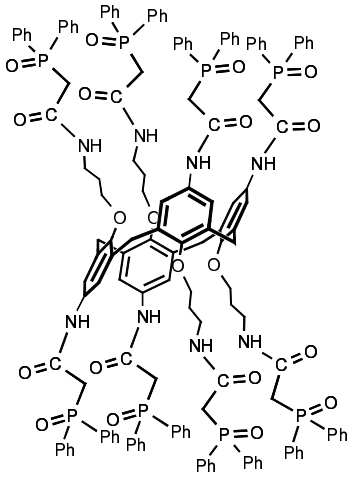
5,11,17,23-Tetra-CMPOamido-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 18 (***1,3-alternate***).



To a clear solution of tetraamine **17 (*1,3-alternate*)** (0.25 g, 0.14 mmol) in dichlormethane (35 ml) was added the AE (0.27 g, 0.72 mmol) as powder and few drops of NEt_3, which were kept under stirring at ambiance temperature over night. The *p*-nitro phenol was extract with a solution of NaOH 5 % (3 x 100 ml) by several washing of the organic phase. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was dissolved in dichlormethane (5 ml) while the desired compound was obtained as white powder by repricipitation from hexane. (0.35 g, 91 %). mp 150-152 °C

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17 (bt, 8H, -CH_2-CH_2-CH_2-), 2.70 (bt, 8H, -CH_2-N), 3.25 (bt, 8H, O-CH_2-), 3.46 (bs, 8H, Ar-CH_2-Ar), 3.60, 3.88 (2d, 16H, ^2J = 12.48 Hz -CH_2-P), 7.10 (s, 8H, Ar*H*), 7.37-7.89 (m, 80H, -Ph_2*H*), 8.87, 9.93 (2s, 8H, -N*H*).

5,11,17,23-Tetra-CMPOamido-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 18 (*1,2-alternate*)

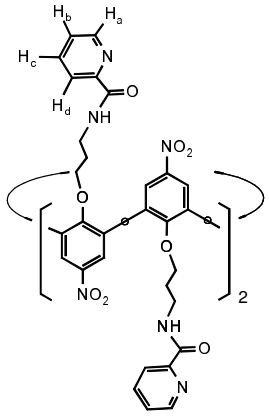


The desired compound octa-CMPO in the ***1,2-alternate*** was obtained as white powder in 65 % yield following the similar procedure, which was described for **18 (*1,3-alternate*)**. mp 157-159 °C

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85, 1.10 (2bm, 8H, -CH_2-CH_2-CH_2-), 2.49, 2.64, 3.11 (3bm, 16H, -CH_2-N, O-CH_2-), 2.92 (d, 2H, ^2J = 12.48 Hz, Ar-CH_2-Ar), 3.53, 3.71 (2d, 16H, ^2J = 14.3, 13.6 Hz, -CH_2-P), 3.62 (s, 4H, Ar-CH_2-Ar), 3.89 (d, 2H, ^2J = 11.4 Hz, Ar-CH_2-Ar), 6.98, 7.21 (2bs, 8H, Ar*H*), 7.36-7.85 (m, 80H, -Ph_2*H*), 9.92 (s, 8H, -N*H*).

Compound **19** is described in chapter 2 as **35**, while compounds **20** and **22** are identical with **16** and **17**, respectively from Scheme 4.

5,11,17,23-Tetra-nitro-25,26,27,28-tetra-picolinamidopropoxy-calix[4]arene 21 (*1,3-alternate*).

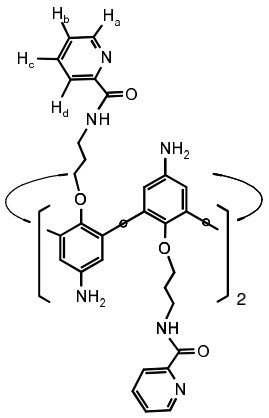


In a suspension of tetraamine **7 (*1,3-alternate*)** (0.21 g, 0.26 mmol) in chloroform (30 ml) was added the *F*-AE (0.3 g, 1 mmol) as powder, which were kept under stirring at ambiance temperature until the tlc shows that no starting material left. The pentafluor *p*-nitro phenol, which is realized during the reaction is extracted with a solution of Na_2CO_3 5 % (4 x 100 ml) by several washing of the organic phase.

After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was dissolved in dichlormethane (5 ml) while the desired compound was obtained as yellow powder by repricipitation from hexane. (0.16 g, 50 %). m.p. 118-120 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (m, 8H, -CH_2-CH_2-CH_2-), 3.67-3.73 (m, 16H, -CH_2-N, Ar-CH_2-Ar), 3.95 (t, 8H, ^3J = 7.0 Hz, O-CH_2-), 7.42 (m, 4H, H_b), 7.83 (m, 4H, H_c), 7.98 (s, 8H, Ar*H*), 8.17 (m, 4H, H_d), 8.39 (bt, 4H, -N*H*), 8.56 (m, 4H, H_a).

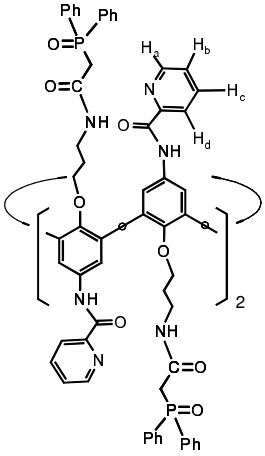
5,11,17,23-Tetra-amino-25,26,27,28-tetra-picolinamidopropoxy-calix[4]arene 23 (***1,3-alternate***).



A clear solution of the tetranitro compound **10 (*1,3-alternate*)** (0.32 g, 0.26 mmol) in THF (30 ml) was hydrogenated under atmospheric pressure in the presence of Ra-Ni at rt. After the hydrogen uptake was complete the catalyst was filtered off and the solvent was evaporated. The dry residue was dissolved in chloroform (10 ml) and the tetraamine was reprecipitated with hexane (20 ml) as white powder (0.16 g, 56 %). mp 110-112°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 8H, -CH_2-C*H*$_2$-CH_2-), 3.33-3.55 (m, 32H, O-C*H*$_2$-, -N*H*$_2$, -C*H*$_2$-N, Ar-C*H*$_2$-Ar), 6.49 (s, 8H, Ar*H*), 7.37 (m, 4H, *H*$_b$), 7.80 (m, 4H, *H*$_c$), 8.14 (m, 4H, *H*$_d$), 8.29 (bt, 4H, -N*H*), 8.50 (m, 4H, *H*$_a$).

5,11,17,23-Tetra-picolinamide-25,26,27,28-tetra-CMPOamidopropoxy-calix[4]arene 24 (***1,3-alternate***).

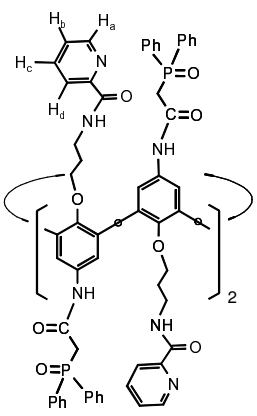


In a suspension of tetraamine **22 (*1,3-alternate*)** (0.05 g, 0.02 mmol) in chloroform (10 ml) was added the *F*-AE (0.04 g, 0.14 mmol) as powder, which were kept under stirring at ambiance temperature until the tlc shows that no starting material left. The pentafluor *p*-nitro phenol, which is realized during the reaction is extracted with a solution of Na_2CO_3 5 % (3x 20 ml) by several washing of the organic phase.

After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was dissolved in dichlormethane (5 ml) while the desired compound was obtained as yellow powder by repricipitation from hexane. (0.02 g, 47 %). mp 124 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (m, 8H, -CH_2-C*H*$_2$-CH_2-), 2.86 (bt, 8H, -C*H*$_2$-N), 3.33-3.47 (bm, 16H, O-C*H*$_2$-, P-C*H*$_2$-) 3.71 (bs, 8H, Ar-C*H*$_2$-Ar), 7.38-7.79 (m, 60H, *H*$_b$, *H*$_c$, *H*$_d$, Ar*H*, -Ph_2*H*), 8.27 (bt, 4H, -N*H*), 8.45 (m, 4H, *H*$_a$), 10.2 ((bs, 4H, -N*H*).

5,11,17,23-Tetra-CMPOamide-25,26,27,28-tetra-picolinamidopropoxy-calix[4]arene 25 (***1,3-alternate***).



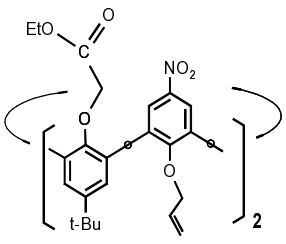
To a clear solution of tetraamine **23 (*1,3-alternate*)** (0.15 g, 0.13 mmol) in chloroform (40 ml) was added the N-AE (0.24 g, 0.63 mmol) as powder and few drops of NEt_3, which were kept under stirring at ambiance temperature over night. The *p*-nitro phenol was extract with a solution of NaOH 5 % (3 x 100 ml) by several washing of the organic phase. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure and the formed residue was

dissolved in dichlormethane (5 ml) while the desired compound was obtained as white powder by repricipitation from hexane. (0.16 g, 58 %). mp 157 °C

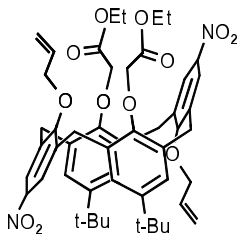
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 8H, -CH_2-CH_2-CH_2-), 3.13-3.78 (m, 32H, O-CH_2-,-CH_2-P, -CH_2-N, Ar-CH_2-Ar), 7.16 (s, 8H, Ar*H*), 7.48-7.94 (m, 52H, H_b, H_c, -Ph_2H, -N*H*), 8.43 (m, 4H, H_d), 8.81 (bt, 4H, -N*H*), 9.70 (m, 4H, H_a).

5,17-Di-*t*-butyl-11,23-dinitro-25,27-diallyloxy-26,28-diethoxycarbonylmethoxy -calix[4] arene 28 (*1,3-alternate*) and 28 (*partial cone*)

A stirred suspension of dinitro-calixarene **27** (1.3 g, 1.6 mmol) and Cs_2CO_3 (4 g, 12.8 mmol) in dry DMF (40 ml) was heated to 40 °C under nitrogen. After 1 h allylbromide (1.1 ml, 12.8 mmol) was added and the reaction was continued for 7 days. The DMF was removed under reduced pressure and the residue was treated with chloroform (25 ml) and water (75 ml). The organic phase was washed with water (2x75 ml), dried ($MgSO_4$) and the solvent was evaporated to give a yellow oil. Analysis by t.l.c showed the presence of two compounds, which were separated and purified by column chromatography ($CHCl_3$) and identified by NMR as the *1,3-alternate* and the *partial cone* isomers.

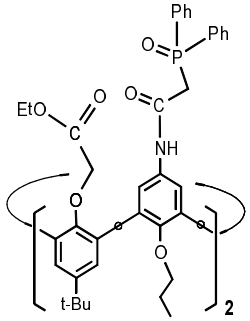


28 (*1,3-alternate*): White-yellow crystals, yield 0.3 g, 21 %; mp 199.8-201 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 6H, ^3J = 6.1 Hz, -CH_2-CH_3), 1.24 (s, 18H, *t*-Bu), 3.66, 4.07 (2d, 4/4H, ^2J = 14.7, 15.1 Hz, Ar-CH_2-Ar), 3.99 (s, 4H, -CH_2-O-), 4.19 (m, 8H, O-CH_2), 5.14 (m, 4H, CH_2=CH-), 5.78 (m, 2H, CH_2=C*H*-), 6.98, 8.02 (2s, 4/4H, Ar*H*).



28 (*partial cone*): Yellow powder, yield 0.54 g, 39 %; mp 222-223 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 18H, *t*-Bu), 1.31 (t, 6H, ^3J = 7.3 Hz -CH_2-CH_3), 3.22, 3.65, 4.07 (3d, 2/2/2H, ^2J = 13.6, 13.9, 13.6 Hz, Ar-CH_2-Ar), 4.15-4.37 (m, 14H, 3xO-CH_2-, Ar-CH_2-Ar), 4.94, 5.40 (2m, 2/2H, - -CH=CH_2), 6.06, 6.12 (2m, 2/2H, -C*H*=CH_2), 6.50, 6.88 (2d, 2/2H, ^4J = 2.5, 2.5 Hz, Ar*H*), 8.03, 8.37 (2s, 2/2H, Ar*H*)

5,17-Di-*t*-butyl-11,23-diCMPO-25,27-dipropoxy-26,28-diethoxycarbonylmethoxy-calix[4]arene 29 (*1,3-alternate*)

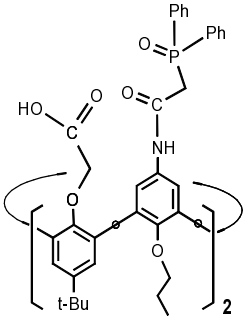


Pd/C (0.1 g) was added to a solution of the dinitro compound **28** (0.3 g, 0.34 mmol) in THF (15 ml) and the suspension was stirred under hydrogen atmosphere at rt. After the hydrogen uptake was complete, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in dichlormethane (15 ml) when a clear solution is formed. N-AE (80 mg, 0.09 mmol) and few drops of triethylamine are added. The reaction is stirring at rt for

12 h when an aqueous solution of NaOH (30 ml, 5 %) is added. The stirring is still continued for additional 30 min. The reaction mixture is washing three times with the basic solution (3 x 30 ml) and after drying over $MgSO_4$ the solvent is evaporated under reduced pressure. The desired diCMPO is reprecipitated from $CHCl_3$/hexane (15 ml, 1:2) as a white powder in 92 % (0.11 g) yield. mp 210-212 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73, 1.13 (2t, 6/6H, ^3J = 7.7, 7.3 Hz, 2x-CH_2-CH_3), 1.20 (m, 22H, t-Bu, -CH_2-), 3.35, 4.01 (2t, 4/4H, ^3J = 7.7, 6.99 Hz, 2xO-CH_2-), 3.44 (d, 4H, ^2J = 12.9 Hz, -CH_2-P), 3.57 (s, 4H, O-CH_2-), 3.64, 3.93 (2d, 4/4H, ^2J = 15.8 Hz, Ar-CH_2-Ar), 6.92, 7.15 (2s, 4/4H, Ar*H*), 7.43-7.78 (m, 20H, *m*, *p*-Ph_2H, *o*-Ph_2H), 9.06 (bs, 2H, N*H*).

5,17-Di-*t*-butyl-11,23-diCMPO-25,27-dipropoxy-26,28-dicarboxymethoxy-calix[4]arene 30 (*1,3-alternate*)



To a solution of **30** in THF (7 ml) and MeOH (4 ml) is added an aqueous solution of LiOH (98 mg/2 ml water) and the reaction is stirred at rt over night. The basic solution is neutralized with solution of HCl. After separation of the phases, the acid is isolated from the organic phase by precipitation from water. The white precipitate is filtrated and washed with water. The desired diacid **31** is obtained as white powder in 96 % yield. mp 264 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.65 (t, 6H, ^3J = 7.4 Hz, -CH_2-CH_3), 1.15 (m, 4H, -CH_2-CH_3), 1.23 (s, 18H, t-Bu), 1.96 (s, 2H, -COO*H*), 3.31 (t, 4H, ^3J = 7.4 Hz, O-CH_2-), 3.67, 3.92 (2d, 4/4H, ^2J = 16.2 Hz, Ar-CH_2-Ar), 3.76 (d, 4H, ^2J = 16.0 Hz, -CH_2-P), 3.69 (s, 4H, O-CH_2-), 7.00, 7.16 (2s, 4/4H, Ar*H*), 7.51-7.84 (m, 20H, *m*, *p*-Ph_2H, *o*-Ph_2H), 9.46 (bs, 2H, N*H*).

3.9. References.

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Chapter 4

Conformational Properties of Cyanomethoxy Calix[4]arenes

4. Introduction.

As we discussed in chapter 2, the main topic of this thesis is to functionalize the calix[4]arene in the *1,3-alternate* conformation via amino groups. They can be prepared by O-alkylation with N-(ω-bromoalkyl) phthalimides[1] or ω-bromonitriles[2], followed by hydrazinolysis or reduction. To obtain the aminoethyl ethers the alkylation is restricted to bromo (/chloro) acetonitrile[3], since bromoethylphthalimide can not be used due to reasons already discussed. To synthesise a tetraamine in the *1,3-alternate* conformation where all amino groups are attached to the same side of the skeleton, we follow the same strategy namely di-O-alkylation, *ipso*-nitration of the *t*-butyl phenol units and fixing the conformation by O-alkylation with allylbromide in the presence of Cs^+ cation. We found out that the resulting tetraether (two cyanomethoxy and two allyloxy residues in alternative arrangement) is conformationally unstable, because the cyanomethoxy groups can pass through the annulus of the calix[4]arene cavity allowing a *syn-anti* interconversion.

Miyano et al[4] observed that the cyanomethoxy residues can pass through the ring of the *p-t*-butyl thiacalix[4]arenes which is about 10 % larger then for the classical calix[4]arenes, where this passage was not observed. They studied the *syn-anti* interconversion of the cyanomethoxy in thiacalix[4]arenes, by NMR spectroscopy in different solvents at room temperature.

Earlier a Korean group[5] studied the complete conversion at room temperature of the *1,3-alternate* to *partial cone* of the *p*-H calix[4]arene which carries at the lower rim two CH_2-CN and two CH_2-COOEt groups. This *syn-anti* interconversion is due to the passage of a one cyanomethoxy through the interior. Only at elevated temperature the formed *partial cone* isomer of the tetraether coexists in equilibrium in 1:1 ratio with the *cone* conformation, which is formed by the passage of the second cyanomethoxy residue through the ring. Thus both cyanomethoxy residues are again in *syn* orientation.

Puddephatt et al[6] observed a slow passage of the propargyloxy residue at room temperature in tetraethers of calix[4]arenes bearing four propargyloxy residues. Here the isomers interconvert from the *1,3-alternate* isomer to the *partial cone* one. The propargyl groups are comparable in size and flexibility with the cyanomethyl groups.

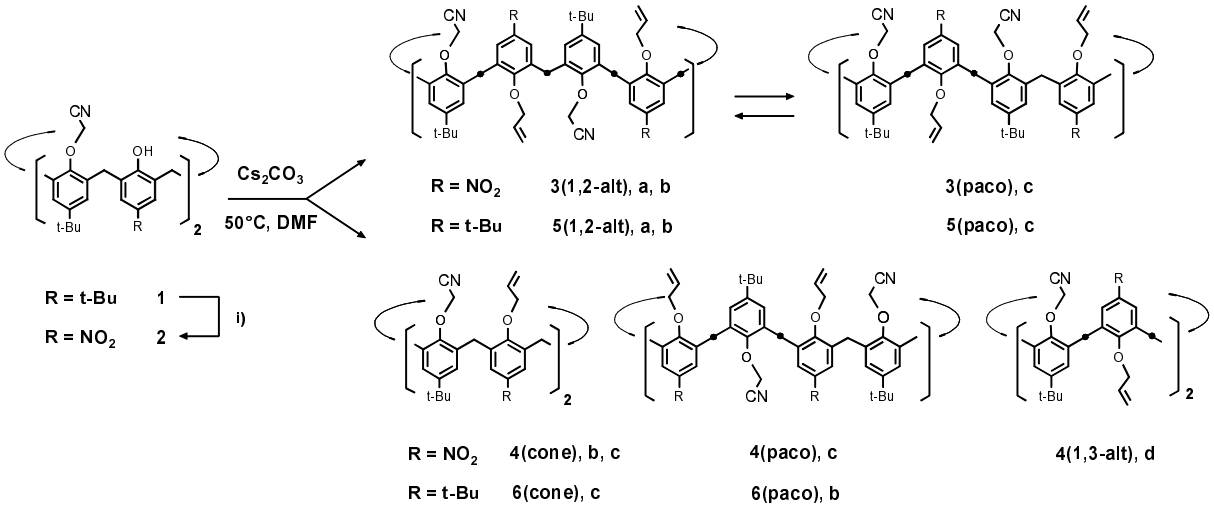
In the following, we present in detail thermodynamic and kinetic studies of the *syn-anti* interconversion of the cyanomethyl residue followed by ^{1}H-NMR spectroscopy. To the best of our knowledge, the present study is the first to give a quantitative thermodynamic description of such an equilibrium involving two conformers with *syn*- and *anti*-orientation of the cyanomethoxy group (and

anti-orientation of the remaining allylether groups). Kinetic studies for such a conversion were also not yet reported.

4.1. Synthesis.

The 1,3-diether **1** is obtained from *t*-butyl-calix[4]arene in 55 % yield using an excess (4 equiv.) of chloroacetonitrile in presence of K_2CO_3 as base (4 equiv.) in boiling acetone. The tri-O-alkylated compound is found as main side product confirmed by MS-FAB. The 1,3-*syn*-diether **1** adopts a *cone* conformation in solution. The ^{1}H-NMR spectrum shows a pair of doublets for the methylene bridges, one singlet for the O-CH_2-CN, two singlets for the aromatic protons and for the *t*-butyl groups. Using selective *ipso*-nitration conditions of the phenol units, the desired dinitro compound **2** is obtained in 37 % yield. Its ^{1}H-NMR spectrum clearly shows that the compound **2** adopts the *cone* conformation (similar set of signals with **1** is displayed in the ^{1}H-NMR, one singlet of the *t*-butyl groups which are replaced by the nitro groups is missing and the signal of the aromatic protons of phenol rings which bear the nitro groups is downfield shifted). X-Ray analysis of **2** shows that the dinitro compound adopts a *cone* conformation in the solid state, although this is not a proof for the conformation in solution. The ^{1}H-NMR studies at different temperature (25 °C, 40 °C and 50 °C) of the dinitro compound **2** in $CDCl_3$-d_1 show a conformationally stable compound stabilized by hydrogen bonds.
In the second O-alkylation step the calix[4]arene should be fixed in the *1,3-alternate* conformation using allylbromide in the presence of Cs_2CO_3. A mixture of at least three compounds is obtained as the TLC shows. Slow crystallization from chloroform/methanol led to single crystals of an isomer **3** in the *1,2-alternate* conformation with an *anti*-allyl orientation. This orientation of the allyloxy residue is usually encountered in the *partial cone* isomer, which is usually formed as a by-product in reactions fixing the calix[4]arene in the *1,3-alternate* conformation. After several days 34 % of the **3(*1,2-alt*)** could be collected by filtration. It was observed by ^{1}H-NMR spectra that the conformation of the **3(1,2-alt)** in solution is unstable, due to the passage of one cyanomethoxy groups through the annulus of the skeleton. Thus, the **3(paco)** isomer is formed in equilibrium with the **3(1,2-alt)** isomer. This thermodynamic studies of equilibrium will be later disscused.
Further single crystals were formed afterwards in the filtrate which belong to the isomer **4** in the *partial cone*, **4(*paco*)** conformation. Here, a *syn*- orientation of the allyl residues is found which would correspond to the desired *1,3-alternate*. This means that in both compounds the position of the cyanomethoxy residues has been changed from *syn* to *anti*. We may consider that one cyanomethoxy residue has passed through the annulus during the synthesis or the working up of the reaction mixture. After several days, 18 % of powder was isolated which consists of a mixture of the *cone* isomer **4(*cone*)** with **4(*paco*)**, while the *1,3-alternate* isomer **4(*1,3-alt*)** was not detected.

Scheme 1 presents a reaction sequence and the possible conformers which the tetraether can adopt due to the *syn-anti* interconversion of the cyanomethoxy group.



Scheme 1 Synthesis of *tetra-O*-alkylated derivatives **3**, **5**, **4** and **6**. [a)] isolated as pure compounds; [b)] single crystals; [c)] isolated as binary mixture only; [d)] deduced from NMR-signals in a complex mixture.

Since after the second O-alkylation step many isomers of the tetraethers calix[4]arene derivatives are isolated or identified by ^{1}H-NMR spectra or in some cases additionally by X-ray analysis we classify the isomers in respect to the allyl ether residues orientation as follows: a) with *anti*-allyl orientation, where two isomers are possible as *partial cone* and *1,2-alternate*, b) a *syn*-allyl orientation, where three isomers are possible as *cone*, *partial cone* and *1,3-alternate* but as mentioned before the presence of **4(*1,3-alt*)** was not detected in the mixture.

The reaction was repeated again under similar conditions, which led to analogous results. After the isolation of **3(*1,2-alt*)** in the 12 % yield, the mother liquor was evaporated and the resulting residue powder was analyzed. The ^{1}H-NMR spectrum shows a mixture which contains about 9 % **3(*1,2-alt*)**, 44 % **3(*paco*)**, 20 % **4(*cone*)**, and 20 % **4(*paco*)**.

When the *O*-alkylation with allylbromide was carried out with **1** under the same conditions a similar result was obtained. 11 % of the *1,2-alternate* conformer **5(*1,2-alt*)** could be isolated in pure form by recrystallization, while the mother liquor contained 68 % of the *partial cone* and *cone* isomers **6(*paco*)** and **6(*cone*)**. The absence of the nitro groups led to a stronger overlap of signals in this case, and hence to a lower accuracy in the determination of concentration ratios. X-Ray analysis proved the structure of **5(*1,2-alt*)** and **6(*paco*)**.

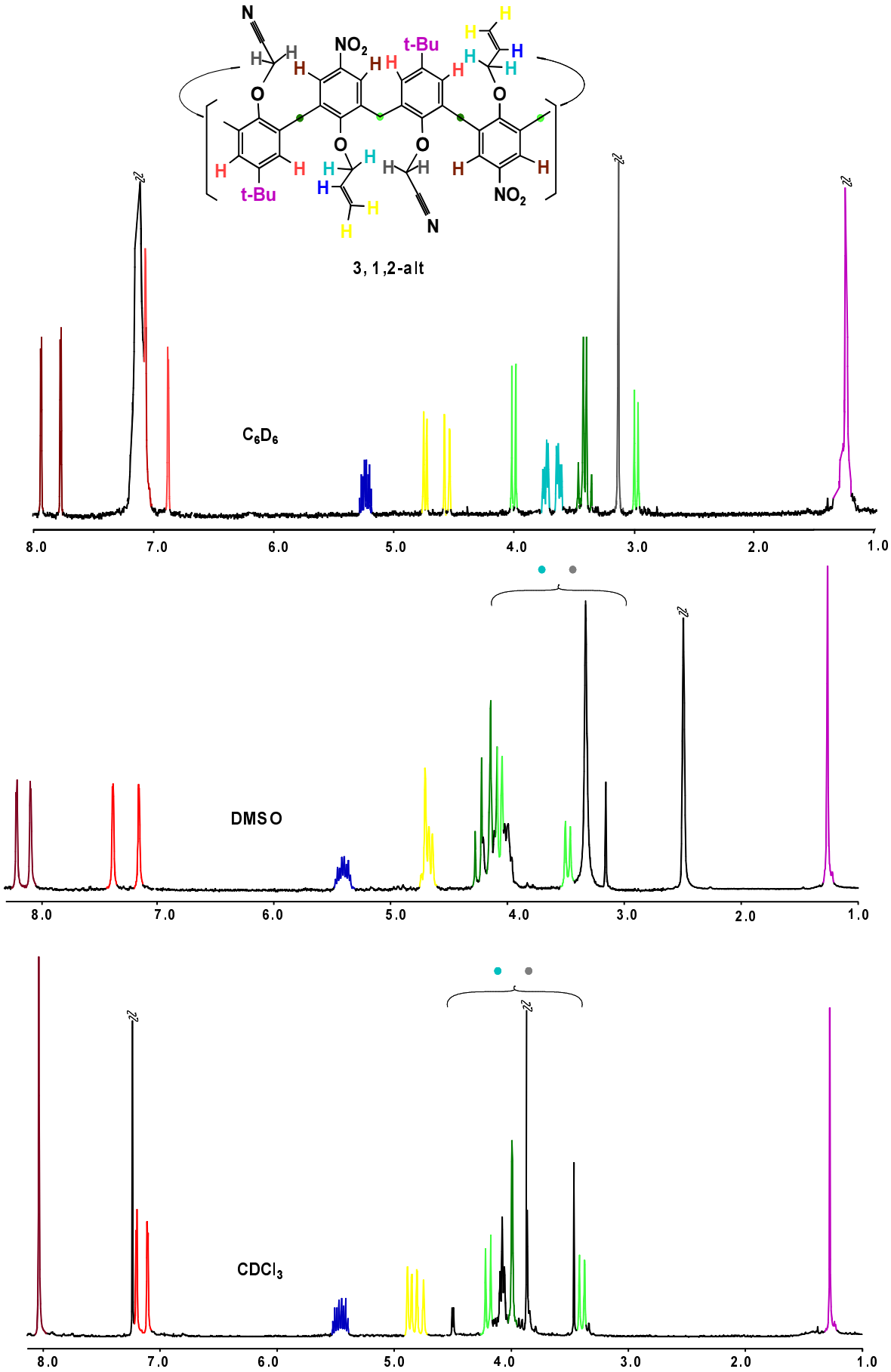


Figure 1. Comparison ^{1}H-NMR spectra of the **3(*1,2-alt*)** different solvents as C_6D_6, DMSO, $CDCl_3$.

4.2. Conformational studies.

The ^{1}H-NMR spectra of **3(*1,2-alt*)** measured in different solvents (C_6D_6, TCE-d_2, DMSO-d_6) are in agreement with the structure found in the crystalline state (figure 1). For example, the ^{1}H-NMR spectrum in benzene-d_6 displays a pair of doublets as AX-system at 3.05/4.01 ppm (J = 13.3 Hz) for the methylene bridge between *syn*-orientated aromatic rings and an AB-system at 3.38/3.45 ppm (J = 16.8 Hz) for the methylene bridge between *anti*-orientated units. A *m*-coupled doublets for the aromatic protons appear (δ = 6.89/7.08 and 7.78/7.95 respectively) for the *t*-butyl- and nitrophenyl rings, respectively (Figure 2a).

After a short time a set of signals appears additionally, which is increasing in intensity with the time until an equilibrium is reached (figure 2b). These signals belong to the **3(*paco*)** which is formed due to the passage of one cyanomethoxy residue through the ring. The signals for the two conformational isomers are partly overlapped, but the spectra allow to establish the ratio of the two isomers by simple integration. Thus, the equilibrium constant K can be calculated under eqn. 1.

(1) $$\mathbf{3(1,2\text{-}alt)} \underset{k_{II}}{\overset{k_I}{\rightleftharpoons}} \mathbf{3(paco)} \qquad K = \frac{c\,(paco)}{c\,(1,2\text{-}alt)}$$

This has been done for three different solvents as a function of temperature [lnK = f(1/T)] which is graphically shown in figure 3 according to eqn. 2 (van't Hoff equation).

(2) $$\ln K = -\Delta G_0/RT = -\Delta H_0/RT + \Delta S_0/R$$

From the slope and the intercept the enthalpy ΔH_0 and the entropy ΔS_0 can be calculated. The results are presented in table 1.

Solvent	ΔH_0 (kJ·K^{-1}mol^{-1})	ΔS_0 (J·mol^{-1})
TCE-d_2	-7.60	18.61
C_6D_6	-9.7	25.76
DMSO-d_6	-8.47	18.11

Table 1. The values of the standard enthalpy ΔH_0 and entropy ΔS_0 for the interconversion (1).

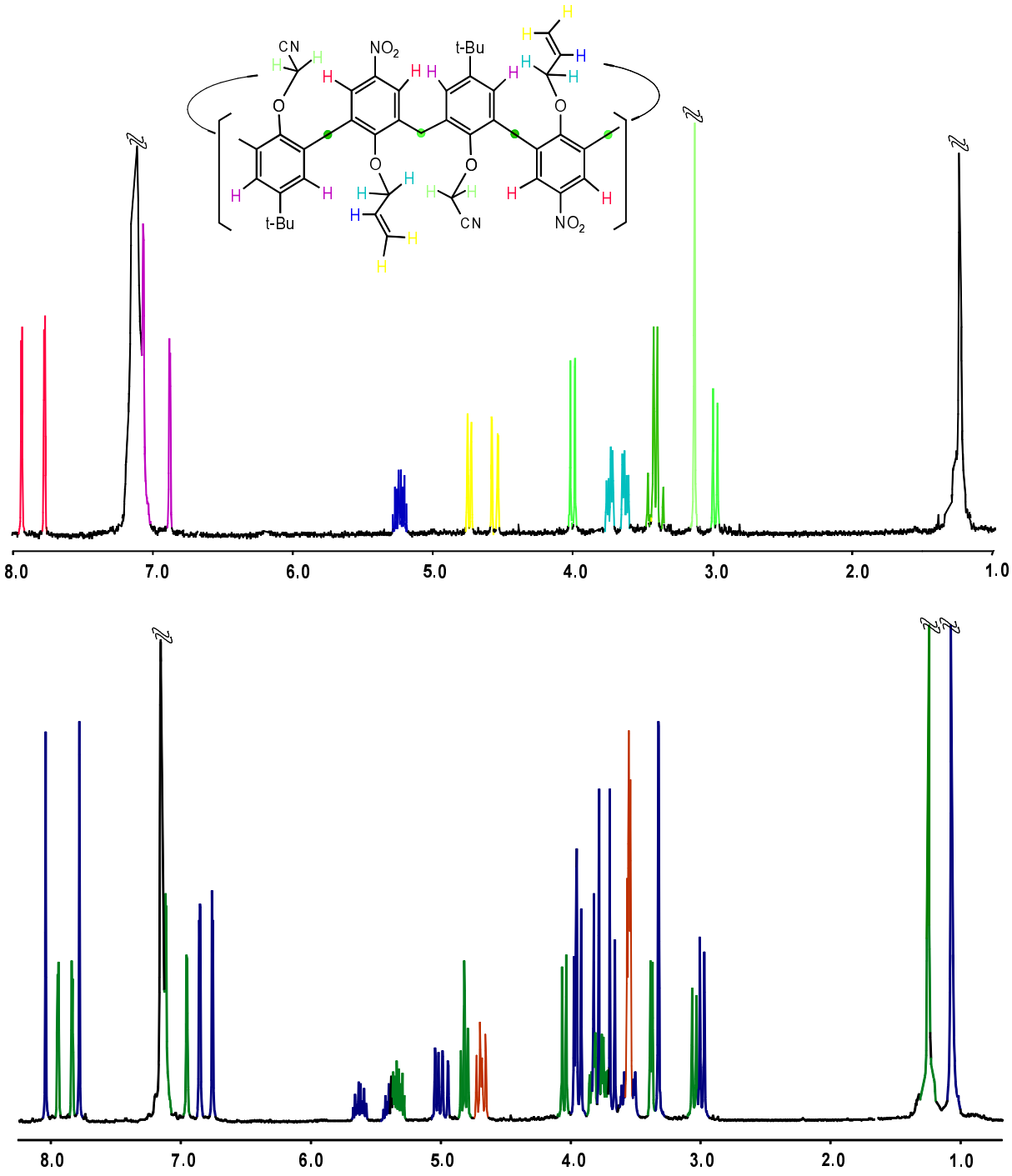


Figure 2. ^{1}H-NMR spectrum of **3(*1,2-alt*)** in C_6D_6 at rt, immediately after dissolution (a); ^{1}H-NMR spectrum of the equilibrium mixture of **3(*1,2-alt*)** [green signals] and **3(*paco*)** [blue signals] C_6D_6 at 75°C; overlapping signals in red (b).

The equilibrium shifts toward the *1,2-alternate* (*anti*) isomer (endothermic process) with increasing temperature while lowering the temperature favors the *partial cone* (*syn*) isomer (exothermic process in respect to Chatelier's principle). In conclusion the formation of the *partial cone* isomer from the *1,2-alternate* isomer is exothermic and entropically favored.

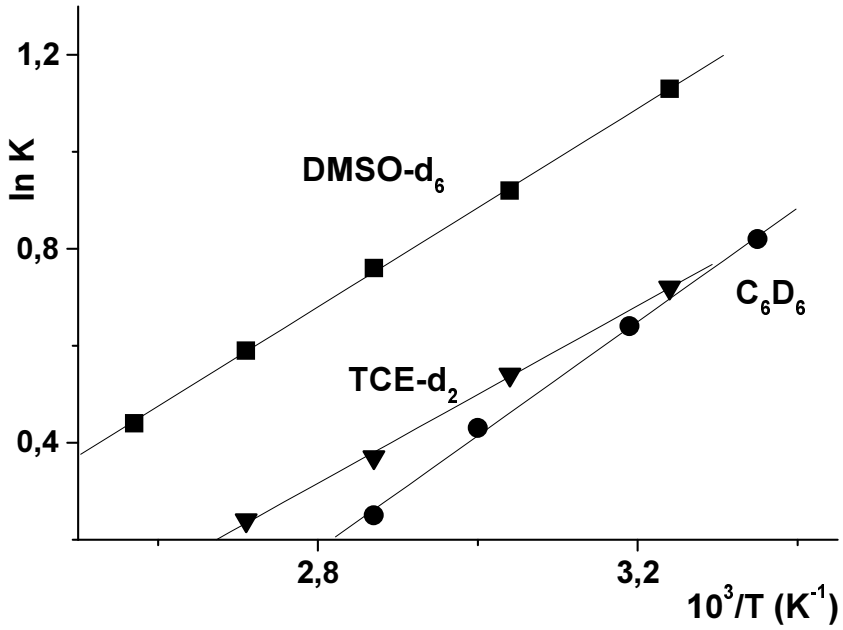


Figure 3. Plot of lnK vs 1/T for the equilibrium **3(*1,2-alt*)** $\rightleftharpoons$ **3(*paco*)** in different solvents.

DMSO-d_6	10^3/T (K^{-1})	2.57	2.71	2.87	3.04	3.24
	ln K	0,44	0,59	0,76	0,92	1,13
TCE-d_2	10^3/T (K^{-1})	2.71	2.87	3.04	3.24	
	ln K	0.24	0.37	0.54	0.72	
C_6D_6	10^3/T (K^{-1})	2.87	3.00	3.19	3.35	
	ln K	0.25	0.43	0.64	0.82	

Table 2. The numeric data for the plot lnK vs 1/T.

For the equilibrium **4(*cone*)** $\rightleftharpoons$ **4(*paco*)** an equilibrium constant of K = 2 is found in C_6D_6. No significant change in K is detected between T = 298 K and T = 323 K. This means, that ΔH_0 is close to zero in this case, if the unlikely assumption is excluded, that the energy barrier E_a is too high in this case, to shift the equilibrium in reasonable times. An ^{1}H-NMR spectrum of the mixture **4(*cone*)** and **4(*paco*)** recorded in CD_2Cl_2 is shown in figure 4.

Analyzing the chemical shifts of the equilibrium **3(*1,2-alt*)** $\rightleftharpoons$ **3(*paco*)** one can observe additionaly strong changes (0.1 ppm or more) for various protons with the increasing temperature for each isomer (see figure 5 and 6).

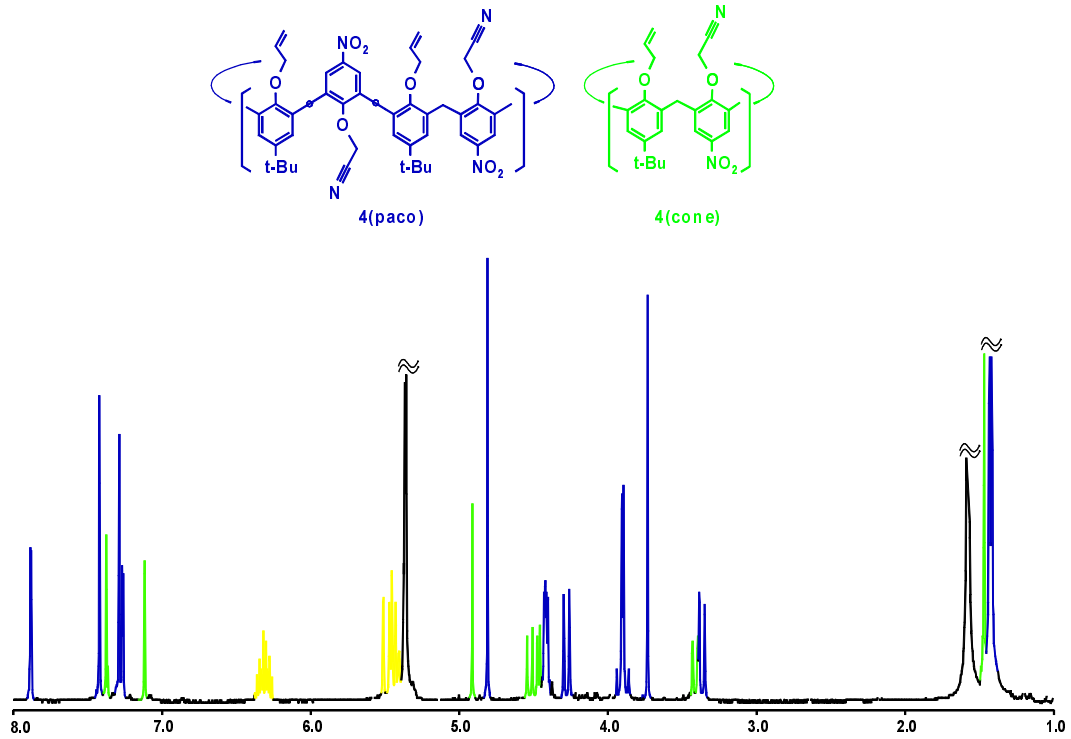
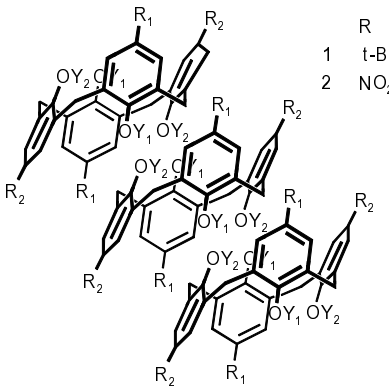


Figure 4. The H-NMR spectrum of the mixture **4(*cone*)** and **4(*paco*)**, in CD_2Cl_2 (the overlapped signals are in yellow colored)

This could be explained by the assumption that the conformational equilibrium (eqn.1), which is slow on the NMR time scale is superimposed by a kinetically rapid equilibrium (or equilibria) of one (or both) conformers.

This consists in a possible association chains of **3(*1,2-alt*)** (see below) [or **3(*paco*)**] units which would lead to an average signal for a given proton. This interpretation is supported by the observation that dilution of the solution (7.28 x 10^{-3} mol/l from 2.91 x 10^{-2} mol/l) leads to similar chemical shift changes as an increase of the temperature. The formation of the olygomeric chains can be induced by the nitro group which has a large dipole moment. But this remains just an interpretation.



	R	Y
1	t-Bu	$-CH_2CN$
2	NO_2	$-CH_2CH=CH_2$

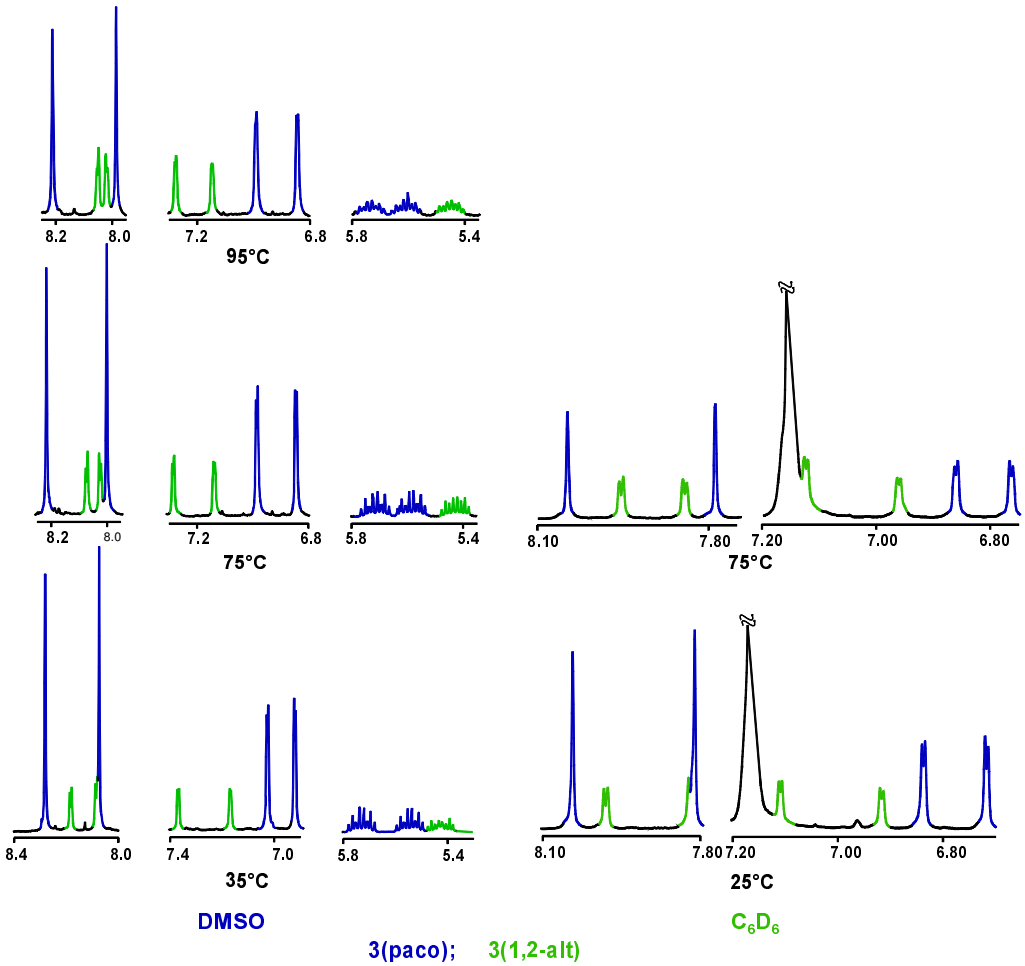


Figure 5. Comparison of the chemical shifts of aromatic and signals for double bond for the equilibrium between **3(*1,2-alt*)** and **3(*paco*)** at different temperatures in DMSO (left column) and C_6D_6 (right column).

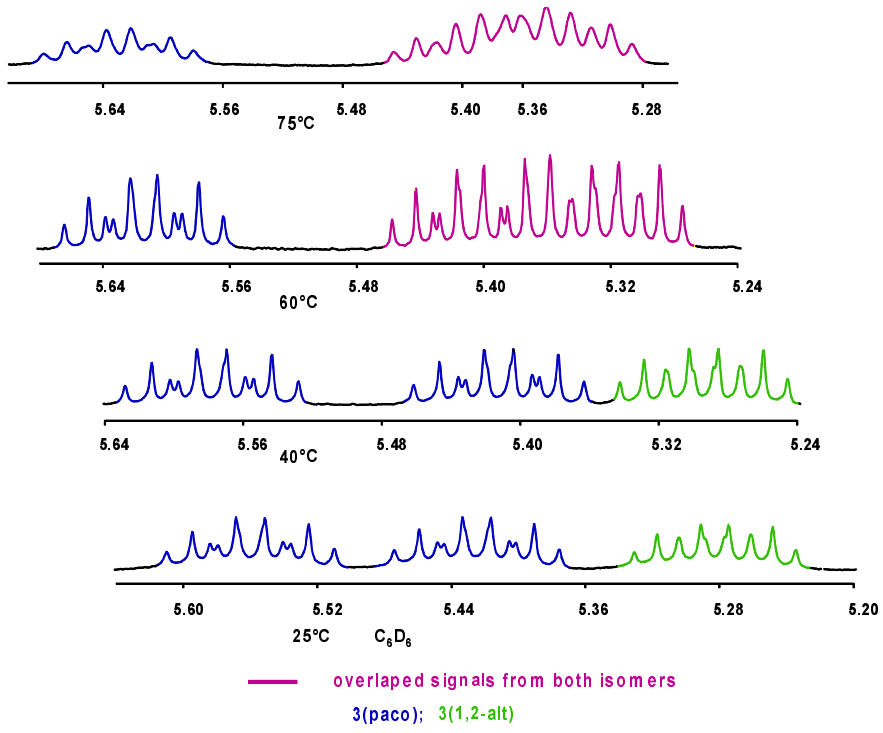


Figure 6. Comparison of the chemical shifts of signals for double bond of the system **3(*1,2-alt*)** and **3(*paco*)** in equilibrium at different temperatures in C_6D_6.

To see if the nitro group has an influence on the conformation stability of **3(*1,2-alt*)**, the compound **1** was O-alkylated under similar conditions as **2** (see synthesis part). The synthetic results are similar in both cases, but due to the absence of the nitro groups a stronger overlap of signals in the ^{1}H-NMR spectra (figure 7) occurs. The equilibrium **5(*1,2-alt*)** $\rightleftharpoons$ **5(*paco*)** cannot be studied as exactly/easily as in the case of **3**.

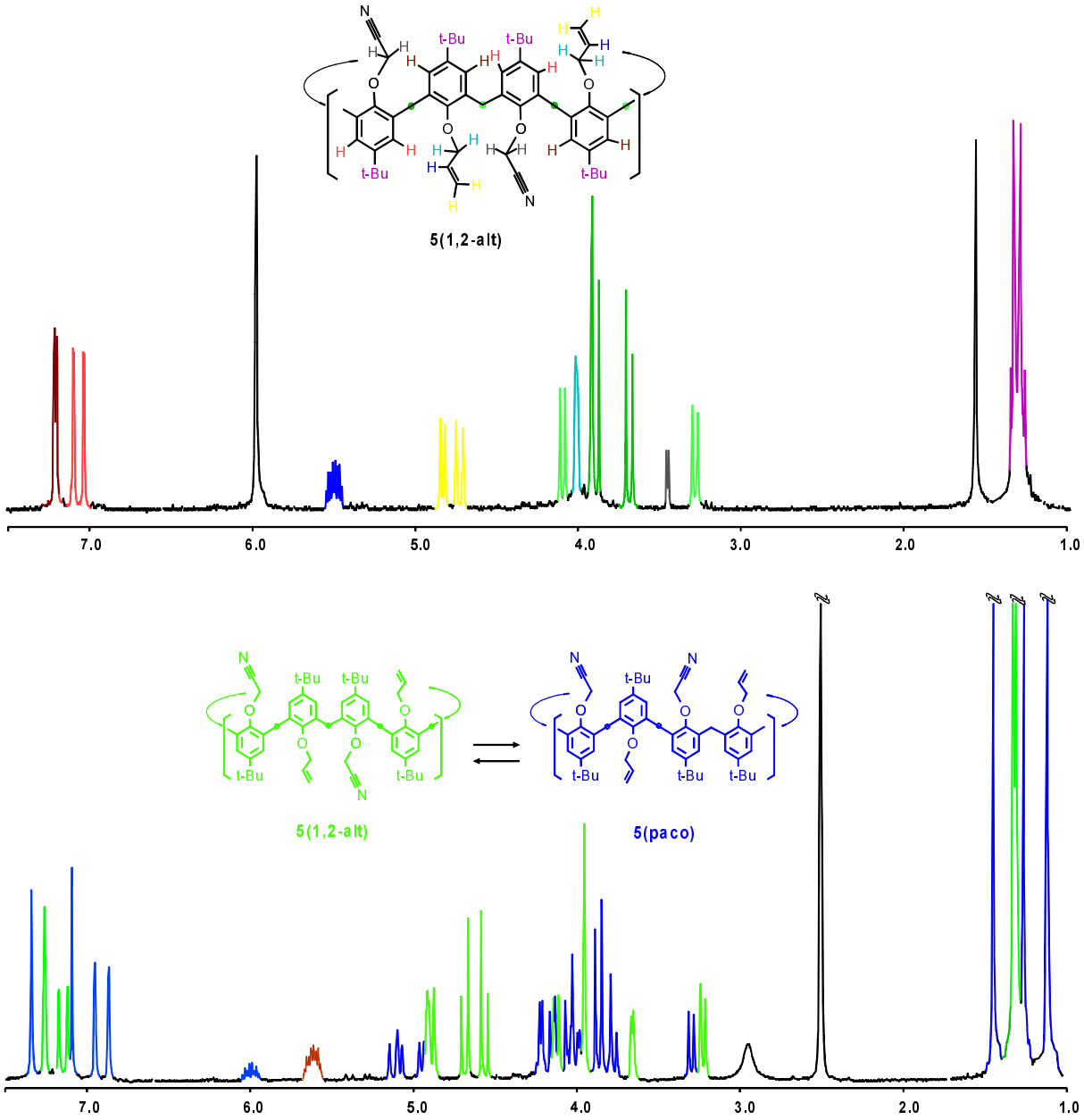


Figure 7. ^{1}H-NMR spectrum of **5(*1,2-alt*)** in TCE-d_2 at rt, immediately after dissolution (above); ^{1}H-NMR spectrum of the equilibrium **5(*1,2-alt*)** $\rightleftharpoons$ **5(*paco*)** in TCE-d_2 at 115°C (below), the signal proton colored in red represent the overlapped signal protons from the both isomers.

In $C_2D_2Cl_4$ (TCE-d_2) an equilibrium constant of K = 1.24 was determined at 115°C, which corresponds to the value found for **3**. The replacement of *t*-butyl by nitro groups obviously has no significant influence on the relative stability of these conformers.

We studied kinetically *anti-syn* interconversion of **3(*1,2-alt*)** by ^{1}H-NMR spectroscopy. Since **3(*1,2-alt*)** isomer is isolated as powder, this solid state represents one extreme of the equilibrium. The powder of **3(*1,2-alt*)** is dissolved in DMSO-d_6 at ambiance temperature to form the sample for ^{1}H-NMR measurements. The sample is introduced in the spectrometer where the temperature is different than that one at which the powder was dissolved (e.g. 45 °C). This suddenly increasing of the temperature applied to the solution of **3(*1,2-alt*)** shifts the equilibrium in that manner to be adjusted to the new conditions. A series of ^{1}H-NMR spectra can be recorded to visualize the shifting in time of equilibrium until may achieved the new temperature. The ^{1}H-NMR spectra show the appearance and increasing of additional set of signals corresponding to *partial cone* isomer. From integration (ratio) of signals of isomers along the recording of ^{1}H-NMR spectra the concentration of **3(*paco*)** can be established. It increases from a C_0 (initial) to C_E corresponding to the equilibrium, always passing through the value of a momentum concentration C_t.

Kinetic at 45, 55, 65 and 75 °C are studied. The plot of ln C_E–C_0/C_E–C_t against time represent the conversion of **3(*1,2-alt*)** into **3(*paco*)** at different temperatures is drawn in figure 8.

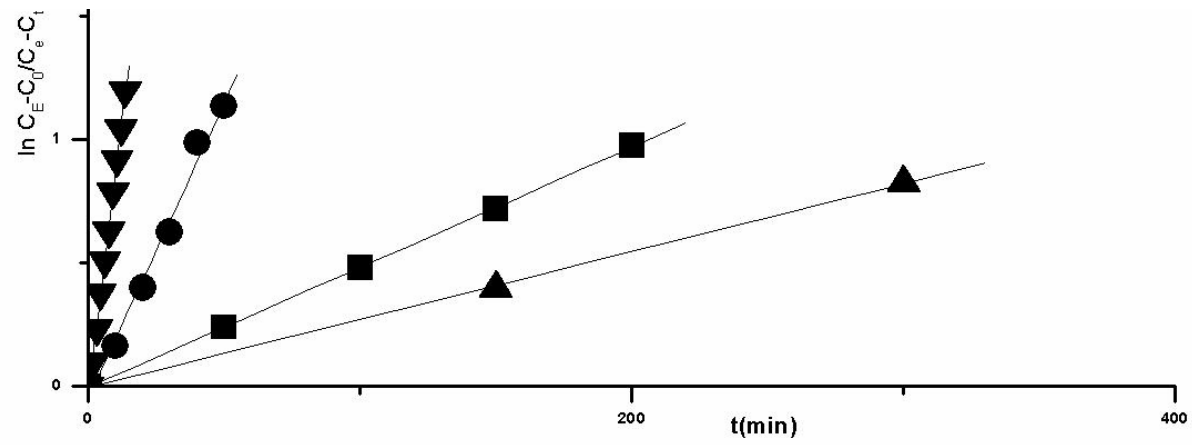


Figure 8. First order plots for the conversion of **3(*1,2-alt*)** to the equilibrium mixture at different temperatures (▲ 45 °,■ 55 °,● 65 °,▼ 75 °C).

From the first apparent order rate constant $k_{(1)} = k_I + k_{II}$ and the equilibrium constant $K = k_I/k_{II}$ the rate constant k_I for the conversion of **3(*1,2-alt*)** into **3(*paco*)** can be calculated. Figure 9 illustrates the Arhenius plot for $k_{(1)}$, which leads to an activation energy of E_a = 110.5 kJ/mol.

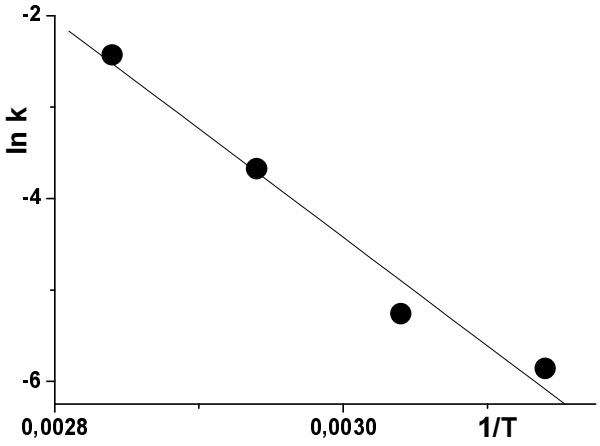


Figure 9. The Arhenius plot for $k_{(1)}$.

4.3. X-Ray structures.

Five compounds were characterized by single crystal X-ray analysis, namely **3(*1,2-alt*)**, **5(*1,2-alt*)**, **4(*paco*)**, **6(*paco*)** and **2(*cone*)**. Geometrical parameters are gathered in table 2.

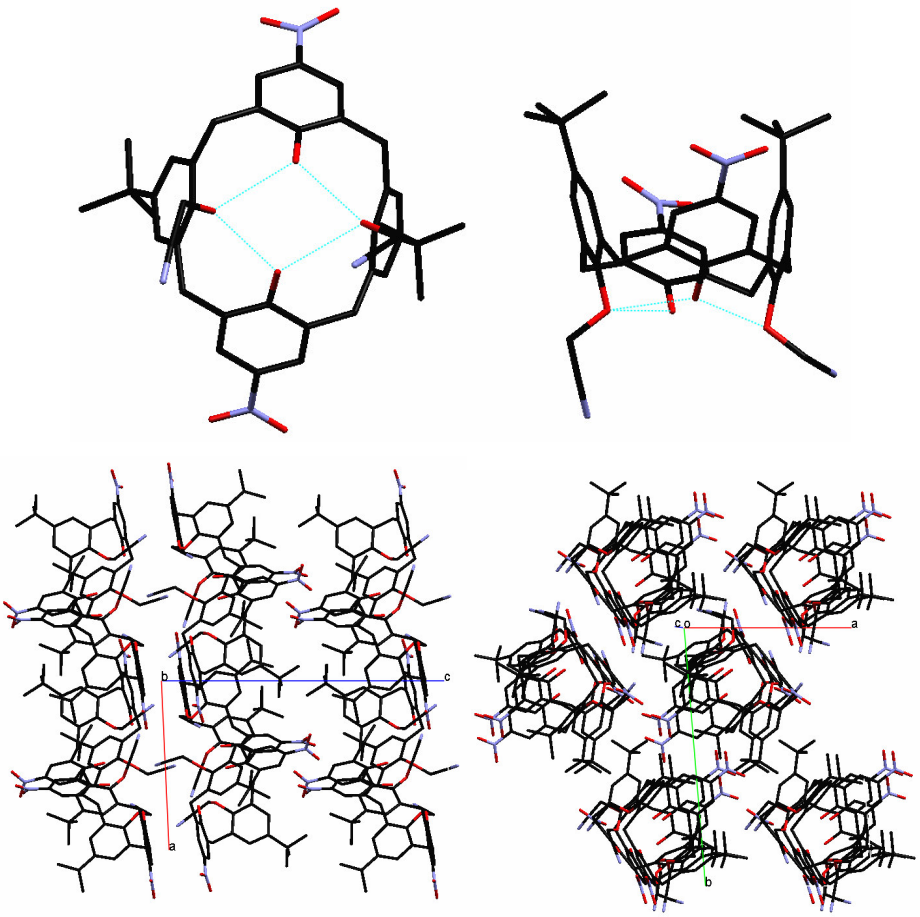
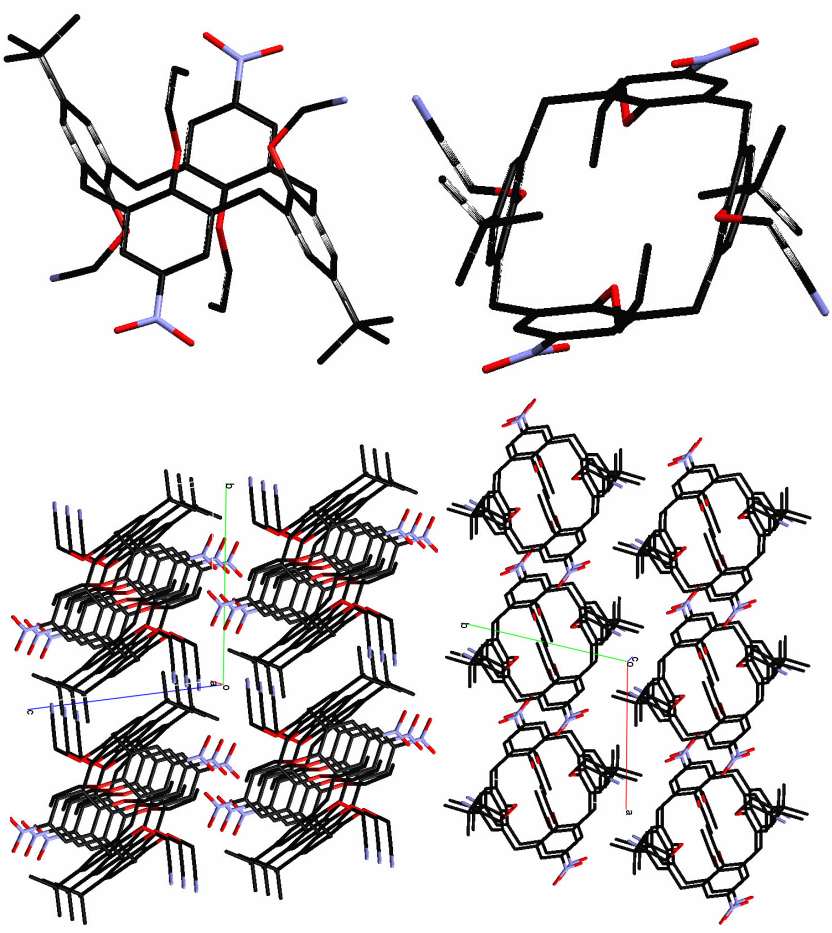


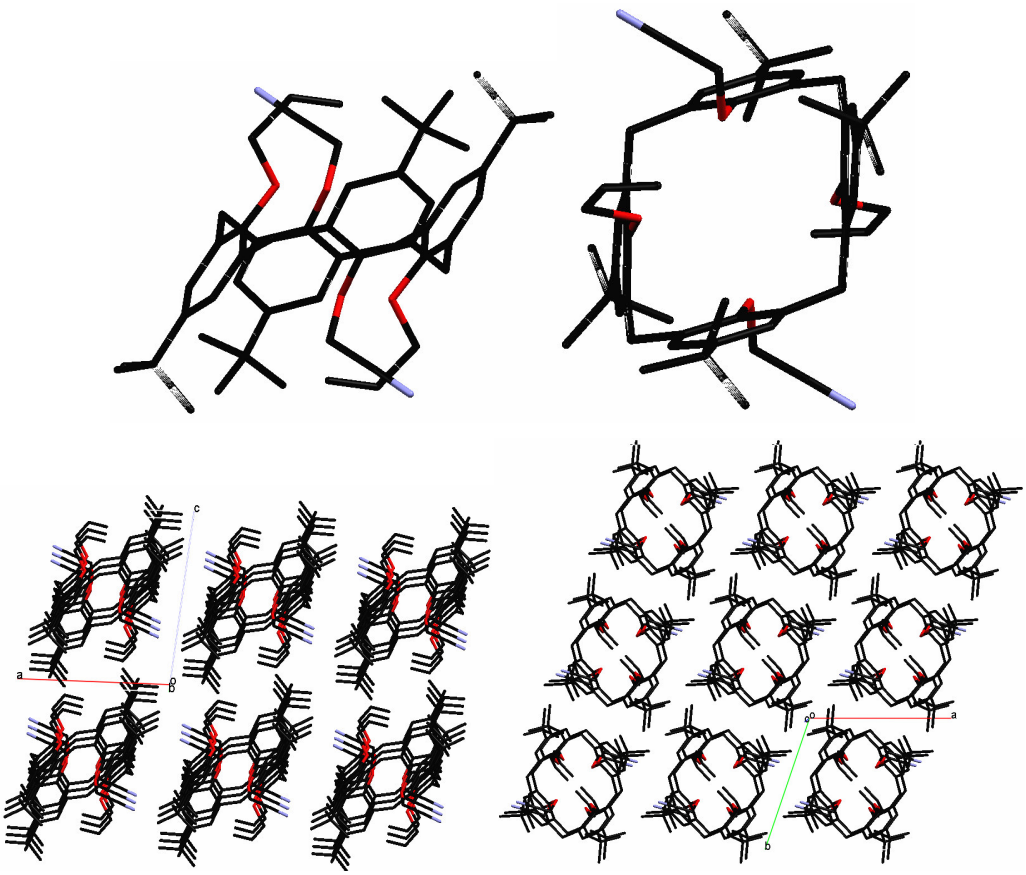
Figure 10. Two independent molecules seen from different directions of **2(cone)**. The packing diagram seen along the *b* (left) and *c* axis (right).

The X-ray analysis of the *syn*-diether **2** confirm that it adopts a *cone* conformation in the solid state which is in agreement with the ^{1}H-NMR data in solution. The *cone* is pinched and stabilized by intramolecular –OH...H hydrogen bonds, drawn with blue lines in figure 10. The angle with the reference plan (defined by carbon of methylene bridges) is larger for phenol units than for phenolether units (one of which is even perpendicular in one of the two molecules) (see table 3).

In the case of *1,2-alternate* isomers of **3** and **5**, the X-ray analysis reveal a parallelepipedic-like shape which has as walls the aromatic rings and as basses imaginer parallelogram who is passing through the *p*-position of each aromatic rings. The inclinations of phenol units to the reference plane have the same values (118,8 °) in the case of **5**. In the both cases the cyano groups are outward orientated. In their packing diagrams the molecules are aligned in columns in all three directions (see figure 11).

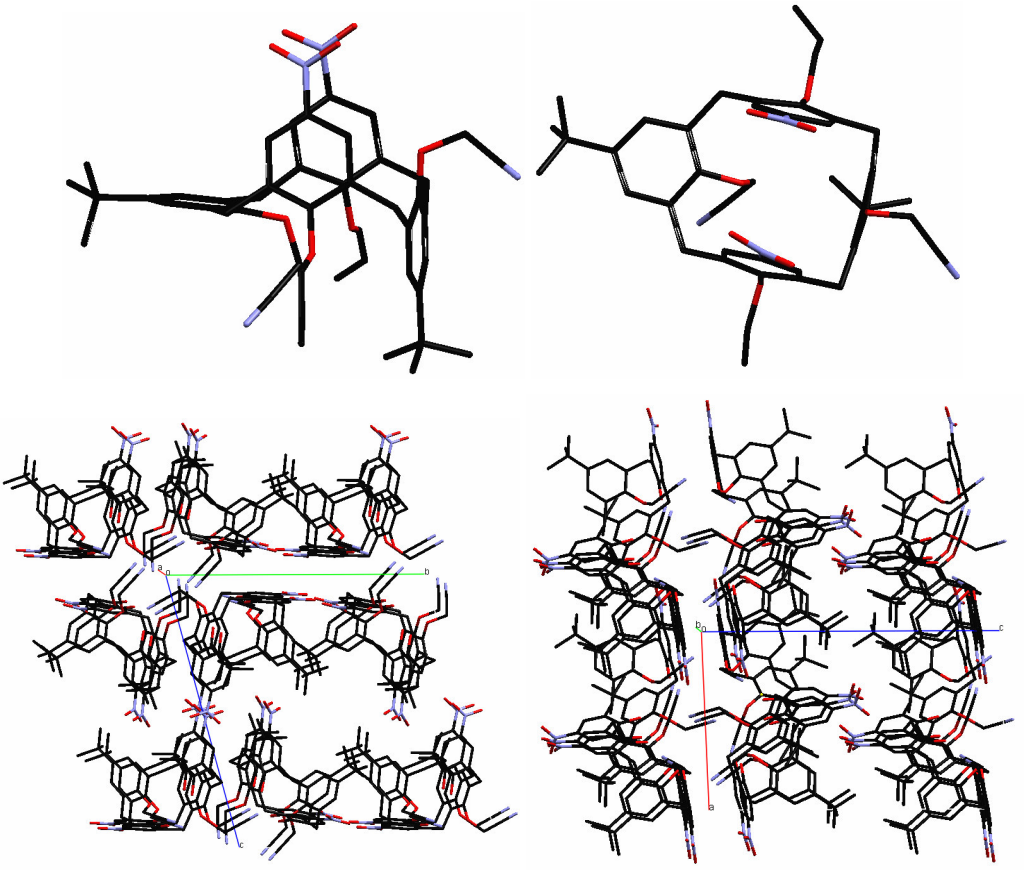


3(*1,2-alt*)

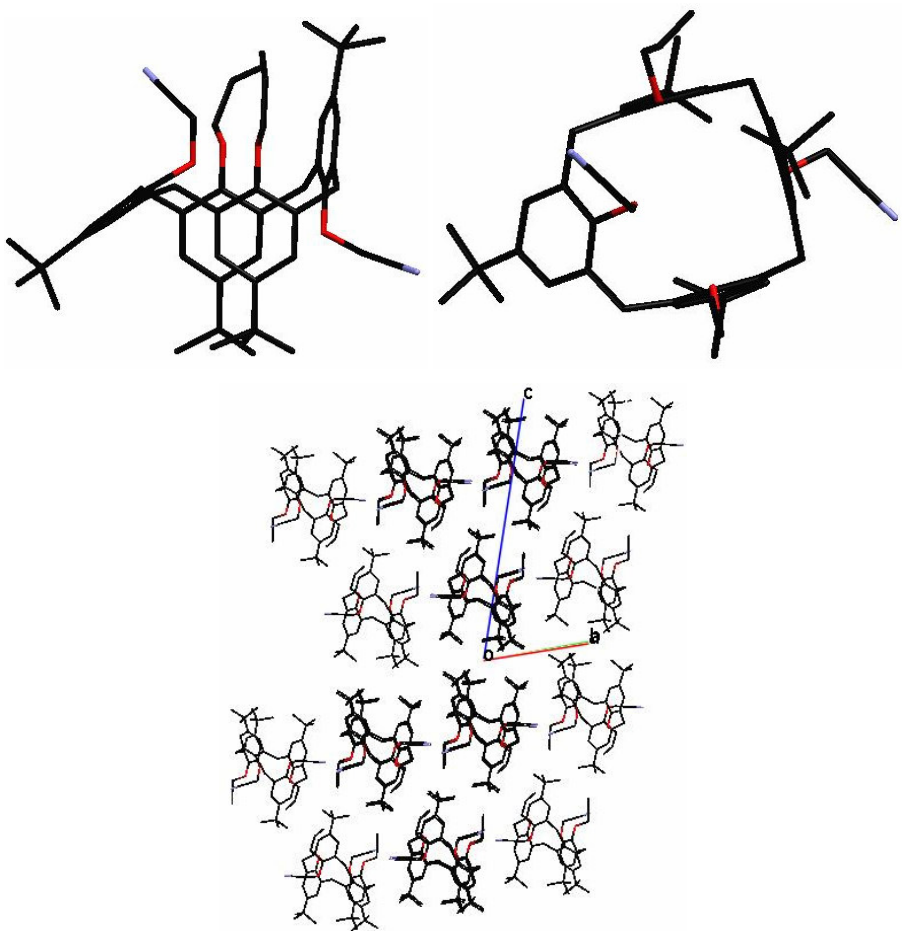


5(*1,2-alt*)

Figure 11. View from different directions of **3(*1,2-alt*)** and **5(*1,2-alt*)** and their packing diagrams along axis.



4(*paco*)



6(*paco*)

Figure 12. View from different directions of **4(*paco*)** and **6(*paco*)** and their packing diagram.

Two single crystals analyzed by X-ray which show the both are in the *partial cone* conformation. For **4(*paco*)** a remarkable distortion of the *partial cone* conformation is observed. While the two nitrophenyl residues are bent inwards (< 90 °), one cyanomethoxy-*t*-butyl ring lies nearly in the reference plane (169 °). Such structure can be considered as a transition state between *cone* and *1,3-alternate* conformations. The opposite "inverted" phenolic unit is nearly perpendicular to the reference plane (100 °). For the **6(*paco*)**, two independent molecules are found in the crystal unit[7]. Two opposite allyloxy *t*-butyl aromatic unit are almost parallel to each other.

Table 2. Crystallographic data.

Compound	**3(*1,2-alt*)**	**5(*1,2-alt*)**	**4(*paco*)**	**2(*cone*)**	**6(*paco*)**
Formula	$C_{46}H_{48}N_4O_8$	$C_{54}H_{66}N_2O_4$	$C_{46}H_{48}N_4O_8$	$C_{41}H_{43}ClN_4O_{8,.5}$	$C_{54}H_{66}N_2O_4$
M_W	784.88	807.09	784.88	763.24	807.09
Crystal system	triclinic	triclinic	triclinic	triclinic	triclinic
Space group	*P*-1	*P*-1	*P*-1	*P*-1	*P*-1
T / K	173	173	293	100	173(2)
a / Å	9.7073(14)	10.4041(19)	10.3157(11)	11.4637(8)	11.1136(14)
b / Å	10.5690(14)	10.6679(19)	12.4728(12)	18.3534(12)	18.706(2)

c / Å	10.9986(15)	11.557(2)	17.753(2)	19.8397(14)	26.013(3)
α °	92.126(11)	105.672(14)	99.611(8)	74.256(5)	68.951(9)
β °	109.791(10)	91.147 (15)	103.810(8)	85.809(6)	79.257(9)
γ °	101.734(11)	108.061(14)	99.245(8)	83.824(5)	79.858(9)
V / Å	1032.7(2)	1166.6(4)	2138.5(4)	3990.1(5)	4923.3(10)
Z	1	1	2	4	4
μ (mm^{-1})	0.087	0.071	0.084	0.153	0.068
Reflns. Measured	11250	14867	27339	32778	26182
Unique refins [$I > 2\sigma(I)$]	2611	3565	5324	10482	0.0750
wR(F2)[$I > 2\sigma(I)$]	0.1031	0.3160	0.1962	0.2126	0.1111

The torsion angles are measureed in the same way as were measured for discussed crystals (chapter 2) (see figure 13).

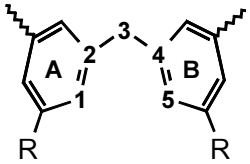


Figure 13. Schematic representation for the determination of the torsion angles in calixarenes. The torsion angles are: 1-2-3-4 (Cα6-Cα1-Cα-Cα3, α=1-4) and 2-3-4-5 (Cα1-Cα-Cα3-Cα4)

Table 3. Selected crystallographic data: **I)** Torsion angles (°) around the Ar-CH2-bonds; **II)** Distances within the reference plane, the best plane through the carbon atoms of the methylene bridges(Å); **III)** Inclination δ (°) of the aromatic units wit respect to the reference plane.

	3(*1,2*-alt)	**5(*1,2-alt*)**	**4(*paco*)**	**2**[a]	**2**[a]	**6(*paco*)**	**6(*paco*)**
I. Torsion angles							
C16-C11-C1-C43	78.74	-140.46	-104.06	-102.52	100.94	104.86	-108.48
C11-C1-C43-C44	-80.16	-129.27	-111.25	80.34	-54.48	-61.67	68.85
C26-C21-C2-C13	136.73	75.18	-136.87	-72.43	81.05	63.90	-60.49
C21-C2-C13-C14	139.06	-81.83	62.87	94.10	-106.86	-99.90	108.77
C36-C31-C3-C23	-78.74	140.46	-58.24	-106.27	98.91	-115.65	118.37
C31-C3-C23-C24	80.16	129.27	132.72	80.66	-71.20	-119.25	109.90
C46-C41-C4-C33	-136.73	-75.18	166.68	-72.15	63.15	110.37	-117.14
C41-C4-C33-C34	-139.06	81.83	105.68	98.52	-108.27	117.22	-117.78
II. Reference planes C1 – C4							
Distance C1 − C2	5.093	5.128	5.060	5.099	5.083	5.110	5.109
Distance C2 − C3	5.127	5.101	5.079	5.089	5.089	5.081	5.095
Distance C3 − C4	5.093	5.128	5.060	5.105	5.080	5.121	5.102

Distance C1 − C4	5.127	5.101	5.028	5.095	5.102	5.101	5.112
Distance C1 − C3	7.764	6.681	7.162	7.408	7.038	7.306	7.246
Distance C2 − C4	6.647	7.746	7.133	6,992	7.335	7.674	7.191
III. Inclination of the aromatic units(δ)							
C11 − C16[b]	118.8	-112.7	81.5	134.2	139.2	139.3	145.36
C21 − C26[c]	-118.8	119.8	169.1	110.8	109.2	95.45	90.06
C31 − C36[b]			100.1	137.8	139.3	93.55	90.23
C41 − C46[c]			95.1	110.6	89.2	90.28	83.18

[a)] two crystallographically different/independent molecules [b)] allyloxy or hydroxy and nitro or *t*-butyl [c)] cyanomethoxy and *t*-butyl

4.4. Experimental part.

Kinetics measurements.

a) at 45 °C

The powder of **3(*1,2-alt*)** (11 mg) was dissolved in DMSO-d_6 (0.8 ml) and it was shaken for 3 min at rt and further 2 min standing in NMR spectrometer at 45°C. The intervals of time between ^{1}H-NMR measurements is 15 min., the number of scans is 24 and the number of H-NMR spectra recorded are 60 in 15 h. The ratios of the integrated proton signals between **3(*1,2-alt*)** and **3(*paco*)** are gathered in Table below.

Time	Ratio between the Ar-H proton signals of *1,2-alternate* and *partial cone*			
	3(*1,2-alt*)	**3(*paco*)**	**3(*1,2-alt*)**	**3(*paco*)**
0	1	0.0269	1	0.0348
150	1	0.3532	1	0.3651
300	1	0.744	1	0.7614
450	1	1.0823	1	1.1451
600	1	1.5183	1	1.4968
750	1	1.9078	1	2.0727
900	1	2.144	1	2.337

b) at 55 °C

The powder of **3(*1,2-alt*)** (11 mg) was dissolved in DMSO-d_6 (1.38 ml) and it was shaken for 3 min at rt and further 6 min standing in NMR spectrometer at 55°C. The intervals of time between ^{1}H-NMR measurements is 10 min., the number of scans is 16 and the number of H-NMR spectra recorded are 59 in 9 h 50 min. The ratios of the integrated proton signals between **3(*1,2-alt*)** and **3(*paco*)** are gathered in Table below.

Time	Ratio between the Ar-H proton signals of *1,2-alternate* and *partial cone*			
	3(*1,2-alt*)	**3(*paco*)**	**3(*1,2-alt*)**	**3(*paco*)**
0	1	0.0383	1	0.03818
50	1	0.2178	1	0.224
100	1	0.4203	1	0.4185
150	1	0.6083	1	0.6446
200	1	0.8413	1	0.8644
250	1	1.064	1	1.085
300	1	1.3067	1	1.0305

c) at 65 °C

The powder of **3(*1,2-alt*)** (11 mg) was dissolved in DMSO-d_6 (0.9 ml) and it was shaken for 3 min at rt and further 2 min standing in NMR spectrometer at 65°C. The intervals of time between ^{1}H-NMR measurements is 2 min., the number of scans is 8 and the number of H-NMR spectra recorded are 90 in 3 h. The ratios of the integrated proton signals between **3(*1,2-alt*)** and **3(*paco*)** are gathered in Table below.

Time	Ratio between the Ar-H proton signals of *1,2-alternate* and *partial cone*			
	3(*1,2-alt*)	**3(*paco*)**	**3(*1,2-alt*)**	**3(*paco*)**
0	1	0.035	1	0.03888
10	1	0.1592	1	0.1522
20	1	0.3368	1	0.3442
30	1	0.4971	1	0.5456
40	1	0.8278	1	0.8191
50	1	0.9424	1	0.9446
60	1	1.2197	1	1.2465

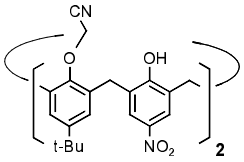
d) at 75 °C

The powder of **3(*1,2-alt*)** (12 mg) was dissolved in DMSO-d_6 (0.8 ml) and it was shaken for 3 min at rt and further 2 min standing in NMR spectrometer at 75°C. The intervals of time between ^{1}H-NMR measurements is 1.5 min., the number of scans is 8 and the number of H-NMR spectra recorded are 80 in 2 h. The ratios of the integrated proton signals between **3(*1,2-alt*)** and **3(*paco*)** are gathered in Table below.

Time	Ratio between the Ar-H proton signals of *1,2-alternate* and *partial cone*			
	3(*1,2-alt*)	**3(*paco*)**	**3(*1,2-alt*)**	**3(*paco*)**
0	1	0.0451	1	0.0519
1.5	1	0.1192	1	0.1162
3	1	0.2134	1	0.222
4.5	1	0.3132	1	0.339
6	1	0.4149	1	0.4281

7.5	1	0.5547	1	0.5473
9	1	0.6427	1	0.644
10.5	1	0.7418	1	0.747
12	1	0.8337	1	0.8487
13.5	1	0.9515	1	0.9599

5,17-Di-*t*-butyl-11,23-dinitro-25,27-*bis*-cyanomethoxy-26,28-dihydroxy-calix[4]arene 2



Nitric acid (65 %, 13 ml) was added with stirring to a cold (0 °C) solution of **1** (3.2 g, 4.3 mmol) in dry CH2Cl2 (130 ml). In 10 min the color changed from black-indigo to yellow and the reaction was complete. Water was added (100 ml) and the mixture was stirred for 30 min. After phase separation the organic phase was washed with water (3x100 ml) until a neutral pH was reached, dried (MgSO4) and the solvent was evaporated. The residue was dissolved in chloroform (20 ml) and the pure product was obtained after twofold recrystallization from methanol (30 ml) as yellow powder (1.2 g, 37 %). m.p 326-327°C

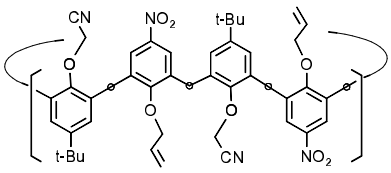
1H-NMR (300 MHz, CDCl3) δ 0.93 (s, 18H, *t*-Bu), 3.61, 4.23 (2d, 8H, ^2J = 13.97 Hz, Ar-CH2-Ar), 4.85 (s, 4H, -CH2-CN), 6.82 (s, 4H, ArH), 7.01 (s, 2H, OH), 8.11 (s, 4H, ArH).

^{13}C-NMR (400 MHz, $CDCl_3$) δ 30.93 (*t*-Bu, $C_{prim.}$), 31.45 (Ar-CH_2-Ar), 34.23 (*t*-Bu, $C_{quat.}$), 60.47 (O-CH_2-), 114.47 (*C*N-), 124.51, 126.82 (aromatic *C*H), 128.26, 130.38, 140.29, 148.74, 150.29, 158.33 (aromatic $C_{quat.}$).

5,17-Di-*t*-butyl-11,23-dinitro-25,27-*bis*-cyanomethoxy-26,28-diallyloxy-calix[4]arene 3

A stirred suspension of dinitro calixarene **2** (0.56 g, 0.8 mmol) and Cs_2CO_3 (2.6 g, 8 mmol) in dry DMF (20 ml) was heated to 50°C under nitrogen. After 1 h allylbromide (0.7 ml, 8 mmol) was added and the reaction mixture was kept under these conditions for 7 days. The DMF was removed under reduced pressure and the residue was treated with chloroform (15 ml) and water (50 ml). The organic phase was washed twice with water (2x50 ml), dried ($MgSO_4$) and the solvent was evaporated. TLC, analysis of the residue showed the presence of three isomers (*1,2-alt*, *cone* and *paco*). Recrystallization from chloroform/methanol (10 ml, 1:4) gave single crystals of **3(*1,2-alt*)** and a white powder (0.21 g, 34 %). From the mother liquor a mixture of **4(*cone*)** and **4(*paco*)** was isolated as yellow powder (0.1 g, 18 %).

3(*1,2-alt*) mp 236°C:



^{1}H-NMR (400 MHz, C_6D_6) δ 1.24 (s, 18H, *t*-Bu), 3.05 (d, 2H, ^2J = 13.3 Hz, Ar-CH_2-Ar), 3.14 (s, 4H, -CH_2-CN), 3.39, 3.47 (2d, 4H, ^2J = 16.8 Hz, Ar-CH_2-Ar), 3.61-3.77 (m, 4H, -CH_2-CH=CH_2), 4.01 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.55-4.77 (m, 4H, CH=CH_2), 5.20-5.30 (m, 2H, -C*H*=CH_2), 6.89, 7.08 (2d, 4H, ^4J = 2.3 Hz, Ar*H*), 7.78, 7.95 (2d, 4H, ^4J = 2.7 Hz, Ar*H*).

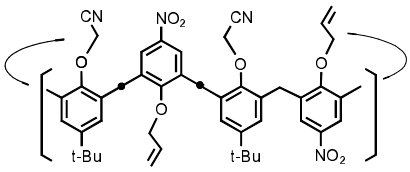
^{1}H-NMR (400 MHz, TCE-d_2) δ 1.30 (s, 18H, *t*-Bu), 3.05 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 3.90, 3.94 (2d, 4H, ^2J = 16.2 Hz, Ar-CH_2-Ar), 4.01, 4.02 (2s, 4H, -CH_2-CN), 4.09 (m, 4H, -CH_2-CH=CH_2), 4.16 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.77-4.90 (m, 4H, CH=CH_2), 5.47 (m, 2H, -C*H*=CH_2), 7.13, 7.21 (2s, 4H, Ar*H*), 8.05 (s, 4H, Ar*H*).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 18H, *t*-Bu), 3.40 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 3.88- 4.01 (m, 12H, -CH_2-CH=CH_2, -CH_2-CN, Ar-CH_2-Ar), 4.21 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.77-4.90 (m, 4H, CH=CH_2), 5.48 (m, 2H, -C*H*=CH_2), 7.12, 7.22 (2d, 4H, ^4J = 2.2 Hz, Ar*H*), 8.05 (s, 4H, Ar*H*).

^{13}C-NMR (400 MHz, $CDCl_3$) after dissolution δ 30.13, 37.82 (Ar-*C*H_2-Ar), 31.36 (*t*-Bu, $C_{prim.}$), 34.38 (*t*-Bu, $C_{quat.}$), 57.20, 74.13 (O-*C*H_2-), 115.40 (*C*N-), 117.23 (*C*H_2=), 124.47, 126.50 126.66, 127.72, (aromatic *C*H), 130.71, 132.81, 134.14, 136.40, 143.09, 148.04, 151.17, 161.13 (aromatic $C_{quat.}$), 132.64 (*C*H=).

Although **3(*paco*)** was not isolated as a pure compound we can derive most of the proton signals in the ^{1}H-NMR spectrum shown by the equilibrium mixture of the *partial cone* and *1,2-alternate* isomers of **3.**

3(*paco*)



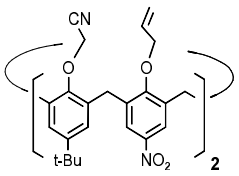
^{1}H-NMR (400 MHz, C_6D_6) δ 1.07 (s, 18H, *t*-Bu), 2.99 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 3.32, 3.325 (2s, 4H, -CH_2-CN), 3.67, 3.79 (2d, 4H, ^2J = 15.6 Hz, Ar-CH_2-Ar), 3.94 (d, 2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.94-5.05 (m, 4H, CH=CH_2), 5.41, 5.65 (2m, 2H, -C*H*=CH_2), 6.75, 6.89 (2d, 4H, ^4J = 2.2 Hz, Ar*H*), 7.78, 8.04 (2s, 4H, Ar*H*).

^{1}H-NMR (400 MHz, TCE-d_2) δ 1.02 (s, 18H, *t*-Bu), 3.27 (d, 2H, ^2J = 13.3 Hz, Ar-CH_2-Ar), 4.46, 4.47 (2d, 4H, ^2J = 15.6 Hz, Ar-CH_2-Ar), 5.48-5.58 (2m, 2H, -C*H*=CH_2), 6.72, 6.91 (2d, 4H, ^4J = 2.2 Hz, Ar*H*), 7.86, 8.13 (2s, 4H, Ar*H*).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 18H, *t*-Bu), 3.37 (d, 2H, ^2J = 12.9 Hz, Ar-CH_2-Ar), 4.45, 4.54 (2d, 4H, ^2J = 15.6 Hz, Ar-CH_2-Ar), 5.54-5.71 (2m, 2H, -C*H*=CH_2), 6.86, 7.01 (2d, 4H, ^4J = 2.2 Hz, Ar*H*), 7.92, 8.21 (2s, 4H, Ar*H*).

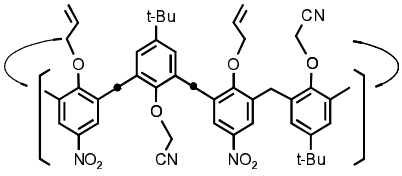
For **4(*cone*)** and **4(*paco*)** only those peaks are listed which are essential and which we can be unambiguously distinguished.

4(*cone*)



^{1}H-NMR (400 MHz, CD_2Cl_2) δ 1.41 (s, 18H, *t*-Bu), 3.37, 4.70 (2d, 8H, ^2J = 14.1, 13.7 Hz, Ar-CH_2-Ar), 6.29 (m, 2H, -C*H*=CH_2), 7.06, 7.32 (2s, 8H, Ar*H*).

4(*paco*)

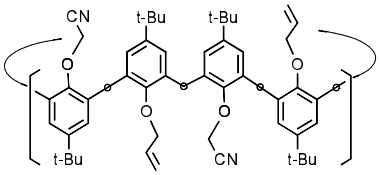


^{1}H-NMR (400 MHz, CD_2Cl_2) δ 1.36, 1.38 (2s, 18H, *t*-Bu), 3.31, 4.22 (2d, 4H, ^2J = 14.5 Hz, Ar-C*H*$_2$-Ar), 3.83, 3.86 (2d, 4H, ^2J = 13.7, 14.1 Hz, Ar-C*H*$_2$-Ar), 6.26 (m, 2H, -C*H*=CH$_2$), 7.21, 7.83 (2d, 4H, ^4J = 2.3 Hz, Ar*H*), 7.23, 7.36 (2s, 4H, Ar*H*).

5,11,17,23-Tetra-*t*-butyl-25,27-*bis*-cyanomethoxy-26,28-diallyloxy-calix[4]arene 5

The reaction was carried out under the same conditions described above starting from 1,3-*di*-O-alkylated compound **1** (2 g, 2.75 mmol) in dry DMF (75 ml) and Cs_2CO_3 (9 g, 27.5 mmol). Recrystallization from chloroform/methanol gave single crystals of **5**(***1,2-alt***) and a total of 0.23 g (11 %). A white powder (1.5 g, 68 %) consisting of a mixture of **6(*cone*)** and **6(*paco*)** was obtained from the mother liquor after slow evaporation of the solvent.

5 (*1,2-alt*) mp 243-245°C:

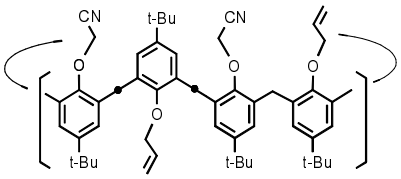


^{1}H-NMR (400 MHz, TCE-d$_2$) δ 1.30, 1.34 (2s, 36H, *t*-Bu), 3.30 (d, 2H, ^2J = 12.92 Hz, Ar-C*H*$_2$-Ar), 3.70, 3.91 (2d, 4H, ^2J = 16.0 Hz, Ar-C*H*$_2$-Ar), 3.93 (s, 2H, -C*H*$_2$-CN), 4.03 (m, 4H, -C*H*$_2$ CH=CH$_2$), 4.11 (d, 2H, ^2J = 12.5 Hz, Ar-C*H*$_2$-Ar), 4.72-4.86 (m, 4H, CH=C*H*$_2$), 5.49 (m, 2H, -C*H*=CH$_2$), 7.05, 7.12 (2d, 4H, ^4J = 2.3 Hz, Ar*H*), 7.22, 7.24 (2d, 4H, ^4J = 2.3 Hz, Ar*H*).

^{13}C-NMR (400 MHz, $CDCl_3$) after dissolution δ 30.04, 38.46 (Ar-*C*H$_2$-Ar), 31.40, 31.51 (*t*-Bu, $C_{prim.}$) 34.11 (*t*-Bu, $C_{quat.}$), 56.67, 73.45 (O-*C*H$_2$-), 115.51 (*C*H$_2$=), 116.47 (*C*N-), 125.63, 126.08, 126.18, 126.68 (aromatic *C*H), 132.18, 132.43, 134.10, 134.24, 145.63, 146.56, 151.36, 152.95 (aromatic $C_{quat.}$), 134.24 (*C*H=).

Although **5(*paco*)** was not isolated as a pure compound we can derive the most representative signals in the ^{1}H-NMR spectrum shown by the equilibrium mixture of the *partial cone* and *1,2-alternate* isomers of **5** at 135°C.

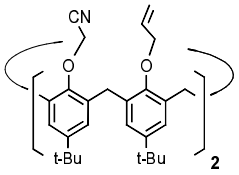
5(*paco*)



^{1}H-NMR (400 MHz, TCE-d$_2$) δ 3.32, 4.29 (2d, 4H, ^2J = 12.5 Hz, Ar-C*H*$_2$-Ar), 4.42, 4.58 (2d, 4H, ^2J = 15.6 Hz, Ar-C*H*$_2$-Ar), 5.43, 6.11 (2m, 2H, -C*H*=CH$_2$)

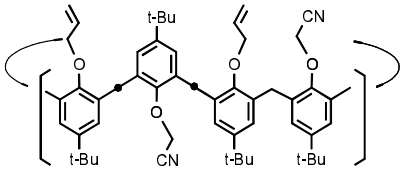
For **6(*cone*)** and **6(*paco*)** only those peaks are listed which are essential and which we can be unambiguously distinguished.

6(*cone*)



^{1}H-NMR (400 MHz, CD_2Cl_2) δ 3.29, 4.38 (2d, 8H, ^2J = 13.3, 12.9 Hz, Ar-C*H*$_2$-Ar), 6.48, 7.19 (2s, 8H, Ar*H*).

6(*paco*)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06, 1.32, 1.37 (3s, 18/9/9H, *t*-Bu), 3.17, 4.18 (2d, 2/2H, ^2J = 13.6 Hz, Ar-C*H*$_2$-Ar), 3.69, 3.80 (2d, 2/2H, ^2J = 13.9 Hz, Ar-C*H*$_2$-Ar), 4.06, 4.07 (2s, 2/2H, -C*H*$_2$-CN), 4.22-4.34 (m, 4H, O-CH_2-), 5.28-5.39 (m, 4H, -CH=C*H*$_2$), 6.24 (m, 2H, -C*H*=CH_2), 6.56, 6.95 (2d, 2/2H, ^4J = 2.3 Hz, Ar*H*), 7.09, 7.29 (2s, 2/2H, Ar*H*).

4.5. References.

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Chapter 5

Cobalt Bis(dicarbollides)(1-) combined with CMPO as ligating functions attached to the calix[4]arene skeleton.

In order to explore the extraction efficiency for actinides and lanthanides we synthesized compounds which bear cobalt bis(dicarbollides)(1-) in combination with CMPO as ligating functions attached to the calix[4]arene platform. This was a joint project with the research group in Rez, near Prague, which is specialized in boron-clusters. Therefore, the calix[4]arene derivatives prepared for the further attachment of the cobalt bis(dicarbollides)(1-) derivatives are synthesized here, in Mainz, and the attachment of the last mentioned boron-cluster occurs in Rez.

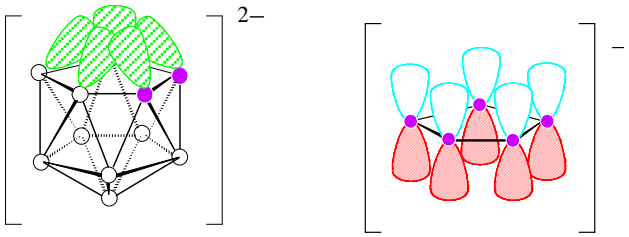
5. Basics of carboranes.

Boron-cluster compounds can be defined as three dimensional aggregates of [BH] units interconnected by two-electron three-center B-B-B, B-H-B and classical two-electron center B-B bonds. Thus, the compounds are considered as electron deficient. The boron cluster is composed by a defined number of [BH] vertices (n), which are arranged in triangular facets of a deltahedral cage. The geometry of the cluster depends on the number of vertices (n) and the number of cage electrons. Here, we discuss only the most stable closed 12-vertex series, which has 26 electron cage localized in the cage orbitals and adopts an *icosahedral* geometry. Such compounds are members of so called *closo* boron clusters with the general formula $[B_nH_n]^{c-}$ (n=12, c=2). Notional replacement of some of the cage $[BH]^-$ by [CH] units leads to carboranes with the general formula $[C_mB_{n-m}H_n]^{c-m}$, where m is 1 or 2 for known carboranes[1] of the *closo* series. If a metal is inserted in the carborane skeleton, a metallacarborane are obtained.

Earlier reports from M. F. Hawthorne[2,3,4,5] show that the orbitals from the open face of the $[C_2B_9H_{11}]^{2-}$ *nido* (structure derived from one vertex removal from the 12-vertex cage of *closo*-carborane) dicarbaborane dianion (dicarbollide anion) are similar to those from cyclopentadiene ion $[C_5R_5]^-$ as is depicted below.

This similarity has been verified by the synthesis of a broad range of mixed and full sandwich dicarbametallaboranes[6]. These are followed by other series of known clusters having a metal atom and one-, di-, three-, four- and five skeletal-carbon atoms and may posses *closo*, (up to 3 carbon atoms)

nido, *arachno* and *hypho* structures (not discussed here), where also the structural types lie in the borderline (especially in the case of carbon rich metallacarboranes).



Dicarbollide dianion Cyclopentadienyl anion

In principal bis-*icosahedral* complexes contain two dicarbollide ligands $[(C_2B_9H_{11})_2\ M]^{c-}$ [c=2, for M(II), c=1, for M(III) and c=0 for M(IV), respectively], which are similar to metallocene complexes. Main difference is the space geometry and the ligand charge (2-), which leads to preference of higher oxidation state of the metal (Co(III) NI(IV) and to a fact, that the metal-dicarbollides posses, in majority, a negative charge). This is delocalizated over a large surface of the molecule. The electron and charge delocalization are responsible for the properties of the metallacarboranes cluster namely thermal, chemical and electrochemical stability.

5.1. Nomenclature.

The boron cluster mostly used as extractant is the [*closo-commo*-(1,2-$C_2B_9H_{11})_2$-3,3'-Co(III)]$^-$ anion shown in figure 1 with numbering[7]. If the molecule is not substituted, the rotation barrier imposed by the partial charge of the carbon δ^+ is low and almost free rotation around the axis which intersects the B_{10}-Co- $B_{10'}$ is expected in solution.

Bulky groups attached to the pentagonal rim of the ligand planes adjacent to the cobalt(III) atom can hinder the free rotation or an *exo*-bridge can definitively stop it.

Concerning the IUPAC nomenclature the name of the boron cluster drawn above is 3,3'-*commo*-cobalta-bis(undecahydro-1,2-dicarba-*closo*-dodecaborane)-(1-)ate which seems too complex and not easy practicable. Thus a *semi*-trivial name has been proposed and can bee found more frequently in the literature as bis (1,2-dicarbollido)-cobalt III (1-)ate. Hawthorne proposed the name[5] cobalt (III) bis (1,2-dicarbollide).

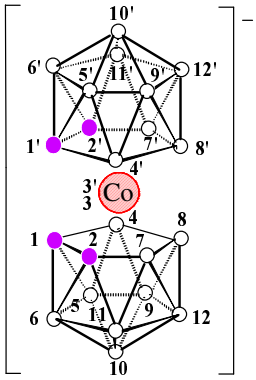


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Figure 1. The structure of COSAN anion.

Trivial or technical names have often appeared in the research reports, patents and even in the literature, such as Cosan (abbreviation from cobaltacarborane, Co-sandwich).

5.2. The main properties of Cosan.

An advantage of using Cosan is also that it is a diamagnetic molecule, which allows easy characterization of its derivatives by ^{11}B, ^{13}C and ^{1}H-NMR spectroscopy[8].

The close electron shell of the cobalt(III) atom and dispersion of the negative charge over the large surface of Cosan lines up this anion among members of a family of so called lowest coordinating[9,10] low nucleophilic ions[11].

X-ray analysis of **1**$^{-}Cs^{+}$[12], or **1**$^{-}Et_3NH^{+}$[13] salts show a large size of the anion, where for instance the mean distance between opposite poles B_{10}-Co-$B_{10'}$ is about 7.820 Å (in comparison with the size of the diagonal of the main plan in calixarene, where this distance is about 7.20 Å).

The Cosan ligand posses high thermal and chemical stability, properties induced by the "pseudoaromaticity" of the anion and the completely filled electronic shell of the Co(III) cation. Co is sterically shielded by two bulky dicarbollide cages, making it chemically intact.

The cesium salt of Cosan is stable toward HNO_3 up to 2 M for several days in contact. Above this concentration a slow hydroxylation takes place. The cage is slowly degraded upon treatment with concentrated solutions of NaOH or KOH in protic solvents.

Cosan **1** can be easily substituted in the position of $B_{8,8'}$ of its hydridic hydrogens by a variety of nucleophiles (Nu^{-}), which leads to the formation of B_8 –Nu, $B_{8,8'}$-Nu_2. Those positions close to the cation are identified as the faces with highest electronic density[14]. Thus, one example is the nucleophilic attack to B_8 by dioxan with formation of zwitterionic[15] dioxonium-Cosan **2** (see below) in

high yield. The reaction runs in the presence of dimethylsulfate (DMS) in acidic medium using dioxane as solvent.

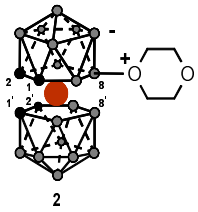

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Figure 2. The structure of the zwitterionic dioxonium-Cosan **2**.

5.3. Calix[4]arene in *cone* conformation bearing a combination of Cosan and CMPO groups.

Calix[4]arenes bearing at the narrow or wide rim four CMPO groups show much better extraction results for lanthanides and actinides than CMPO itself (see discussion in chapter 3). Halogene derivatives of Cosan **1** were designed more than 25 years ago for efficient extraction of $^{137}Cs^{+}$ and $^{90}Sr^{2+}$ from highly acidic solutions[16,17]. Our goal is to combine CMPO with Cosan functions on the narrow rim of the calix[4]arene skeleton. Thus, we synthesized, a series of calix[4]arene derivatives ready to be modified by introducing of Cosan derivatives. The samples were sent to Rez for further substitution with Cosan.

The CMPO should be attached to the narrow rim via an oligomethylene spacer and the Cosan via a diethyleneglycol spacer. The CMPO functions are introduced to the calix[4]arene skeleton using the usual strategy, while for the introduction of Cosan a ring opening reaction of the Cosan derivative **2** is used (see figure 2, where X represents the deprotonated calixarene).

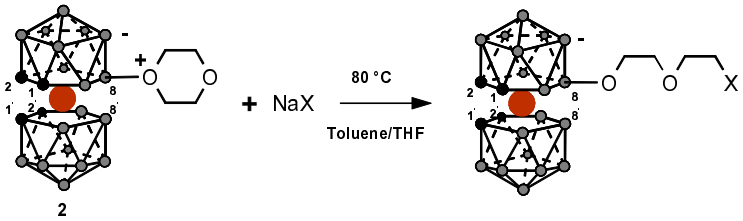

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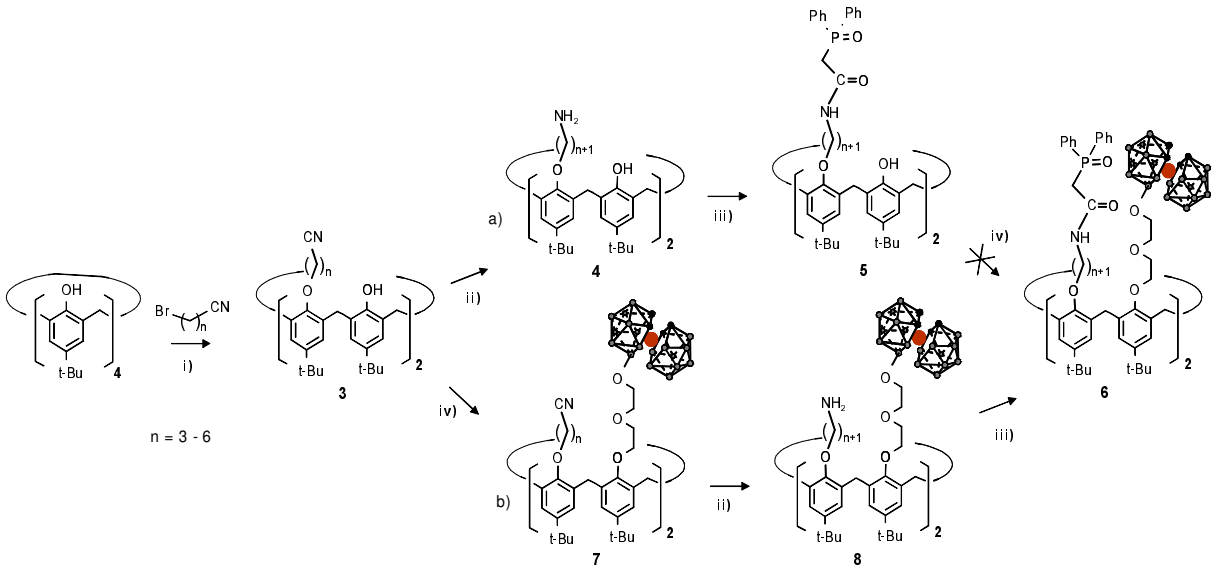
Figure 2. The ring opening reaction of Cosan **2**.

Two ways to synthesize the target calixarenes, bearing CMPO and Cosan functions may be considered here:

a) introduction of CMPO before Cosan: after the first O-alkylation of *t*-butylcalix[4]arene with ω-bromoalkylnitriles (this step is common for both pathways) the cyano groups were reduced. The

resulting di-amine **4** was acylated with N-AE to achieve the diCMPO **5**. Unfortunately, the final O-alkylation of the remaining hydroxyl groups with Cosan **2**, occurs simultaneously with the alkylation of the methylene groups of the CMPO functions leading to a mixture of compounds.

b) Introduction of Cosan before CMPO: The exhaustive O-alkylation of the 1,3-diethers **3** with Cosan **2**, followed by the reduction of the cyano groups give precursors **8**. The formed di-amines were N-acylated with N-AE to achieve the desired compounds **6 (*cone*)**[*]. In the case of n=4, compond **6 (*1,3-alt*)** was also prepared following the same strategy. The O-alkylation of the dinitrile **3** with Cosan **2** in the presence of Cs_2CO_3 afforded the target compound in 48 % yield.



Scheme 1. Strategy to introduce CMPO and Cosan functions at the narrow rim of a calix[4]arene in the *cone* conformation. i) K_2CO_3, CH_3CN, reflux; ii) BH_3SMe_2, THF, rt, for cyano groups; hydrazine, boiling ethanol for phthalimido groups; iii) N-AE, NaH, THF, 60 °C; iv) dioxonium-Cosan **2**, NaH, toluene/THF, 80 °C.

We have also tried to use phthalimide protected ω-bromoalkylamines for the O-alkylation of *t*-butyl calix[4]arene, but sometimes these groups lead to sterical problems during the subsequent attachment of the Cosan derivative which is reflected in a low reaction velocity and lower yields. These disadvantages were tried and observed in the case of n=3.

Summarising the obtained results we have chosen ω-bromoalkylnitriles as alkylating agents for the first O-alkylation step. Since the pathway b) is the only way leading to the desired product in the further syntheses Cosan should be introduced before CMPO.

We have prepared various CMPO/Cosan calixarene derivatives **6** which have different length of the alkyl chain by which CMPO is connected (n =3-7) (see vertical axis in Figure 3). Among them, the

[*] Cesium cations, which compensate the charges of Cosan calixarene derivatives are omitted in all Schemes.

best extraction results were obtained for n=4. Therefore, we prepared also compounds which preserve the same length of the spacer (n=4), but differ in ratio CMPO/Cosan functions such as tetraCosan[18], monoCMPO/triCosan, triCMPO/monoCosan and tetraCMPO[19] calix[4]arene derivatives (horizontal axis).

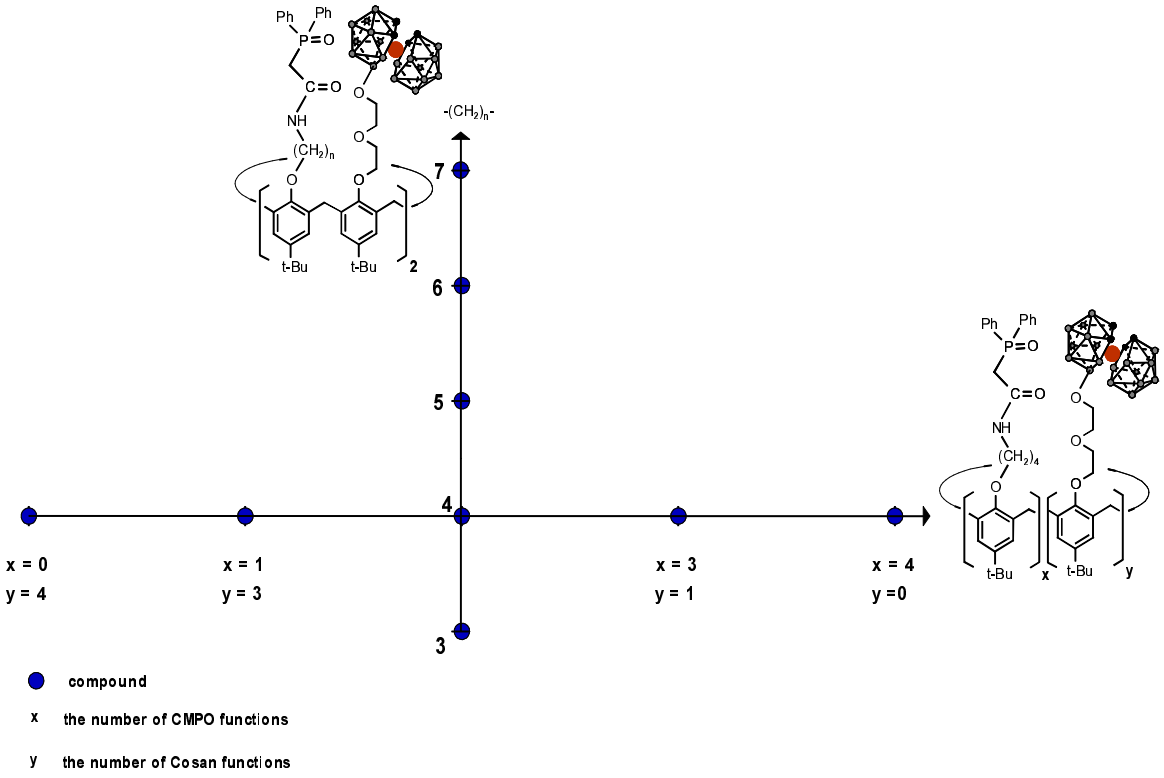
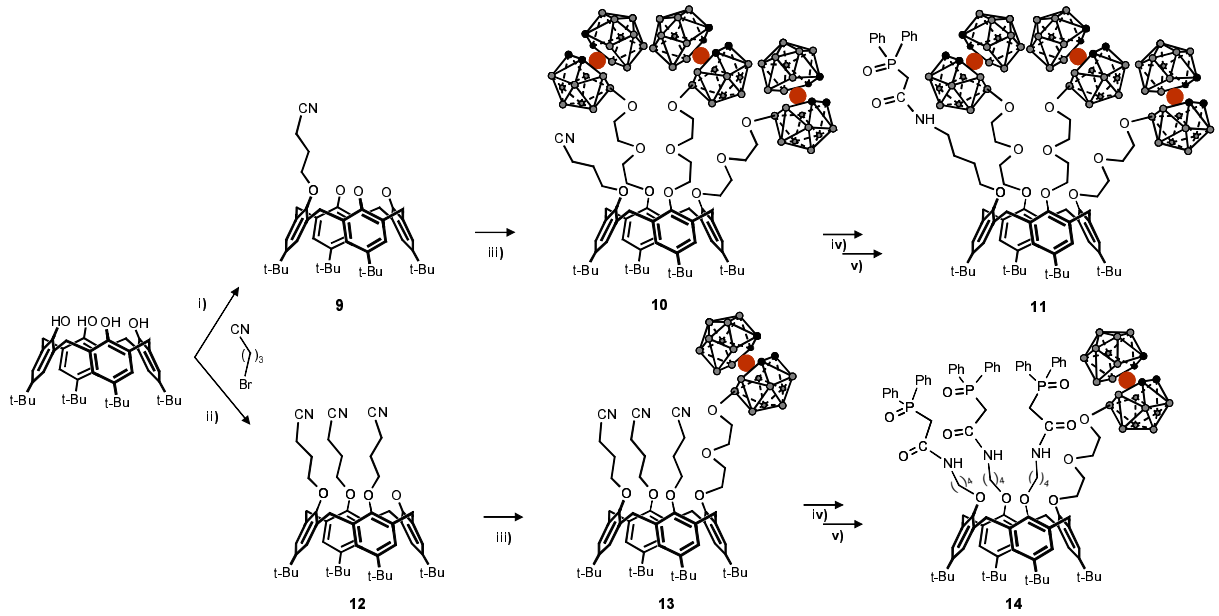


Figure 3. Synthesized compounds which bear Cosan/CMPO ligating functions on the same side of the calix[4]arene in the *cone* conformation.

The synthesis starts with mono-[20] or tri-O-alkylation[21] of *t*-butylcalix[4]arene with bromo-butyronitrile as illustrated in the Scheme 3. The subsequent introduction of Cosan, reduction of cyano groups and final acylation of the respective amines with N-AE afforded the desired compounds **11**, **14**.



Scheme 3. The synthesis of monoCMPO/triCosan, triCMPO/monoCosan derivatives.
i) K_2CO_3, CH_3CN, refulxed; ii) $Ba(OH)_2x8H_2O$, BaO, DMF, rt; iii) dioxonium-Cosan **2**, NaH, toluene/THF, 80 °C; iv) BH_3SMe_2, THF, rt; v) N-AE, NaH, THF, 60 °C.

In Mainz were synthesized di-ethers as **3** (n=3-7), mono ether **9** and tri-ethers **12**, which were sent to Rez. To complete the picture, reference compounds **15** and **17** were additionally obtained (see Figure 4).

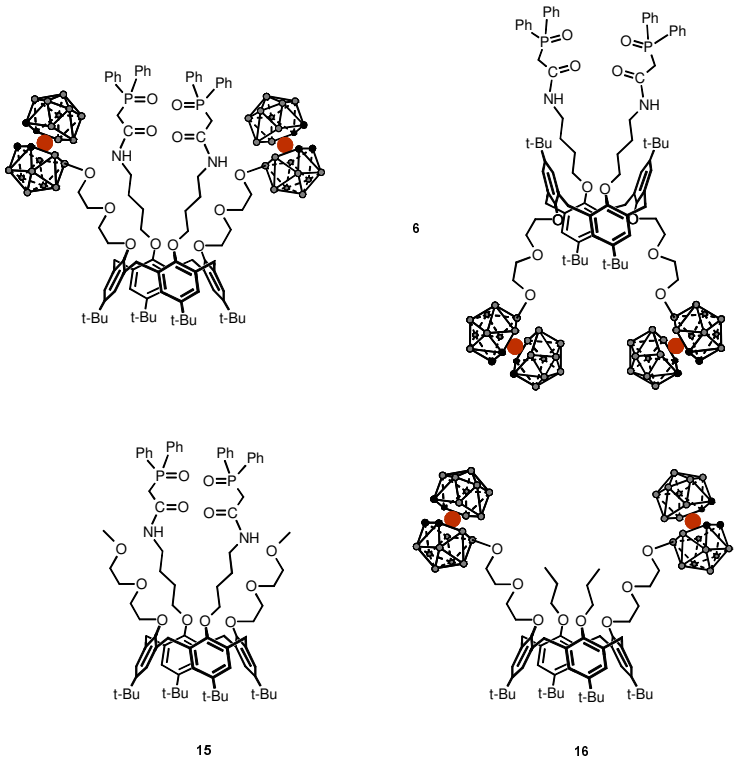
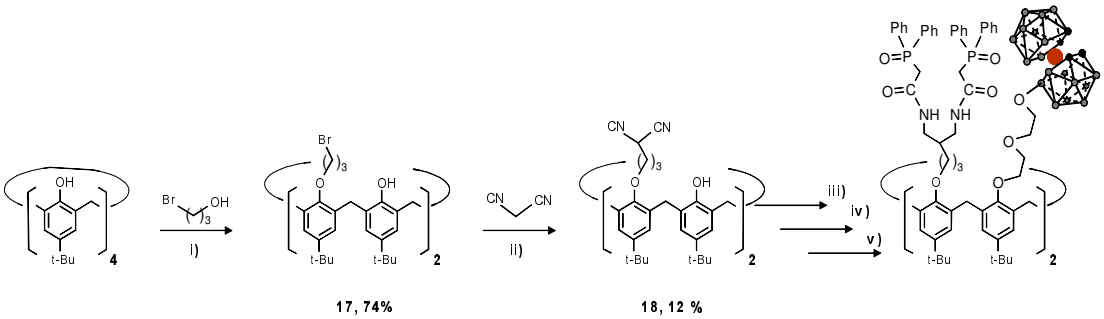


Figure 4. Calix[4]arene based extractant compounds for Am(III) and Eu(III) bearing CMPO and Cosan functions.

Compound **15** bears two CMPO and two diethyleneglycol residues without presence of Cosan in the molecule, while compound **17** bears only Cosan residues and two propoxy groups instead of CMPO. Extraction of trivalent cations (Eu, Am) from aqueous (nitric acid) solution was checked* for all obtained compounds, using HMK/TPH (2-octanone/hydrogenated tetrapropylene 1:1) or dichloroethane (DCE) and also nitrobenzene (NB) as organic solvents. Both isomers of compound **6** are highly efficient extractants for trivalent radionuclides (Eu, Am) even at low concentrations (<< 1 mM) significantly better than the best previously reported narrow and wide rim CMPO-calix[4]arenes **16** and **18**[22,23,19]. An "*intramolecular*" synergistic effect may exist in the case of **6 (*cone*)**. Therefore, a comparison of extraction ability was done for **6 (*cone*)**, **6 (*1,3-alt*)** with 1:1 mixture of di-CMPO **15** and di-Cosan **17**. The extraction results show that both calixarenes **6** bearing two CMPO and two Cosan groups on the same calixarene skeleton are much better extractants than the mixture **15/17**[24]. Among the isomers **6** the *cone* one is slightly better extractant than the *1,3 alternate* one (ten times).

In conclusion, not only two CMPO combined with two Cosan on a common platform is a sufficient condition to obtain the optimum in extraction of trivalent cations but also their orientation, like in **6 (*cone*)**. The structure of extracted species is not known, but it can be assumed that two anionic functions would partly neutralize the charge of the complex, where the cation is bound by two bidentate CMPO functions. Thus, the high extraction efficiency of **6 (*cone*)** may be a result of a kind of "*intramolecular*" synergistic or cooperative effect.



Scheme 4. The proposal synthesis of the tetraCMPO/diCosan derivative.

i) Mitsunobu conditions; ii) LDA, THF, –78 °C; iii) Cosan **2**, NaH, Toluene/DME, 80 °C; iv) BH_3SMe_2, THF, rt; v) N-AE, NaH, THF, 60 °C.

As we observed two CMPO combined with two Cosan groups achieve the optimum extraction results, but we wanted to explore further the field of increasing extraction efficiency for trivalent cations by

* The extraction experiments were done by Dr. Pavel Selucký from Nuclear Research Institute. Rez Plc 250 68 Rez near Prague, Czech Republic

changing the ratio CMPO/Cosan to 4/2 in a common platform. Therefore, a proposal strategy to achieve such a type of extractant is synthesizing now according to the Scheme 4.

The synthesis starts with di-O-alkylation of *t*-butylcalix[4]arene with ω-bromo-alcohol under Mitsunobu's conditions. The length of the alkyl chain under which CMPO is linked to the narrow rim may vary from 2 to 4. In the next step, the alkyl chain is prolonged by the formation of a new C-C bond, when the bromoalkyl calixarene derivative **17** reacts with the acidic proton of dinitrile of malonic acid. During the further alkylation of tetranitrile **18** with Cosan **2** calix[4]arene is fixed in the *cone* conformation. Finally the reduction of nitrile groups, followed by reaction with N-AE should afford the tetraCMPO diCosan calix[4]arene derivative. The synthesis is now in the step of obtaining compound **18**. Further attachment of Cosan and CMPO will carried out in Rez. The synthesis of tetranitrile **18** (n=2) is in progress and also compound **18** (n=4) is also envisaged.

Reaction of dibromoderivative **17** (n=3) with dinitrile of malonic acid was tried using several reaction conditions (see table 3), where a mixture of compounds was obtained in all cases. This is due to the elimination reaction which takes place in competition with substitution (see Figure 5). Tetranitrile **18**, was isolated in 12 % yield when the reaction was running in the presence of lithium diisopropylamide (LDA).

conditions	formed compounds
a) 8 mol LDA/1 mol **17**, THF, –78 °C for 1 h and then at rt additionally 1 h, followed by refluxing for further 4 h. The reaction was checked by tlc.	After crystallization **18** is isolated in 12 % yield. In the mother liquor **19** and **20** were identified by Mass-spectra.
b) 5 mol NaH/1 mol **17**, glyme, at low temp. for 1 h and further under refluxing for 4 h. The reaction was followed by tlc.	the following compounds: **21-26** were identified by ^{1}H-NMR and additionally by Mass-spectra
c) 2.5 mol K_2CO_3/ 1 mol **17**, DMF, rt.	a mixture of compounds formed by: **22-24** and starting compound, identified by identical way as is b).

Table 3. Conditions and the obtained compounds during the reaction of the substitution of protons from malonodinitrile by dibromo derivative **17**.

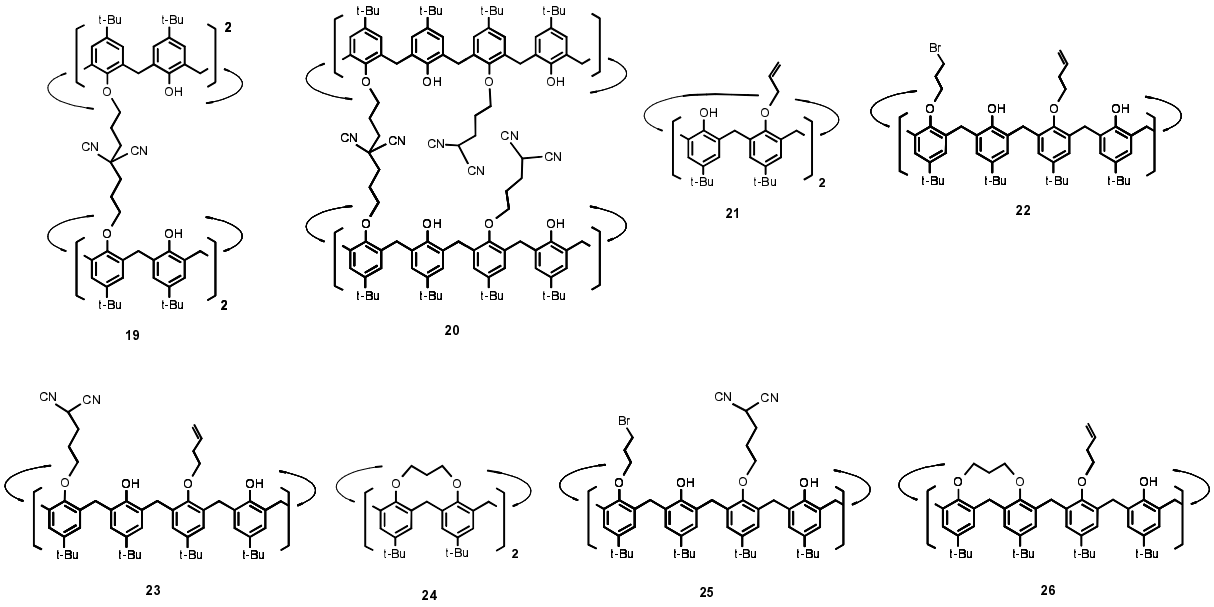
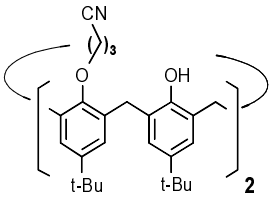


Figure 5. The structures of by products obtained under the conditions of substitution the protons from malonodinitrile by dibromo derivative **17**.

Some of compounds were partly isolated by column chromatography and analyzed by Mass and additionally by ^{1}H-NMR spectroscopy. For those which are isomers, identified by Mass spectrum their structures were further established according to ^{1}H-NMR spectra.

5.4. Experimental part.

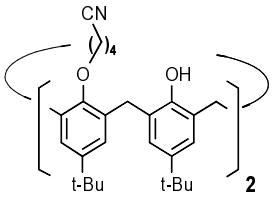
5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-dicyanopropoxy-calix[4]arene 3 (n=3) (*cone*)



To a suspension of *t*-butyl calix[4]arene (5.0 g, 7.7 mmol) in acetonitrile (175 ml) was added K_2CO_3 (2.3 g, 16.9 mmol). After 1 h, 4-Bromobutyronitrile (1.68 ml, 16.9 mmol) was added dropwise and the reaction mixture was refluxed under nitrogen for 2 days. The reaction was stopped and the solvent was evaporated under reduced pressure until a white residue resulted. The residue was dissolved in chloroform (150 ml) and washed with water (3x200 ml). After phases separation, the organic phase was dried over $MgSO_4$, evaporated until the formation of the solid . The 1,3-*syn*-diether **3** (n=3) was isolated by crystalization from chloroform/methanol (30 ml, 1:3) as white powder (4.0 g, 70 %), mp 345-347 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.97, 1.25 (2s, 18/18H, *t*-Bu), 2.31 (m, 4H, -CH_2-), 3.02 (t, 4H, ^{3}J = 6.9 Hz, -CH_2-O), 3.35, 4.14 (2d, 4/4H, ^{2}J = 13.2 Hz, Ar-CH_2-Ar), 4.07 (t, 4H, ^{3}J = 5.5 Hz, -CH_2-CN), 6.83, 7.03 (2s, 4/4H, Ar*H*), 7.39 (s, 2H, O*H*).

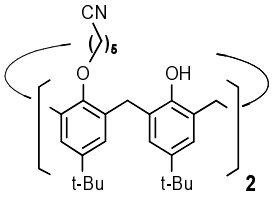
5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-dicyanobutyloxy-calix[4]arene 3 (n=4) (*cone*)



The compound **3** (n=4) was obtained followed the same procedure mentioned above. white powder (3.5 g, 57 %), mp 237-239 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.92, 1.28 (2s, 18/18H, *t*-Bu), 2.12, 2.13 (2m, 4/4H, -CH_2-), 2.64 (t, 4H, ^3J = 6.9 Hz, -CH_2-CN), 3.31, 4.19 (2d, 4/4H, ^2J = 12.8 Hz, Ar-CH_2-Ar), 4.00 (t, 4H, ^3J = 6.6 Hz, -CH_2-O), 6.76, 7.05 (2s, 4/4H, Ar*H*), 7.16 (s, 2H, O*H*).

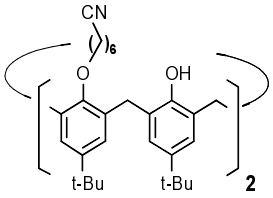
5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-dicyanopentyloxy-calix[4]arene 3 (n=5) (*cone*)



The compound **3** (n=5) was obtained following the same procedure as described above;. white powder (2 g, 31 %), mp 208-209 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.95, 1.28 (2s, 18/18H, *t*-Bu), 1.85, 1.86, 2.03, (3t, 8/4H, ^3J = 6.2, Hz, -CH_2-), 2.45 (t, 4H, ^3J = 6.6 Hz, -CH_2-CN), 3.30, 4.22 (2d, 4/4H, ^2J = 12.8 Hz, Ar-CH_2-Ar), 3.97 (t, 4H, ^3J = 6.2 Hz, -CH_2-O), 6.79, 7.04 (2s, 4/4H, Ar*H*), 7.40 (s, 2H, O*H*).

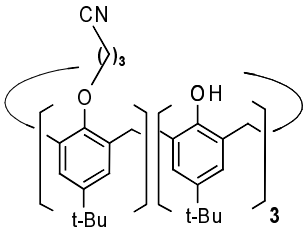
5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-dicyanohexyloxy-calix[4]arene 3 (n=6) (*cone*)



The compound **3** (n=6) was obtained followed the same procedure as above. white powder (4.3 g, 66 %), mp 86-87 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.96, 1.27 (2s, 18/18H, *t*-Bu), 1.63-2.01 (m, 16H, -CH_2-), 2.40 (t, 4H, ^3J = 6.9 Hz, -CH_2-CN), 3.30, 4.25 (2d, 4/4H, ^2J = 12.8 Hz, Ar-CH_2-Ar), 3.96 (t, 4H, ^3J = 6.6 Hz, -CH_2-O), 6.80, 7.04 (2s, 4/4H, Ar*H*), 7.54 (s, 2H, O*H*).

5,11,17,23-Tetra-*t*-butyl 26,27,28-trihydroxy 25 -cyanopropoxy-calix[4]arene 9 (n=3, x=1, y=3) (*cone*)

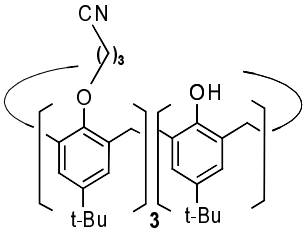


To a suspension of *t*-butyl calix[4]arene (8.0 g, 12.3 mmol) in acetonitrile (320 ml) was added K_2CO_3 (0.8 g, 6.4 mmol). After 1 h 4-Bromobutyronitrile (16.8 ml, 11.2 mmol) was dropwise added and the reaction mixture was refluxed for 2 days. The reaction mixture was worked up using a similar procedure as for the 1,3-syn-di-ethers. The mono-alkylated compound **3** was isolated after several crystallizations from chloroform/methanol as white

powder (2 g, 24 %). The 1,3-syn-diether was also obtained (2.1 g, 25 %) as side product. mp 213-215 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.17, 1.20, 1.21 (3s, 18/9/9H, *t*-Bu), 2.43 (m, 2H, -CH_2-), 3.06 (t, 4H, ^3J = 6.9 Hz, -CH_2-CN), 3.44, 4.23 (2d, 2/2H, ^2J = 13.9 Hz, Ar-CH_2-Ar), 3.34, 4.25 (2d, 2/2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 4.21 (t, 4H, ^3J = 6.2 Hz, -CH_2-O), 6.99, 7.05 (2d, 2/2H, ^4J = 2.57 Hz, Ar*H*), 7.06, 7.08 (2s, 2/2H, Ar*H*), 9.34, 10.00 (2s, 2/1H, O*H*).

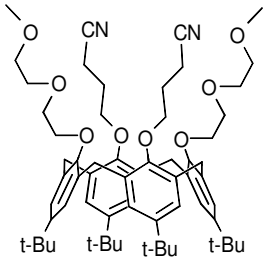
5,11,17,23-Tetra-*t*-butyl 25 -monohydroxy 26,27,28-tricyanopropxy-calix[4]arene 12 (n=3, x=3, y=1) (*cone*)



To a suspension of *t*-butyl calix[4]arene (8.0 g, 12.3 mmol) in DMF (200 ml) was stirred at 60 °C. After 1 h the temperature was cooled to rt and $Ba(OH)_2x8H_2O$ (13.6 g, 43.1 mmol), BaO (12.7 g, 82.9 mmol) and 4-Bromobutyronitrile (12.2 ml, 123.3 mmol) were added. after 3 days, the reaction was stopped by added water (200 ml). The further work up was similar with that described above obtaining the desired tri-O-alkylated compound as white powder (6.5 g, 68 %). mp 216-218 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.80, 1.32, 1.34 (3s, 18/9/9H, *t*-Bu), 2.24 (m, 6H, -CH_2-), 2.72 (m, 6H, -CH_2-CN), 3.25, 4.22 (2d, 2/2H, ^2J = 13.6 Hz, Ar-CH_2-Ar), 3.30, 4.20 (2d, 2/2H, ^2J = 13.2 Hz, Ar-CH_2-Ar), 3.89-4.03 (m, 6H, -CH_2-O), 4.21 (t, 4H, ^3J = 6.2 Hz, -CH_2-O), 4.73, (s, 1H, O*H*), 6.49, 5. 05 (2d, 2/2H, ^4J = 2.2 Hz, Ar*H*), 7.08, 7.16 (2s, 2/2H, Ar*H*).

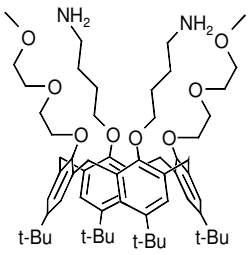
5,11,17,23-Tetra-*t*-butyl 25,27-di-[2-(2methoxyethoxy)]- 26, 28 -dicyanopropoxy-calix[4] arene (*cone*)



A suspension of diether (3.1 g, 3.6 mmol) in DMF (40 ml) and NaH (0.33 g, 14.5 mmol) was stirred at rt for 1 h under nitrogen. A solution of 4-bromobutironitrile (1.45 g, 14.5 mmol) in DMF (5 ml) was added. The mixture was stirred under nitrogen at room temperature for 6 days. The solvent was removed under reduced pressure when a solid was obtained. The residue was dissolved in chloroform (40 ml) and washed several times with water (150 ml). After phases separation, the organic solution was dried over $MgSO_4$. The solvent was removed under reduced pressure when a solid residue was obtained. The product was isolated via crystallization from chloroform/methanol (50 ml, 1.3) as white powder (2.8 g, 80 %). mp 118-120 °C

^{1}H-NMR (400MHz, $CDCl_3$) δ 0.82, 1.29 (2s, 18/18H, *t*-Bu), 2.38 (m, 4H, -CH_2-), 2.68 (t, 4H, ^3J = 7.3 Hz, -CH_2-NH), 3.11, 4.33 (2d, 4/4H, ^2J = 12.5 Hz, Ar-CH_2-Ar), 3.37 (s, 6H, CH_3), 3.56, 3.68, 3.78, 3.93 (4t, 4/4/4/4H, ^3J = 5.1/4.09/6.4/6.4 Hz -CH_2- CH_2), 4.05, (t, 4H, ^3J = 7.3 Hz, -CH_2-O), 6.48, 7.06 (2s, 4/4H, Ar*H*).

5,11,17,23-Tetra-*t*-butyl 25,27-di-[2-(2methoxyethoxy)]- 26, 28 -diaminobutyloxy-calix[4] arene (*cone*)

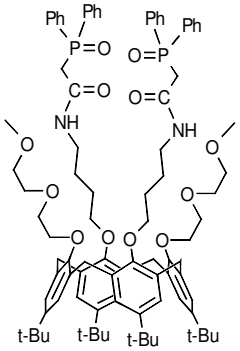


A solution of dinitrile derivative (3.2 g, 3.25 mmol) in ethanol/THF (1:4, 50 ml) and aqueous NaOH (6 %, 40 ml) was stirred with Raney-Ni under hydrogen atmosphere. After the hydrogen uptake was complete the catalyst was removed by filtration through sea sand and the solvent was removed under reduced pressure. The white residue was extracted with chloroform, the solution washed several times with water, dried ($MgSO_4$) and evaporated to dryness. The residue was triturated with CH_2Cl_2/hexane (1:10, 10 ml) to give a white powder, yield 1.7 g, 53 %. mp 98-99 °C.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.02, 1.09 (2s, 18/18H, *t*-Bu), 1.56, 2.01 (2m, 4/4H, -CH_2-), 2.79 (t, 4H, ^3J = 7.1 Hz, -CH_2-NH), 3.10, 4.36 (2d, 4/4H, ^2J = 12.6 Hz, Ar-CH_2-Ar), 3.37 (s, 6H, CH_3), 3.54, 3.65, 3.96, 4.11 (4t, 4/4/4/4H, ^3J = 5.1/4.09/6.4/6.4 Hz -CH_2- CH_2), 3.84, (t, 4H, ^3J = 7.8 Hz, -CH_2-O), 6.71, 6.80 (2s, 4/4H, Ar*H*).

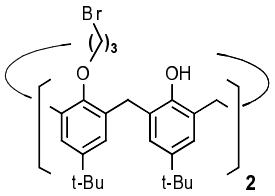
5,11,17,23-Tetra-*t*-butyl 25,27-di-[2-(2methoxyethoxy)]- 26, 28 -diCMPObutyloxy-calix [4]arene 15 (*cone*)

The desired compound was obtained using the same procedure as that used for the CMPO calixarene derivatives from the amines. The expected compound was isolated by column chromatography (chloroform/ methanol, 9.8:0.2) as white powder (320 mg, 55 %). mp 123-125 °C, FD-MS, (M^++Na) m/z = 1501.9.



^{1}H-NMR (400MHz, DMSO-d_6) δ 0.96, 1.06 (2s, 18/18H, *t*-Bu), 1.42, 1.82 (2m, 4/4H, -CH_2-), 3.05 (t, 4H, ^3J = 6.4 Hz, -CH_2-NH), 3.10, 4.27 (2d, 4/4H, ^2J = 12.6 Hz, Ar-CH_2-Ar), 3.20 (s, 6H, CH_3), 3.42, 3.56, 3.88, 3.97 (4t, 4/4/4/4H, ^3J = 4.4/4.09/5.7/5.4 Hz -CH_2- CH_2), 3.51 (d, 4H, ^2J = 14.3 Hz, -CH_2-P), 3.69, (t, 4H, ^3J = 7.1 Hz, -CH_2-O), 6.68, 6.86 (2s, 4/4H, Ar*H*), 7.47-7.80 (2m, 12/8H, *m*, *p*-Ph_2H, *o*-Ph_2H,), 7.96 (t, 2H, ^3J = 5.4 Hz, N*H*).

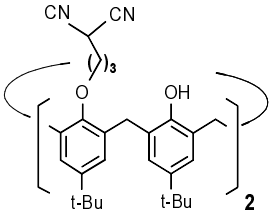
5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25,27-dibromopropoxy-calix[4]arene 17 (n=3) (*cone*)



A solution of triphenylphosphine (6,0 g, 23 mmol) in THF (40 ml) was cooled down to 0-5°C (ice bath) and di-*iso*-propyl azodicarboxylate (DIAD) (23 mmol, 4.5 ml) was added dropwise under nitrogen atmosphere. After 30 min a white precipitate was formed and a suspension of *t*-butyl calix[4]arene (5.0 g, 7.7 mmol) and *3*-bromo-propanol (2 ml, 23 mmol) in THF (100 ml) and was slowly added. The reaction mixture was stirred 1 h at 0-5°C and then left to warm to rt when the suspension became yellowish clear (5 h). The solvent was partially removed under reduced pressure until a pale yellow precipitate formed. This was filtered, washed with water (50 ml) and methanol (30 ml) to give the pure product as white powder (5 g, 74 %). mp 336-337 °C

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.00, 1.25 (2s, 18/18H, *t*-Bu), 2.51 (m, 4H, -CH_2-), 3.33, 4.25 (2d, 4/4H, ^2J = 12.8 Hz, Ar-CH_2-Ar), 4.00 (t, 4H, ^3J = 6.6 Hz, -CH_2- O), 4.42 (t, 4H, ^3J = 5.2 Hz, Br-CH_2-), 6.86, 7.03 (2s, 4/4H, Ar*H*), 7.67 (s, 2H, O*H*).

5,11,17,23-Tetra-*t*-butyl 26,28-dihydroxy 25, 27-di-dinitrilebutyloxy-calix[4]arene 18 (n=3) (*cone*)



Freshly distilled THF (10 ml) is cooled at –78 °C when LDA (2.3 ml, 4.6 mmol) is added dropwise. Thus, a dark red solution is formed. A solution of dinitrile of malonic acid (0.3 ml, 4.2 mmol) in THF (10 ml) is added dropwise and the color of the reaction mixture turns in yellow. After a certain time (30 min) the solution of dibromo calix[4]arene **10** (0.5 g, 0.56 mmol) in THF (10 ml) is added, while the temperature is increasing at rt (~1 h) and then until refluxing. After 4 h, the reaction mixture was stopped according to tlc (at least three spots were present during to the last 2 h) and washed several times with water. The organic phase was dried over $MgSO_4$, followed by evaporation of the solvent under reduced pressure until the residue. The desired compound **11** (n=3) was isolated by crystallization from chloroform/methanol (25 ml, ~1:2) as yellow powder (60 mg, 12 %). mp 189-191 °C, FD-MS, (M^++H) m/z = 860.6

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.18-1.20 (2s+m, 18/18/2H, *t*-Bu, -C*H*), 2.46 (m, 4H, -CH_2-), 2.86 (t, 4H, ^3J = 7.7 Hz, -CH_2-CH), 3.39, 4.17 (2d, 4/4H, ^2J = 12.8 Hz, Ar-CH_2-Ar), 4.12 (bt, 4H, O-CH_2-), 7.00, 7.07 (2s, 4/4H, Ar*H*), 8.99 (s, 2H, O*H*).

5.5. References.

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Chapter 6

Perylene imide dyes attached to the calix[4]arene fixed in *1,3-alternate* conformation.

6. Introduction and synthesis

A joint project with the research group in Würzburg, which is specialized in perylene dyes was developed concerning the attachment of these dyes to the calix[4]arene skeleton. The purpose of this dyes calix[4]arene derivatives is the assessment of conformational effects on optical properties. A first attempt to attach such dyes to the calix[4]arene skeleton was described by Vysotsky et all[1], bis-calix[4]arenes derivatives fixed in *cone* conformation connected via perylene-bisimide dye spacers. The electron-rich calixarene act as fluorescence quencher for the local environment of perylene bisimides making them atractive for calixarene-based fluorescence sensor. Therefore, calix[4]arene-based dye cascades cofacially positioned is reported[2]. Here, calix[4]arene is fixed in the *cone* conformation, while the perylene bisimide dyes in up to five have an array arrangement. Also, the *1,3-alternate* platform could replace the *cone* one, difference which should be reflected in their photophysical properties. A first attempt in using calix[4]arene derivative fixed in *1,3-alternate* conformation-based for perylene dyes derivatives is functionalization the platform to the wide rim and study their photophysical properties.

A short description of perylene dyes may be appropriate. Perylene bisimide are known as fluorescent dyes and redoxsystems which have been introduced into cyclic,[3] dendritic,[4] polymeric,[5] liquid-crystalline,[6] and mesoscopic[7] systems via covalent linkage or self-assembly. Concerning their geometry they can be considered as nanosized planar building blocks that can be further functionalized starting with the 3,4:9,10-perylene tetracarboxylic dianhydride **1** (see Figure 1). Generally, 3,4:9,10-perylene tetracarboxylic (dicarboxyimide) **3** and monoanhydride monoimide **2** are condensation products of corresponding dianhydride **1** with amines[8,9]. They have excellent resistance to light, heat and solvents.

Their lipophilicity is remarkable increased by substituting the hydrogens in the bay positions (1/6, 7/12) by alkyl/aryl/heterocycles groups (see Scheme 1). Some of products are used as dyes or pigments[10].

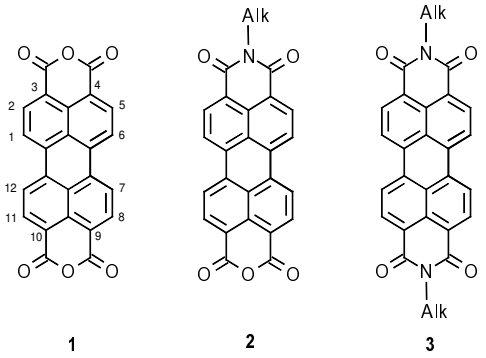
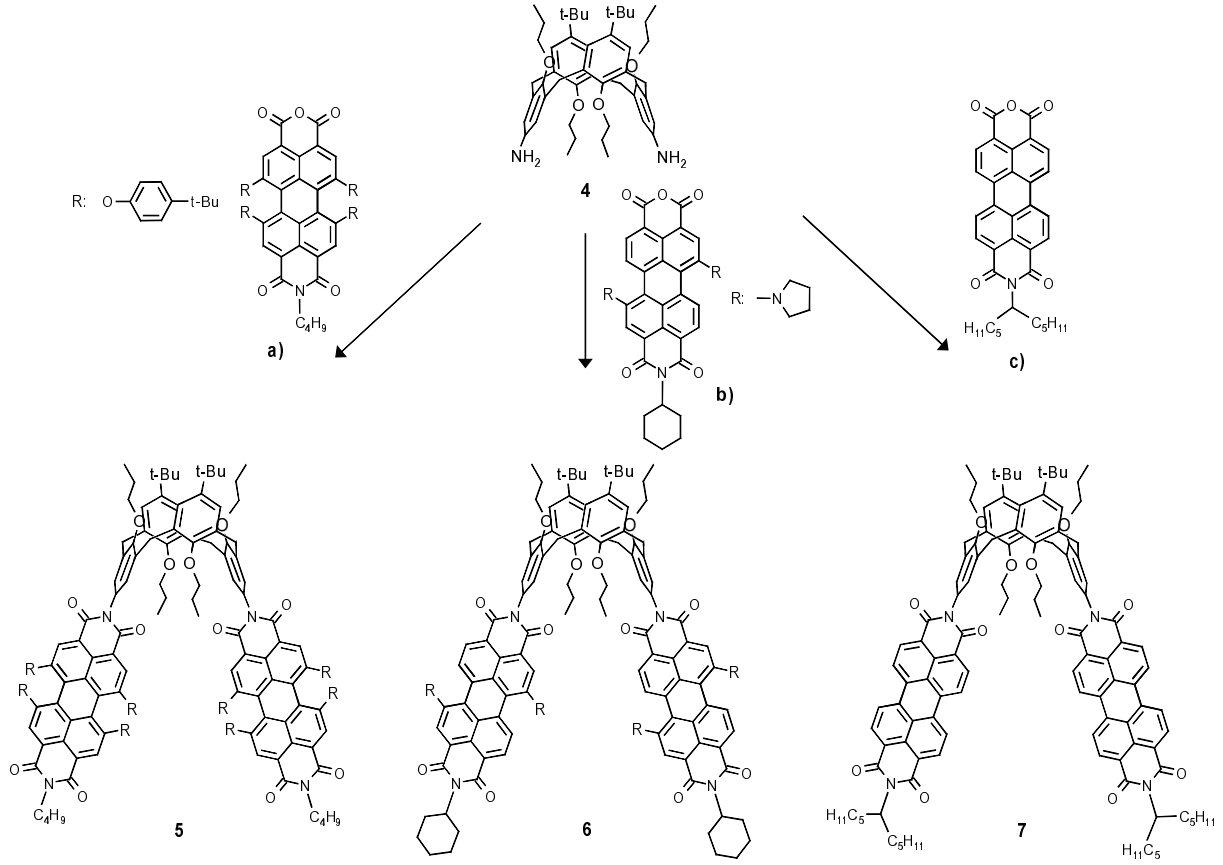


Figure 1. 3,4: 9,10-perylene tetracarboxilic dianhydride (**1**) and their mono-, bis-imides (**2**, **3**).

Perylene imides attached to the calix[4]arene skeleton by covalent linkage could lead to molecules with an extended cavity; to new chromo- or fluorophoric sensor molecules; and to larger building blocks for self-assembly via π-π interactions of the dyes structures.

We synthesized wide rim perylene imides calix[4]arene derivatives fixed in *1,3-alternate* conformation, where the perylene could be unsubstituted [**c)** orange] or substituted in the bay positions by four *t*-butylphenyloxy groups [**a)** dark red] or by two pyrrolidine rings **[b)** green]. The monoanhydride monoimides **a**, **b**, and **c** were given us from Würzburg.



Scheme 1. The synthesis of perylene calix[4]arene derivatives **5**, **6** and **7** fixed in *1,3-alternate* conformation.

The synthesis starts with diamine **4** (identical with diamine **17** in chapter 2), which is N-acylated by mono-anhydride mono-imide perylene derivatives to achieve the corresponding bis-unsymmetrical imides **5**, **6**, and **7** (see Scheme 1). The reaction conditions in cases of **5** and **6** follow similar procedure, namely $Zn(OAc)_2$ as catalyst in boiling pyridine for 2-3 days. For the hardly soluble **c**), quinoline was chosen as solvent and a higher reaction temperature about 150 °C for 14 h. The working up of reaction mixtures is similar for all three cases. It consists in treating the reaction with an aqueous solution of 0.1 N HCl (~10 ml). A colored (depending on the color of introduced dyes) precipitate is formed, which is filtered off and dissolved in dichloromethane (~5 ml). The solvent is evaporated and the residue is further dried at high vacuum.

The ^{1}H-NMR spectra of **5** and **6** show a purity about 85-90 % in both cases. Thus, the imidization reaction is almost quantitatively, but since the purification of such dye-calixarene derivatives is quite difficult, at least to achieve the "optical" purity, they were sent in Würzburg with this degree of purity as is shown for the case of compound **5** in Figure 2.

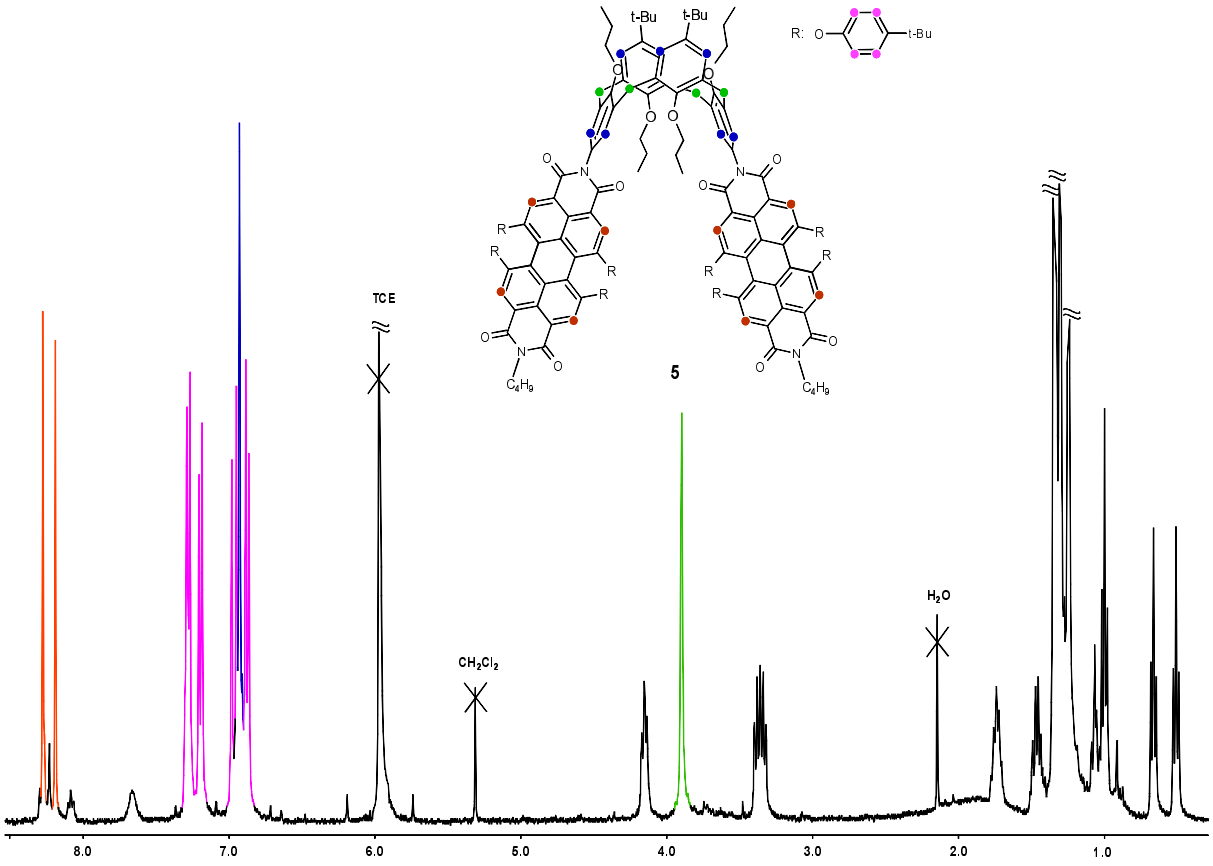


Figure 2. The ^{1}H-NMR spectrum in TCE (1,1,2,2-tetrachloethane) of compound **5**, before column separation.

As was explained, these difficulties consist in formation of aggregates (during column separation) of different sizes due to π-π stacking between perylene moieties, which are formed at a certain

concentration of methanol. The solvent used in some cases for the purification process is dichloromethane combined with a low concentration of methanol.

The distances between wide rim dyes fixed to the *cone* and *1,3-alternate* conformations are different. For this reason, differences in their photophysical properties of dyes calixarene derivatives fixed in *cone* and *1,3-alternate* conformations could be observed. Thus, similar compounds as **5**, **6**, and **7**, but fixed in *cone* conformation were synthesized in Würzburg. A comparison of their photophysical data is not yet available. The photophysical properties of the series of compounds fixed in *1,3-alternate* conformation are reported below.

6.1. ^{1}H-NMR characterization

As we mentioned before the ^{1}H-NMR spectroscopy is the most valuable tool to distinguish the different isomers based on pattern for the methylene bridge and aromatic protons. Thus, a close pair of doublets ($\Delta\delta$ = 0.1 ppm) shown in the ^{1}H-NMR spectrum is characteristic for the *1,3-alternate* isomer. The ^{1}H-NMR spectrum of amine derivative **4**, shows an AB-system (3.65/3.70, ^{2}J = 15.6 Hz) for the methylene bridges and two singlets for the aromatic protons (6.39/6.93). When the amine **4** is imidized by perylene derivatives, the pair of doublets corresponding to methylene bridges becomes even less separated especially in the case of **7**. In cases of **6** and **7**, the signal of the methylene bridges is down field shifted with 0.16, 0.11 ppm respectively in comparison with the chemical shift of the same signal in **5**. The chemical shifts of aromatic protons are very close to each other in comparison to starting amine, namely: 6.90/6.93 in **5**, 7.01/7.02 in **6** and 7.02/7.05 in **7**. A comparison of their ^{1}H-NMR spectra are shown in Figure 3.

The perylene units in compound **5** are chiral. Two naphthalene units of the perylene core are twisted under a certain angle[11,12] due to repulsions between the lone pair electrons of oxygen atoms of *t*-butylphenyloxy units. Thus, adjacent *t*-butylphenyloxy groups are oriented “up” and “down” of the perylene unit. Two diastereoisomers of compound **5** should exist under a pair of enantiomers (C_2-symmetry) and a mesoform (C_S-symmetry, the symmetry plane passes through *t*-butyl aromatic units). But, the ^{1}H-NMR spectrum shows a C_{2v}-symetrical compound which suggests that the movement “up” and “down” between *t*-butylphenyloxy units is too fast in NMR time scale.

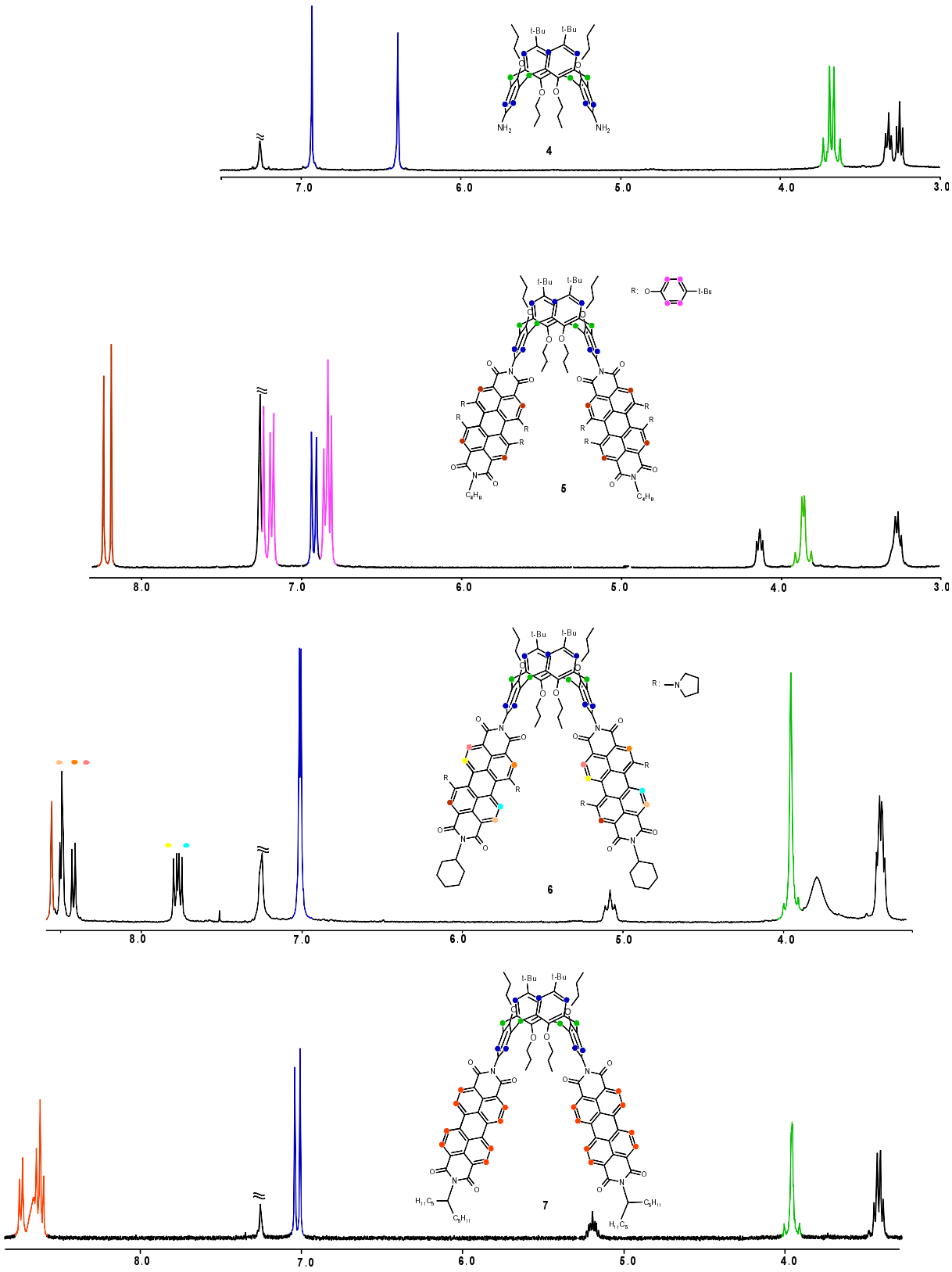
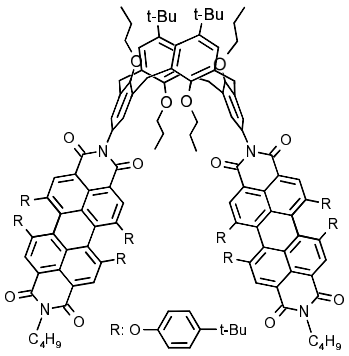


Figure 3. Comparison of the ^{1}H-NMR spectra ($CDCl_3$)of compounds **4**, **5**, **6** and **7**.

6.2. Experimental part

wide rim perylene calix[4]arene derivative 5



To a stirred clear solution of wide rim diamines **4** (20 mg, 0.0272 mmol) in pyridine (4 ml) is added monoimide mono-anhydride perylene (62.2 mg, 0.06 mmol), catalyst $Zn(OAc)_2$ (4 mg) and is refluxed under nitrogen atmosphere for 3 days. A solution of HCl (10 ml, 0.1N) is added and the stirring is continue for additional 30 min., when a dark red precipitate is formed. The precipitate is filter off and it is dissolved in dichloromethane (5 ml). The solvent is evaporated under reduced pressure and the formed residue is dry under high vacuum at 50 °C. The desired compound **5** is isolated by column chromatography in 28 % yield as red dark powder (CH_2Cl_2/Hexan = 60:40, R_f = 0.38), mp > 400 °C.

HR-MS (ESI in $CHCl_3$/Acetonitril) for $C_{184}H_{192}N_4O_{20}K$ $[M+K]^+$: M/z = 2816.3765; found M/z = 2816.3762

^{1}H-NMR (400MHz, $CDCl_3$) δ 0.41–0.45 (m, 6H, Alkyl-*H*), 0.57 (t, 6H, ^3J = 7.7 Hz, Alkyl-*H*), 0.79–0.88 (m, 6H, Alkyl-*H*), 0.94 (t, 6H, ^3J = 7.4 Hz, Alkyl-*H*), 1.22, 1.24, 129 (3s, 36/36/18H, *t*-Bu), 1.40, 1.66 (2m, 4/4H, -CH_2-), 3.82, 3.86 (2d, AB-system, 8H, ^2J = 17.0 Hz, Ar-CH_2-Ar), 3.22, 3.27 (m, 8H, O-CH_2), 4.12 (t, 4H, ^3J = 7.6 Hz, N-CH_2), 6.80, 6.85 (m, 16H, Phen-*H*), 6.90, 6.93 (2s, 4/4H, Ar-*H*), 7.16-7.25 (m, 16H, Phen-*H*), 8.18, 8.23 (2s, 4/4H; Per-*H*).

UV-Vis (CH_2Cl_2): λ (nm) [ε ($M^{-1}cm^{-1}$)]: 574 [82200].
Fluorescence (CH_2Cl_2): λ_{max} (nm): 609; Φ_{fl} = 0.44 in CH_2Cl_2, Standard: PSt (Φ_{fl} = 0.96 in $CHCl_3$).

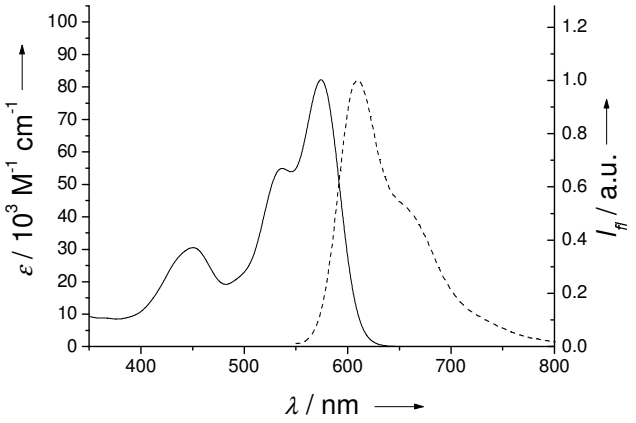
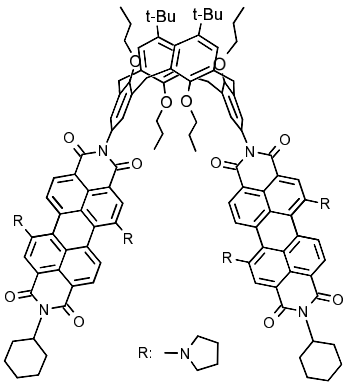


Figure 4. UV/Vis absorption (black, solid) and fluorescence emission spectrum (black dashed) (CH_2Cl_2, for both cases).

wide rim perylene calix[4]arene derivative 6



To a stirred clear solution of wide rim diamines **4** (20 mg, 0.0272 mmol) in pyridine (4 ml) is added monoimide mono-anhydride perylene (36.6 mg, 0.06 mmol), catalyst $Zn(OAc)_2$ (4 mg) and is refluxed under nitrogen atmosphere for 3 days. A solution of HCl (10 ml, 0.1N) is added and the stirring is continue for additional 30 min., when a green precipitate is formed. The precipitate is filter off and it is dissolved in dichloromethane (5 ml). The solvent is evaporated under reduced pressure and the formed residue is dry under high vacuum at 50 °C. The desired compound **6** is isolated by column chromatography in 8 % yield as green fine powder (CH_2Cl_2/Methanol = 97:3, R_f = 0.50). mp > 400°C.

HR-MS (ESI in $CHCl_3$/Acetonitril) for $C_{124}H_{132}N_9O_{12}$ $[M+NH_4]^+$: M/z = 1938.9995; found M/z = 1938.9990

^{1}H-NMR (400MHz, $CDCl_3$) δ 0.64, 0.73 (2t, 6/6H, ^3J = 7.6/7.5 Hz, Alkyl-*H*), 0.86–0.97 (m, 4H, Alkyl-*H*), 1.29 (s, 18H, *t*-Bu), 1.33–1.53 (m, 10H, Cy-*H*, Alkyl-*H*), 1.73–1.78 (m, 6H, Cy-*H*), 1.90–2.16 (m, 20H, Pyrr-*H*, Cy-*H*), 2.57–2.66 (m, 4H, Cy-*H*), 2.88 (bs, 8H, Pyrr-*H*), 3.37–3.42 (m, 4/4H, O-C*H*$_2$), 3.80 (bs, 8H, Pyrr-*H*), 3.98, 3.99 (AB-system, 8H, ^2J = 17.8 Hz, Ar-C*H*$_2$-Ar), 5.05–5.11 (m, 2H, Cy-*H*), 7.01, 7.02 (2s, 4/4H, Ar-*H*), 7.76, 7.79 (2d, 2/2H, ^3J = 8.1 Hz, Per-*H*), 8.42 (d, 2H, ^3J = 8.1 Hz, Per-*H*), 8.49, 8.50 (d, s, 2/2H, ^3J = 8.1 Hz, Per-*H*), 8.56 (s, 2H, Per-*H*).

UV-Vis (CH_2Cl_2): λ (nm) [ε ($M^{-1}cm^{-1}$)]: 696 [74000].

Fluorescence (CH_2Cl_2): λ_{max} (nm): 740; Φ_{fl} = 0.11 in CH_2Cl_2, Standard: PSt (Φ_{fl} = 0.96 in $CHCl_3$)

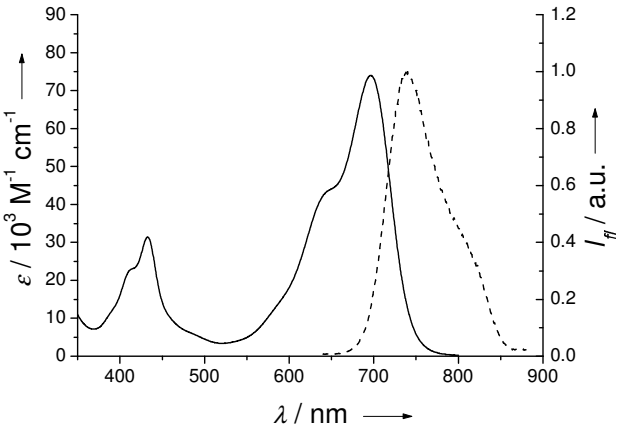
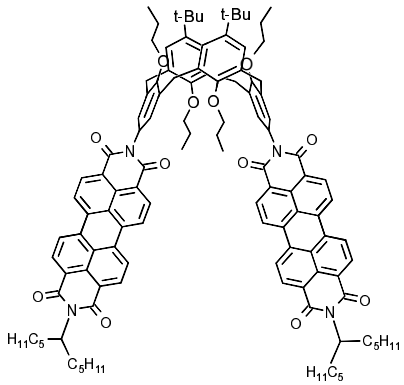


Figure 5. UV/Vis absorption (black, solid) and fluorescence emission spectrum (black dashed) (CH_2Cl_2, for both cases).

wide rim perylene calix[4]arene derivative 7



To a stirred clear solution of wide rim diamines **4** (15 mg, 0.0241 mmol) in quinoline (4 ml) is added monoimide mono-anhydride perylene (17.0 mg, 0.09 mmol), catalyst $Zn(OAc)_2$ (4 mg) and is heated at 150 °C for 14 h. A solution of HCl (10 ml, 0.1N) is added and the stirring is continue for additional 30 min., when a green precipitate is formed. The precipitate is filter off and it is dissolved in dichloromethane (5 ml). The solvent is evaporated under reduced pressure and the formed residue is dry under high vacuum at 50 °C. The desired compound **7** is isolated by column chromatography in 37 % yield as orange fine powder (CH_2Cl_2/Methanol = 97:3, R_f = 0.50). mp 374 °C.

HR-MS (ESI in Acetonitril/$CHCl_3$) $C_{118}H_{124}N_4KO_{12}$ $[M+K]^+$: M/z = 1827.8854; found M/z = 1827.8847

^{1}H-NMR (400MHz, $CDCl_3$, 25°C) δ 0.65, 0.74 (2t, 6/6H, ^3J = 7.6/7.5 Hz, Alkyl-*H*), 0.84 (t, 12H, ^3J = 7.2 Hz, Alkyl-*H*), 0.95, 1.48, 1.89, 2.26 (4m, 4/4/4/4H, 12H, Alkyl-*H*), 1.26–1.39 (m, s, 42H, Alkyl-*H,* *t*-Bu), 3.39–3.45 (m, 8H, O-CH_2), 3.93, 3.94 (AB-system, 4/4H, ^2J = 18.2/ 17.7 Hz, Ar-CH_2-Ar), 5.18–5.22 (m, 2H, N-C*H*), 7.02, 7.05 (2s, 4/4H, Ar-*H*), 8.60 – 8.67, 8.75 (d, m, 16H, ^3J = 8.0 Hz; Per-*H*).

UV-Vis (CH_2Cl_2): λ (nm) [ε ($M^{-1}cm^{-1}$)]: 524 [144400]

Fluorescence: (CH_2Cl_2): λ_{max} (nm): 542 und 484; Φ_{Fl} = 0.28 in CH_2Cl_2, Standard: Fluorescence in (Φ_F= 0.92 in 0.1 N NaOH).

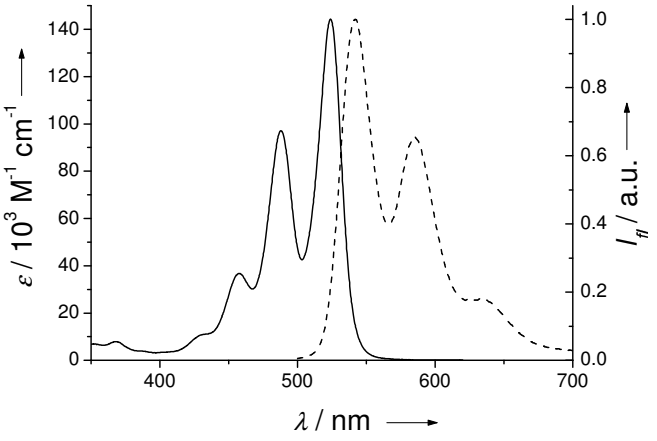


Figure 6. UV/Vis absorption (black, solid) and fluorescence emission spectrum (black dashed) (CH_2Cl_2, for both cases).

6.3. References.

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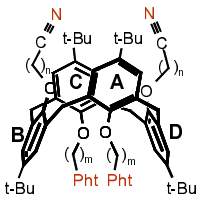
Summary

Calix[4]arenes fixed in the *1,3-alternate* conformation offer an interesting platform for the attachment of further functionalities which has been less frequently used than the *cone* conformation. They may be considered also as building blocks for larger structures, covalently linked or self-assembled via reversible bonds. Amino functions are a convenient starting point to attach further groups via N-alkylation or N-acylation [amides, imides, (thio) ureas]. Thus, via N-acylation groups like CMPO (carbamoylmethyl phosphine oxides) or picolinamides or Cosan [cobalt (III) bis (1,2-dicarbollide)] can be introduced to the amino calix[4]arenes in the *1,3-alternate* conformation. The resulting derivatives are used for the extraction of trivalent cations (actinides and lanthanides) from acidic solution (HNO_3) into an organic phase.

To fix a calix[4]arene in the *1,3-alternate* conformation by ether residues larger than ethyl a direct one step O-alkylation of *t*-butylcalix[4]arene is possible. Cs^+ usually (from Cs_2CO_3) is required as countercation. In the exhaustive O-alkylation step, all four ether residues are identical and other isomers (*partial cone, cone, 1,2-alternate*) are always formed as side products. An alternative of complete O-alkylation is a two step strategy. A first di-O-alkylation of *t*-butylcalix[4]arene in the presence of K_2CO_3 selectively leads to 1,3-*syn*-diethers which still exist in the *cone* conformation. Only, the second O-alkylation of the remaining hydroxyl groups requires the presence of Cs_2CO_3 and fixes the calix[4]arene in the *1,3-alternate* conformation. This, two step synthesis offers additionally the possibility to introduce two kinds of ether residues and reduces the number of unwanted isomers to *cone* and *partial cone*.

Here, we developed strategies for further functionalization of calix[4]arene in the *1,3-alternate* conformation via amino functions attached to the narrow/wide rim or both. Precursors for such amines calix[4]arene derivatives are illustrated below:

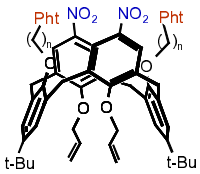
A. Tetraamines, narrow rim



1

n = m = 3

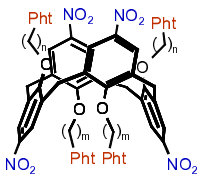
B. Tetraamines, narrow rim/ wide rim



2 a, b, c

n = 2, 3, 4

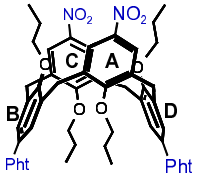
C. Octaamines, narrow rim/ wide rim



3

n = m = 3

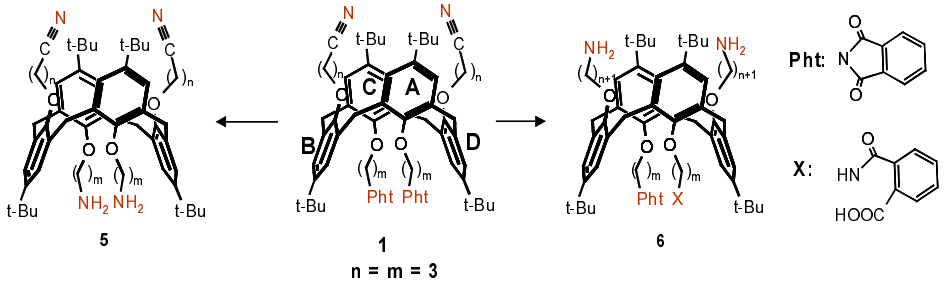
D. Tetraamines, wide rim



4

A. Tetraamines, narrow rim.

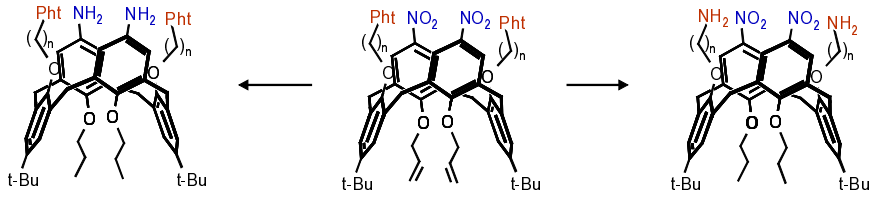
The precursor **1** is obtained in two steps starting from *t*-butylcalix[4]arene (first O-alkylation in the presence of K_2CO_3, followed by exhaustive O-alkylation using Cs_2CO_3 as template). It offers the possibility to introduce further groups to the amino functions oriented pairwise in opposite directions (AC vs. BD). The nitrile and phthalimido groups of **1** can be independently treated to liberate amino groups as is illustrated below. Cleavage of the phthalimido groups leads to compound **5** where the nitrile groups remain intact while reduction of the nitrile groups of **1** should be possible leaving the phthalimido groups unchanged. In the last case a partial hydrolysis of one of the phthalimido groups was observed affording compound **6**.



5 **1** n = m = 3 **6**

B. **Tetraamines, narrow rim / wide rim.**

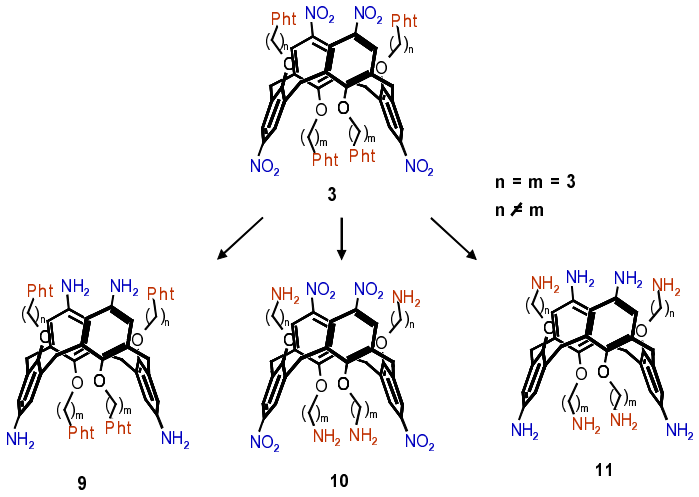
A three step synthesis leads to a precursor for tetraamines, where all four amino groups are oriented pairwise to one side of the *1,3-alternate* skeleton: 1) first O-alkylation in presence of K_2CO_3/or under Mitsunobu conditions for shorter alkyl chains, 2) selective *ipso*-nitration of *t*-butyl phenol units, 3) exhaustive O-alkylation with allyl bromide in the presence of Cs_2CO_3. To obtain the amino groups, one can start either with the reduction of the nitrile groups or with the cleavage of the phthalimido groups of compound **2**. The first pathway leads to wide rim diamines **7**, with the simultaneous (partial) hydrogenation of the allyl groups, while the phthalimido groups remain intact. The second one creates narrow rim diamines **8** where allyl groups are hydrogenated.



7 b, c **2 a, b, c** n = 2, 3, 4 **8 b, c**

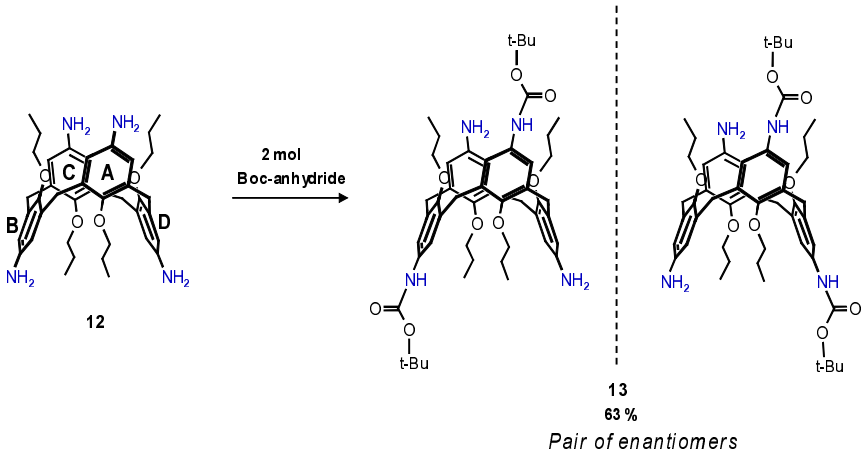
C. Octaamines, narrow rim/ wide rim

Tetraethers with alkyloxy phthalimide residues were obtained in one (equal residues) or two (different residues) O-alkylation steps, followed by *ipso*-nitration. Reduction of the nitro groups and cleavage of the phthalimido groups can be done independently or in one step.



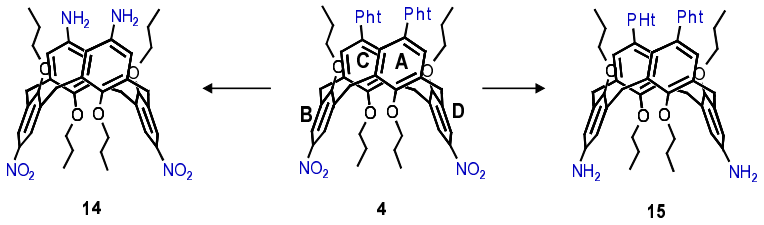
D. Tetraamines, wide rim

The tetraamine **12** is obtained via the precursor **3**. Reaction with Boc-anhydride via di-protection under different conditions gives mono-, 1,2-di-, tri- protected compounds, while the 1,3-di protected compound is not observed. Of special interest is the chiral derivative **13** (C_2-symmetry) which offers an interesting platform for attachment of further functions to adjacent amino groups, which are oriented in opposite directions.



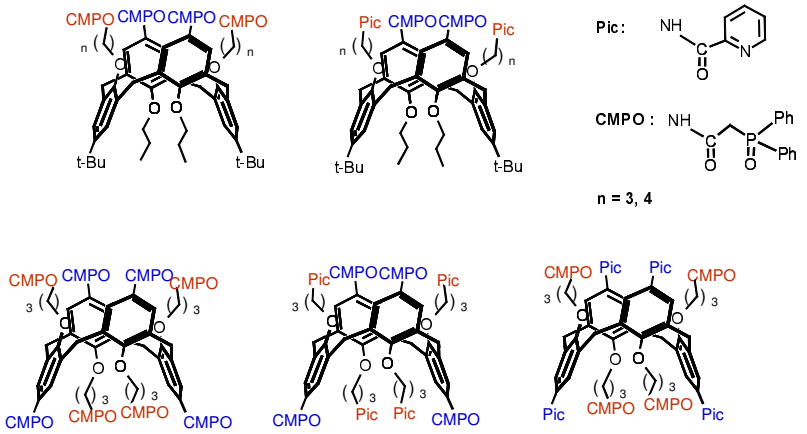
While the di-Boc protection distinguishes the aromatic rings A and B from C and D, a distinction of A and C from B and D requires an other precursor, e.g. **4**. Its synthesis starts with the precursor **2b**, followed by reduction of nitro groups, their protection as phthalimide and *ipso*-nitration. Compound **4**

contains two kinds of precursor for amino groups oriented pairwise in opposite directions (similar to **1**). Here, also each pair of amino groups can be independently obtained as is illustrated below.



E. CMPO derivatives.

Some of these amines presented above were used as platform (one/both sides) for further attachment of CMPO functions, or a combination of CMPO/picolinamide functions to obtain extractants for trivalent cations (designed below).



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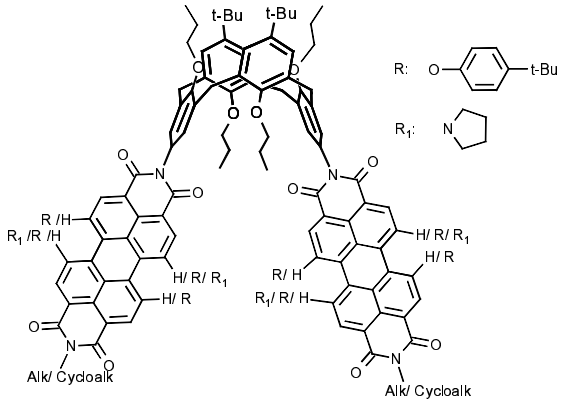

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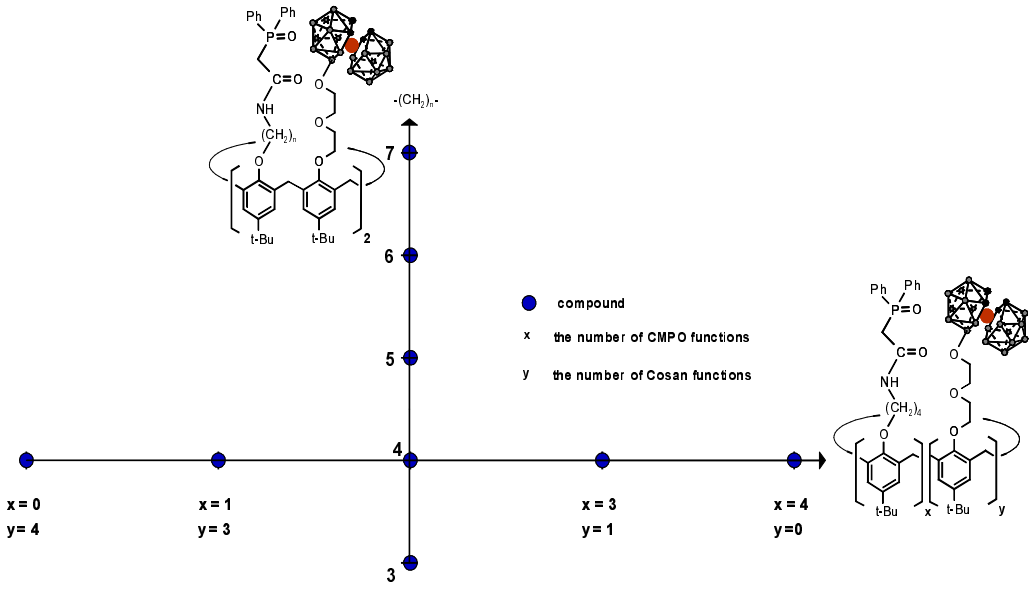

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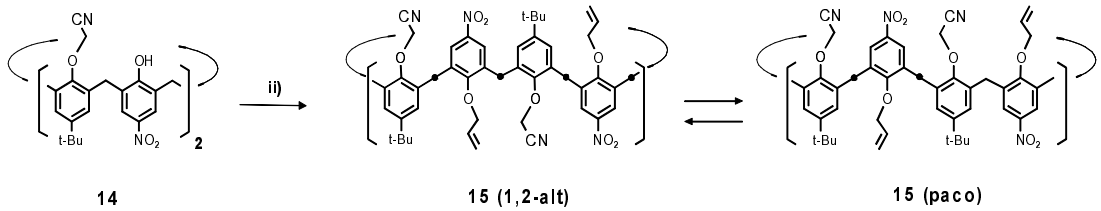
Interesting conformational properties were found in the case of tetraalkylated compound **15**, synthesized by the known procedure (two O-alkylation steps and *ipso*-nitration in between). After the second O-alkylation with allyl bromide of dinitro compound **14**, we found that the resulting tetraethers are conformationally unstable. In contrast to early reports in the literature, the cyanomethoxy group obviously can pass through the annulus of the calix[4]arene skeleton.



Therefore, two possible stereoisomers for **15** in the *partial cone* and *1,2-alternate* conformations exist as an equilibrium mixture which could be quantitatively analyzed by ^{1}H-NMR spectroscopy. The

temperature dependence of this equilibrium leads to ΔH_0 = -7.6 to -9.7 kJ/mol in different solvents (tetrachloroethane, benzene, dimethysulfoxide). Since **15(*1,2-alt*)** could be obtained in pure form and confirmed by X-ray analysis, its isomerisation to the equilibrium mixture with **15(*paco*)** could be followed also kinetically. An activation energy of E_a = 110.5 kJ/mol was found for this process in dmso-d_6.

Author's list of publications

1. Redetermination of 5,11,17,23-tetra- tert-butyl-25,27-di(ethoxycarbonyl methoxy)-26,28-dihydroxy calix[4]arene chloroform disolvate at low temperature, *Acta Cryst*., 2003, E59, o533–o534, Michael Bolte, C. Danila and Volker Böhmer

2. 1,3-Alternate calix[4]arenes, selectively functionalized by amino groups, *Organic & Biomolecular Chemistry*, **2005**, 3, 172, C. Danila, Michael Bolte, Volker Böhmer

3. Conformational properties of cyanomethoxy calix[4]arenes, *Organic & Biomolecular Chemistry*, **2005**, 3, 3508, C. Danila, Volker Böhmer, Michael Bolte

4. Cobalt Bis(dicarbollides)(1-) Covalently Attached to the Calix[4]arene Platform: The First Combination of Organic Bowl-Shaped Matrices and Inorganic Metallaborane Cluster Anions, *Eur. J. Org. Chem.* **2005**, 2022–2039, B. Grüner, L. Mikulásek, J. Báca, I. Císarová, V. Böhmer, C. Danila, M. M. Reinoso-García, W. Verboom, D. N. Reinhoudt, A. Casnati, R. Ungaro

5. Synergistic effect of ligating and ionic functions, prearranged on a calix[4]arene, *Chem. Commun*., **2006**, 4001–4003, L. Mikulasek, B. Gruner, C. Danila, V. Böhmer, J. Caslavsky, P. Selucky

6. 26,28-Diallyloxy-5,11,17,23-tetra- tert-butyl-25,27-bis(cyanomethoxy) calix[4]arene in the partial cone conformation, *Acta Cryst*., **2006**, E62, o4765–o4767, C. Dordea, Volker Böhmer and Michael Bolte

The thesis was also partly presented in following conferences:

7th International Conference in Calixarenes
August 13-16, 2003, Vancouver, BC Canada

8th International Conference in Calixarenes
July 25-29, 2005, Prague, Czech Republic

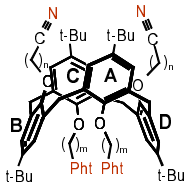
Summary

Calix[4]arenes fixed in the *1,3-alternate* conformation offer an interesting platform for the attachment of further functionalities which has been less frequently used than the *cone* conformation. They may be considered also as building blocks for larger structures, covalently linked or self-assembled via reversible bonds. Amino functions are a convenient starting point to attach further groups via N-alkylation or N-acylation [amides, imides, (thio) ureas]. Thus, via N-acylation groups like CMPO (carbamoylmethyl phosphine oxides) or picolinamides or Cosan [cobalt (III) bis (1,2-dicarbollide)] can be introduced to the amino calix[4]arenes in the *1,3-alternate* conformation. The resulting derivatives are used for the extraction of trivalent cations (actinides and lanthanides) from acidic solution (HNO_3) into an organic phase.

To fix a calix[4]arene in the *1,3-alternate* conformation by ether residues larger than ethyl a direct one step O-alkylation of *t*-butylcalix[4]arene is possible. Cs^+ usually (from Cs_2CO_3) is required as countercation. In the exhaustive O-alkylation step, all four ether residues are identical and other isomers (*partial cone, cone, 1,2-alternate*) are always formed as side products. An alternative of complete O-alkylation is a two step strategy. A first di-O-alkylation of *t*-butylcalix[4]arene in the presence of K_2CO_3 selectively leads to 1,3-*syn*-diethers which still exist in the *cone* conformation. Only, the second O-alkylation of the remaining hydroxyl groups requires the presence of Cs_2CO_3 and fixes the calix[4]arene in the *1,3-alternate* conformation. This, two step synthesis offers additionally the possibility to introduce two kinds of ether residues and reduces the number of unwanted isomers to *cone* and *partial cone*.

Here, we developed strategies for further functionalization of calix[4]arene in the *1,3-alternate* conformation via amino functions attached to the narrow/wide rim or both. Precursors for such amines calix[4]arene derivatives are illustrated below:

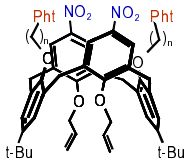
A. Tetraamines, narrow rim



1

n = m = 3

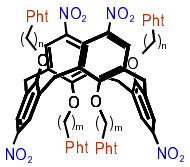
B. Tetraamines, narrow rim/ wide rim



2 a, b, c

n = 2, 3, 4

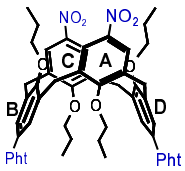
C. Octaamines, narrow rim/ wide rim



3

n = m = 3

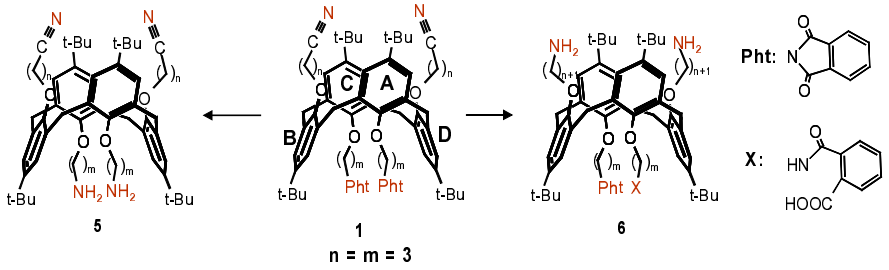
D. Tetraamines, wide rim



4

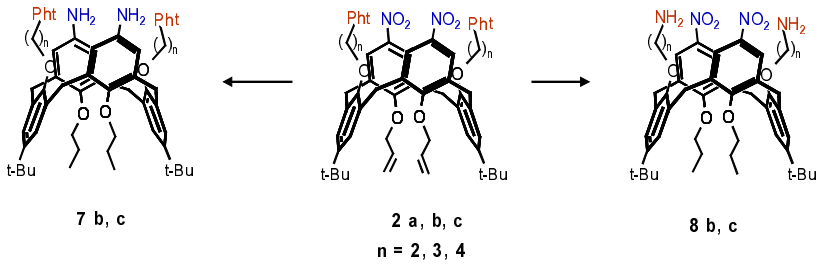
A. Tetraamines, narrow rim.

The precursor **1** is obtained in two steps starting from *t*-butylcalix[4]arene (first O-alkylation in the presence of K_2CO_3, followed by exhaustive O-alkylation using Cs_2CO_3 as template). It offers the possibility to introduce further groups to the amino functions oriented pairwise in opposite directions (AC vs. BD). The nitrile and phthalimido groups of **1** can be independently treated to liberate amino groups as is illustrated below. Cleavage of the phthalimido groups leads to compound **5** where the nitrile groups remain intact while reduction of the nitrile groups of **1** should be possible leaving the phthalimido groups unchanged. In the last case a partial hydrolysis of one of the phthalimido groups was observed affording compound **6**.



B. **Tetraamines, narrow rim / wide rim.**

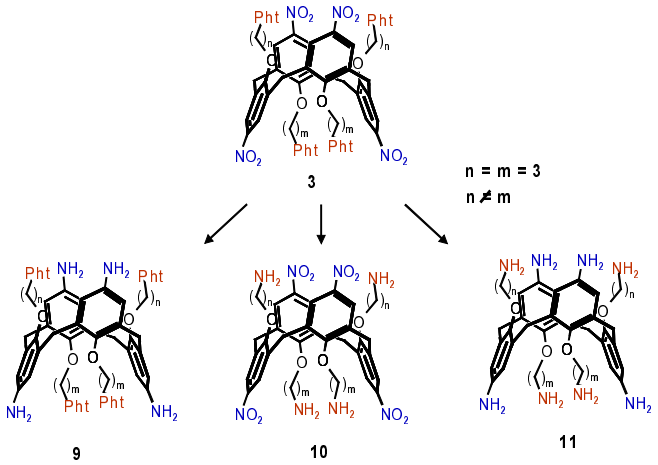
A three step synthesis leads to a precursor for tetraamines, where all four amino groups are oriented pairwise to one side of the *1,3-alternate* skeleton: 1) first O-alkylation in presence of K_2CO_3/or under Mitsunobu conditions for shorter alkyl chains, 2) selective *ipso*-nitration of *t*-butyl phenol units, 3) exhaustive O-alkylation with allyl bromide in the presence of Cs_2CO_3. To obtain the amino groups, one can start either with the reduction of the nitrile groups or with the cleavage of the phthalimido groups of compound **2**. The first pathway leads to wide rim diamines **7**, with the simultaneous (partial) hydrogenation of the allyl groups, while the phthalimido groups remain intact. The second one creates narrow rim diamines **8** where allyl groups are hydrogenated.



C. Octaamines, narrow rim/ wide rim

Tetraethers with alkyloxy phthalimide residues were obtained in one (equal residues) or two (different residues) O-alkylation steps, followed by *ipso*-nitration. Reduction of the

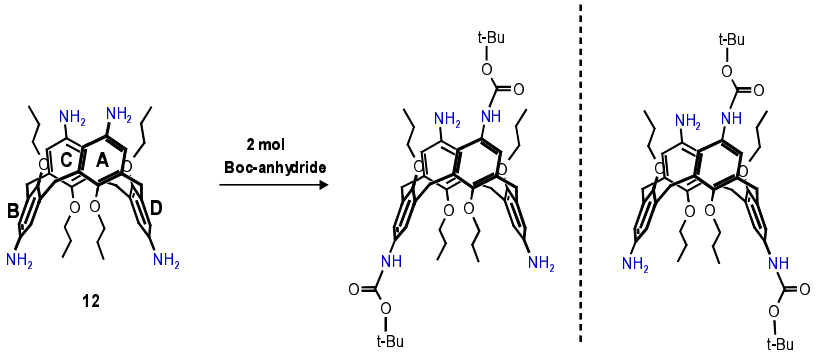
nitro groups and cleavage of the phthalimido groups can be done independently or in one step.



3 9 10 11

D. Tetraamines, wide rim

The tetraamine **12** is obtained via the precursor **3**. Reaction with Boc-anhydride via di-protection under different conditions gives mono-, 1,2-di-, tri- protected compounds, while the 1,3-di protected compound is not observed. Of special interest is the chiral derivative **13** (C_2-symmetry) which offers an interesting platform for attachment of further functions to adjacent amino groups, which are oriented in opposite directions.

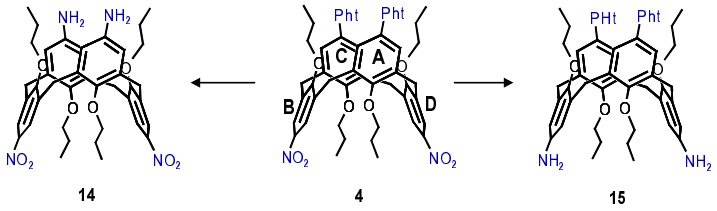


12 13

63 %

Pair of enantiomers

While the di-Boc protection distinguishes the aromatic rings A and B from C and D, a distinction of A and C from B and D requires an other precursor, e.g. **4**. Its synthesis starts with the precursor **2b**, followed by reduction of nitro groups, their protection as phthalimide and *ipso*-nitration. Compound **4** contains two kinds of precursor for amino groups oriented pairwise in opposite directions (similar to **1**). Here, also each pair of amino groups can be independently obtained as is illustrated below.



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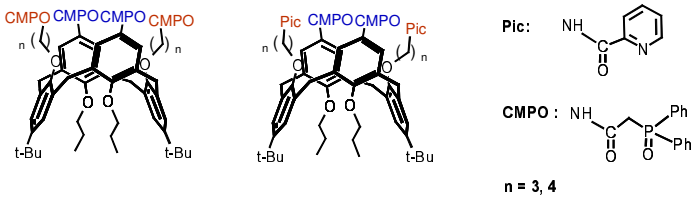

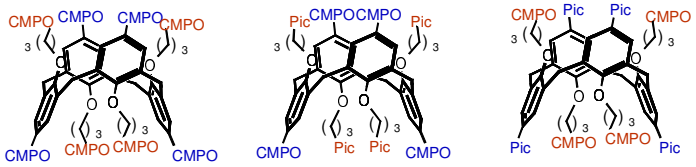

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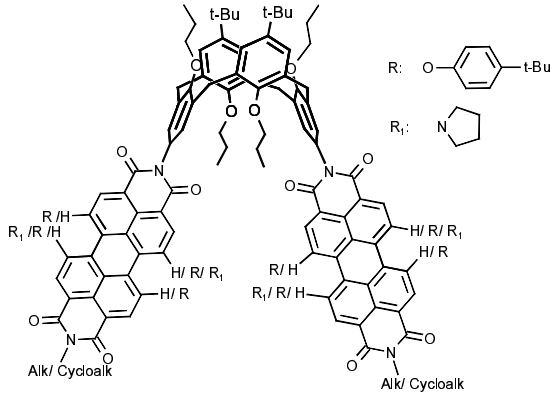

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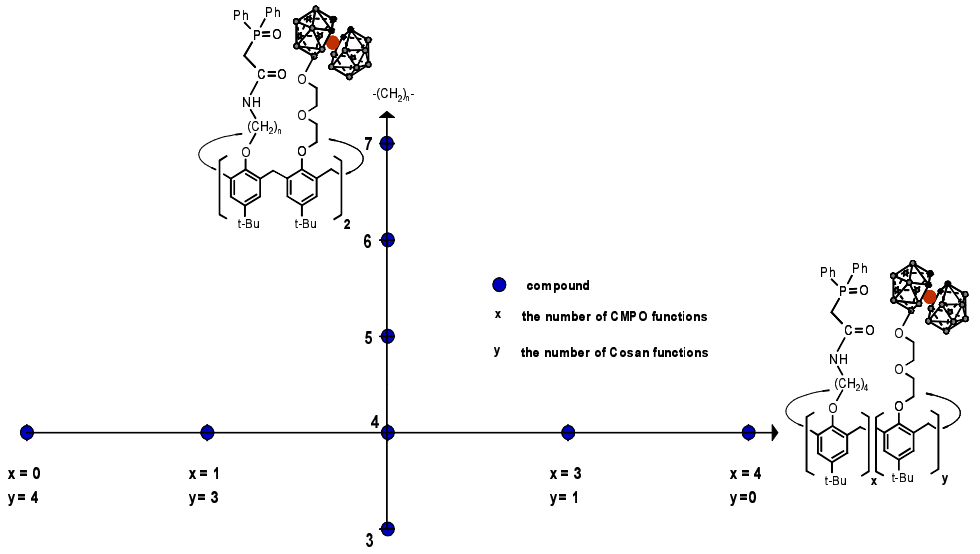

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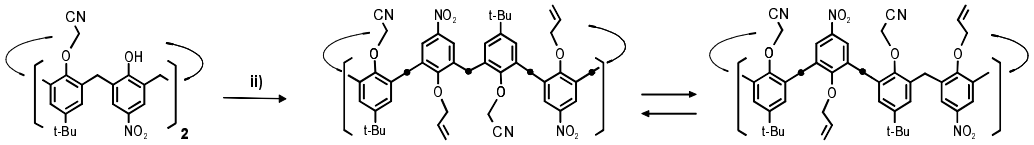

14 **15 (1,2-alt)** **15 (paco)**

Therefore, two possible stereoisomers for **15** in the *partial cone* and *1,2-alternate* conformation exist as an equilibrium mixture which could be quantitatively analyzed by ^{1}H NMR spectroscopy. The temperature dependence of this equilibrium leads to ΔH_0 = -7.6 to -9.7 kJ/mol in different solvents (tetrachloroethane, benzene, dimethysulfoxide). Since **15(*1,2-alt*)** could be obtained in pure form and confirmed by X-ray analysis, its isomerisation to the equilibrium mixture with **15(*paco*)** could be followed also kinetically. An activation energy of E_a = 110.5 kJ/mol was found for this process in dmso-d_6.