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Conformations of calix[4]arenes — an investigation based on CSD data.
Part II. Partial cone, 1,2-alternate and 1,3-alternate conformers of methylene- and heteroatom-bridged calix[4]arenes

In the first part of this investigation (Part I), cone conformers of calix[4]arenes with methylene and hetero-atom bridges from the Cambridge Structural Database (CSD) were investigated. Previously introduced parameters α, β and δ were utilized in describing the conformations of the hydrocarbon base frame of the above mentined compounds. In this part of the investigation, partial cone, 1,2- and 1,3-alternate conformers of methylene- and heteroatom-bridged calix[4]arenes are studied and the influence of inter- and intramolecular interactions on the conformations of these compounds is evaluated.

Keywords: calix[4]arene, conformation, torsion angle, distorsion parameter.

Introduction

Calix[4]arenes with methylene or heteroatom bridges and calix[4]resorcinarenes are interesting classes of macrocyclic compounds which have recently attracted a lot of interest because of their ability to form host-guest complexes and act as enzyme mimics [1–3]. However, design of functional hosts for cations, anions and neutral molecules often requires that the calixarene scaffold adopts a specific geometry. The factors affecting the geometry of the calixarene base frame are numerous [1–6] and the knowledge of how the calixarene base frame is deformed in response on these inter- and intramolecular interactions is essential in molecular design of functional molecules. In the first part of this work (Part I [7]), the previously introduced parameters α, β and δ [8, 9] have been utilized to describe the geometry of the calixarene base frame. Furthermore, the influence of various inter/intramolecular interactions on the value of the parameters α, β and δ (and therefore, on the geometry of the calixarene scaffold) in the *cone* conformers of methylene- and heteroatom-bridged calix[4]arenes was studied.

In the second part this work, the influence of inter/intramolecular interactions on the geometry of the *partial cone*, *1,2-alternate* and *1,3-alternate* moiety in calix[4]arenes with methylene and heteroatom bridges is investigated. As in the *cone* conformers, the previously introduced parameters α, β and δ [8, 9] and data from the Cambridge Structural Database [10] are utilized for this purpose.

The main difference between *partial cone*, *1,2-alternate* and *1,3-alternate* conformers and the previously described *cone* conformers (Part I [7]) is the presence of cavity formed by four calix[4]arene phenyl rings in the case of *cone* conformers. This cavity is nonexistent in *partial cone*, *1,2-alternate* and *1,3-alternate* conformers. In the case of *partial cone* structures, the 'cavity' is formed by three calix[4]arene phenyl rings only; the guest cannot be therefore completely encapsulated and, due to diminished intermolecular van der Waals interactions (three phenyl rings instead of four participate on the guest binding), weaker binding of the guest in the cavity can be expected. This effect is even more pronounced in *1,2-alternate* conformers, which possess a 'half-cavity' formed by two adjacent calix[4]arene phenyl rings only. On the other hand, in

1,3-alternate conformers the 'cavity' is formed by two opposite calix[4]arene phenyl rings, so stronger binding of the guest than in the case of *1,2-alternate* conformers is expected. Furthermore, *1,2-alternate* and *1,3-alternate* conformers contain two such 'cavities' compared to *cone* and *partial cone* conformers. The illustration of the above mentioned effects is summarized in Figure 1.
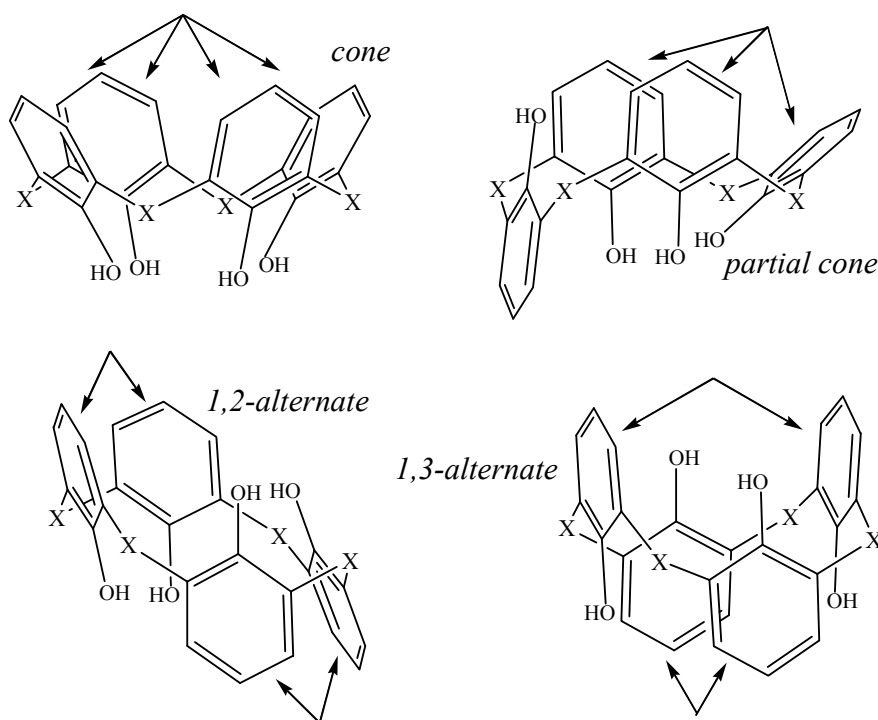

Figure 1. Cavities in cone, partial cone 1,2-alternate and 1,3-alternate calix[4]arenes
(X … CH_2 or heteroatom/heterogroup)

In the next part of this article, the influence of inter- and intramolecular interactions on the geometry of *partial cone*, *1,2-alternate* and *1,3-alternate* structures will be investigated.

Partial cone structures

#### *Methylene-bridged partial cone calix[4]arenes*

The group of *partial cone* conformers of calix[4]arenes with methylene bridge groups contains relatively few hits (93 complete cif files with 106 independent molecules, and 3 incomplete cif files) compared to other groups, especially *cone* (see Part I, [7]), the substitution patterns are also fewer symmetrical than in the *cone* group. Important ones and their corresponding percentages of the *partial cone* group are given in Table 1.

T a b l e   1

**The substitution patterns and the corresponding percentages
of the methylene-bridged partial cone group from [10]**

Type	Hits	%	Independent molecules	%
Symmetrically tetrasubstituted	24	25.0	27	25.5
Distally substituted lower rim, symmetrically tetrasubstituted upper rim	17	17.7	20	18.9
Single atom 'triple bridge'	15	15.6	15	14.1
Other	40	41.7	44	41.5
Total	**96**	**100**	**106**	**100**

The α-β and β-δ plots (Fig. 2, 3) depict the distribution of the *partial cone* calix[4]arenes according to their substitution. Since only 16 % of all cif files belong to complexes, metal-coordinated structures are not distinguished in these plots.
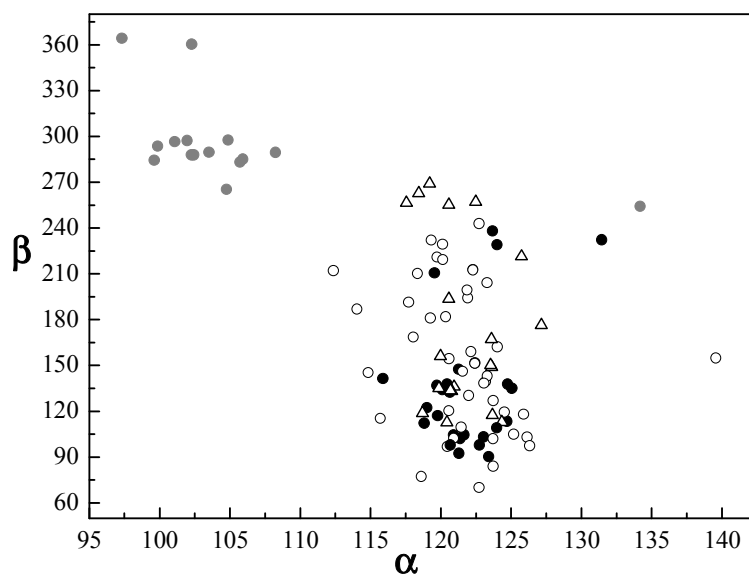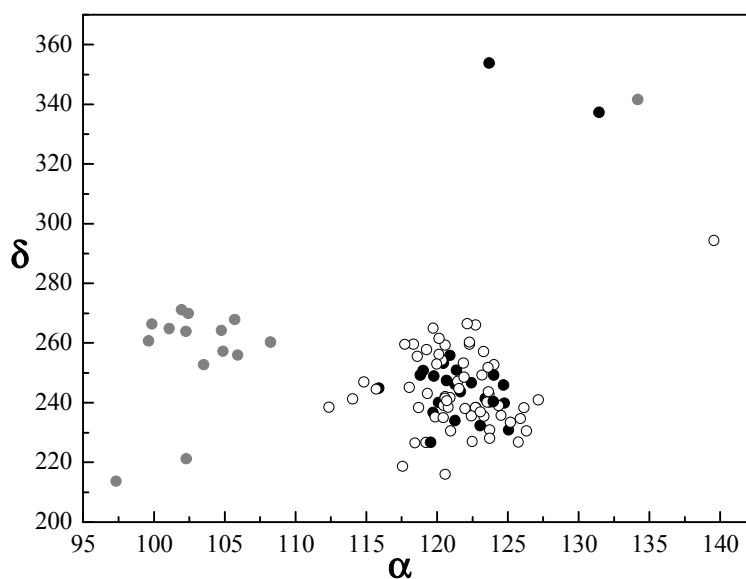
● — symmetrically tetrasubstituted; ● — single atom 'triple bridge' at the lower rim;
△ — distally substituted lower rim and symmetrically tetrasubstituted upper rim; ○ — other substitution patterns

Figure 2. The α-β plot of the group of partial cone methylene-bridged calix[4]arenes

From Figure 2 it can be clearly seen that the symmetrically tetrasubstituted and single atom 'triple-bridged' groups are relatively uniform in parameters α, β with the symmetrically tetrasubstituted group closer to average values of α, β (see Table 4 in Part I [7]). There are two groups of lower rim distally disubstituted structures: one at β < 210° and one at β ~ 240°. Other substitution patterns (relatively uniform in α but distributed in the β parameter) are less important because each of them contains only a few molecules and these substitution patterns are therefore not distinguished.

The α-δ plot (Fig. 3) shows that almost all *partial cone* conformers are uniform in these two parameters regardless of their substitution pattern with the notable exception of lower rim single atom 'triple-bridged' structures which form a very distinct group. Lower rim distally substituted structures are not distinguished in this plot.

● — symmetrically tetrasubstituted; ● — single atom 'triple bridge' at the lower rim; ○ —other substitution patterns

Figure 3. The α-δ plot of the group of partial cone methylene-bridged calix[4]arenes

The main group of the single atom 'triple-bridged' structures ('cluster' 2-I, 15 cif files with 15 independent molecules) is centered at the values [α, β, δ] of [103.35; 288.17; 262.95] with a standard deviation of [2.51; 8.40; 5.44]. There are three deviating structures not included in this group: one at δ ~ 340° and two at δ < 230°.

The main group of the symmetrically tetrasubstituted structures ('cluster' 2-II, 20 cif files with 23 independent molecules) is centered at [121.55; 118.78; 243.39] with a standard deviation of [2.19; 18.35; 6.49]. The four deviating structures with β > 180° in Figure 2 have been excluded from this cluster.

There are two clusters in the lower rim distally disubstituted group: 'cluster' 2-III containing structures with β < 210° (11 cif files with 14 independent molecules) centered at [121.99; 142.33; 240.83] with standard deviation of [2.25; 23.70; 5.78] and 'cluster' 2-IV containing structures with β > 210° (5 cif files with 6 independent molecules) centered at [120.67; 253.64; 223.61] with standard deviation of [2.76; 15.17; 4.50].

The binding mode in 'cluster' 2-I of the single atom 'triple-bridged' group requires bringing of three phenolic oxygen atoms to close proximity because of three relatively short covalent bonds to a single heteroatom and therefore a certain degree of forced opening of the structure reflected by low α, high β and δ ~ 260°. Deformation of the calix[4]arene moiety is very significant in this case and causes the observed separation of this group in parameters α, β (see Fig. 2). Typical example of 'cluster' 2-I structures is structure ABIHIC [10] (see Fig. II-1). All structures from this cluster have the '*partial cone*' phenyl ring not bound to the heteroatom. On the other hand, in the structure ZALGOI [10], the '*partial cone*' phenyl ring is the ring opposite to the unbound ring; this type of lower rim substitution leads to δ < 230° (the two deviating structures in Fig. 3). The one structure with δ ~ 340° (KOCQEY [10], Fig. II-1) has the '*partial cone*' phenyl ring positioned next to the unbound ring. The parameter δ can thus distinguish between the different binding modes within the 'triple-bridged' structures.
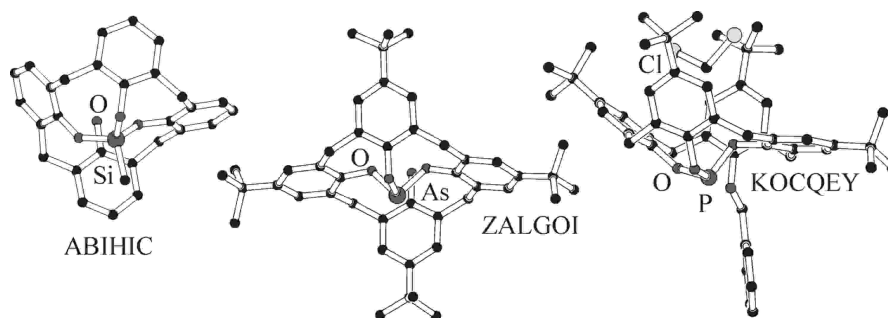

Figure II-1. Structures ABIHIC, ZALGOI and KOCQEY [10]

In Figure 2, there are four symmetrically tetrasubstituted structures with β > 200° which do not fall into 'cluster' 2-II. Two of them are clathrates with solvent molecule or one lower rim substituent inside the 'cavity' formed by three calixarene phenyl rings; see structure JOYHIO [10], Fig. II-4. Because of the filled 'cavity' formed by three calixarene phenyl rings, these structures have more open 'cavity' and therefore higher β.

The other two symmetrically tetrasubstituted structures with parameters β > 200° and δ > 290° are metal complexes and they are out of our discussion now (see Fig. II-2).
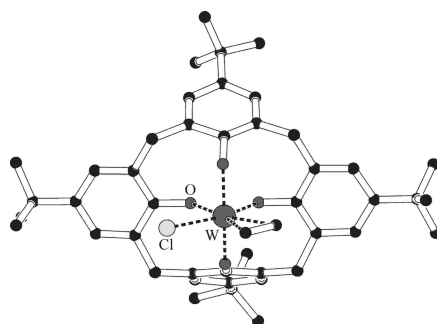

Figure II-2. Structure of tungsten complex GUBTAY [10]

In 'cluster' 2-II, there are relatively few structures which differ from each other significantly in upper/lower rim substitution, occupation of the cavity, possible upper/lower rim coordination etc. Since it is difficult to find common trends within this cluster, these structures will not be explicitly discussed.

From Figure 2, it is obvious that there are two 'clusters' within the lower rim distally disubstituted, upper rim symmetrically tetrasubstituted structures: 'cluster' 2-III at $\beta \sim 140°$, $\delta \sim 240°$ and smaller 'cluster' 2-IV at $\beta \sim 250°$, $\delta \sim 220°$. Structures from 'cluster' 2-IV contain bulky upper rim *t*-butyl groups and are lower rim-bridged by a relatively short crown ether moiety; compared to structure XOZBAP [10] from 'cluster' 2-III with unsubstituted upper rim, longer and more flexible crown ether chain and average geometry ($\beta \sim 110°$, $\delta \sim 240°$). The position of the '*partial cone*' phenyl ring differs in the above-mentioned bridged group and in structure XOZBAP in dependence on sterical hindrance between the *p*-substituent on the '*partial cone*' phenyl ring and lower rim bridge (Fig. II-3). Other structures from 'cluster' 2-III have nonbridged lower rim and are therefore not included in this comparison.
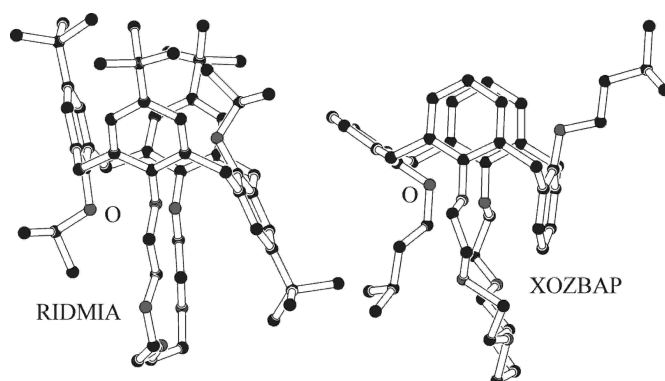

Figure II-3. Structures RIDMIA and XOZBAP [10].
The main difference is the position of the 'partial cone' phenyl ring

As shown previously (structure JOYHIO [10], Fig. II-4), the occupation of the calixarene 'cavity' can have some effect on its geometry. The dependence of parameters α, β on the type of the 'clathrate' for all *partial cone* calix[4]arenes (complexes included) is depicted in Figure 4; 'clathrates' tend to have more open 'cavity' and therefore bigger β than molecules with empty 'cavity'.
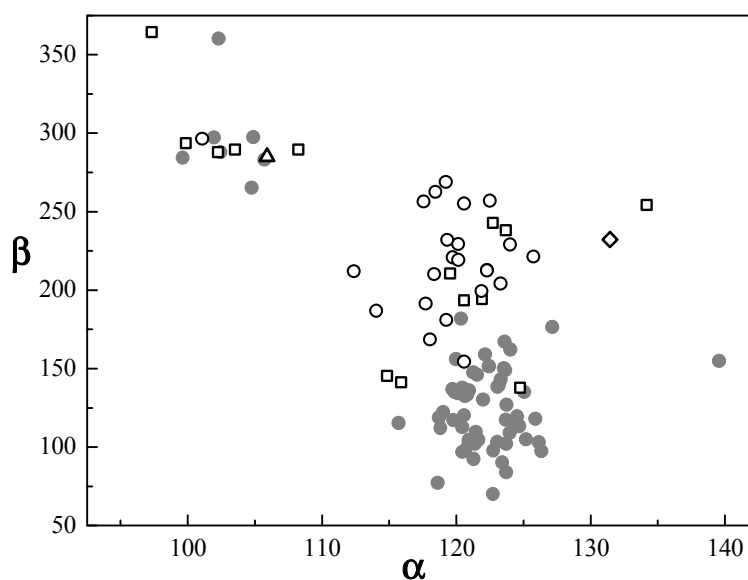
□ — solvent molecule inside the 'cavity'; ○ — lower rim substituent inside the 'cavity'; Δ — unsubstituted upper rim from another calixarene molecule inside the 'cavity'; ◊ — metal ion inside the 'cavity'; ● — nothing inside the 'cavity'

Figure 4. The dependence of the partial cone calix[4]arene geometry on the type of the 'clathrate'

Compared to *cone* structures (Part I, [7]), there are a relatively large number of structures which contain lower rim substituent inside the 'cavity'; this substituent usually comes from the same molecule which is rare in *cone* structures. As a rule, structures which contain another molecule or lower rim substituent inside the 'cavity' tend to be more open and therefore have bigger β; similar but not so profound effect have bulky non-polar upper rim substituents (*t*-butyl). On the other hand, structures where π,π-interaction between the calix[4]arene opposite phenyl rings is not disrupted (empty 'cavity', no upper rim substituents or polar upper rim substituents capable of some type of interaction) have low β and more closed structures. This effect can be observed primarily on structures with π,π-interaction between aromatic upper rim substituents; π,π-interaction between two opposite calix[4]arene phenyl rings or interaction of polar upper rim substituents (see structure HAWYUZ [10], Fig. II-4). The above-mentioned effect of upper rim substituents is depicted in Figure 5.
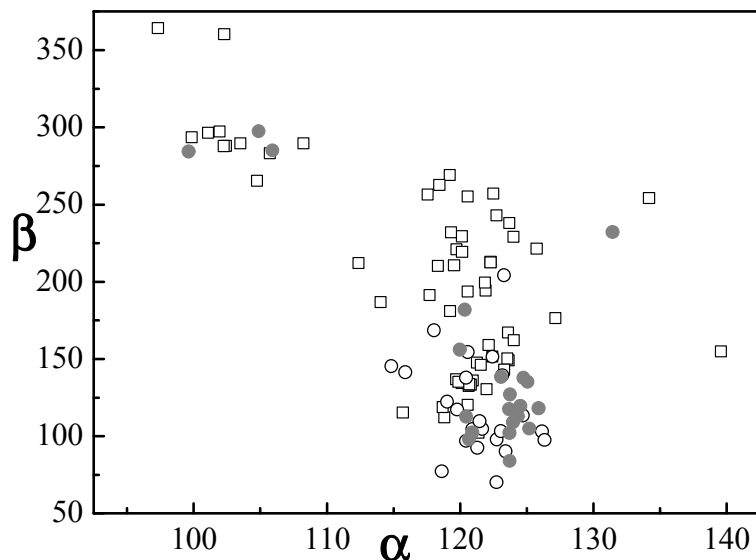
□ — nonpolar substituent at the upper rim; ○ — polar substituent at the upper rim; ● — unsubstituted upper rim

Figure 5. Effect of upper rim substituents on the geometry of partial cone calix[4]arenes

The influence of the lower rim substituents on the geometry of the symmetrically tetrasubstituted calix[4]arene base frame is less transparent and probably much less significant than the above-described effects.

Figure II-4 depicts the arrangement of the calix[4]arene moiety in the previously-mentioned structures HAWYUZ and JOYHIO [10].
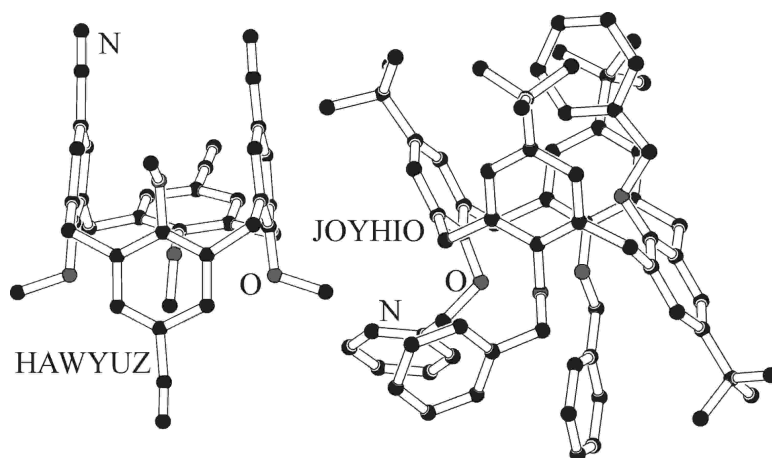

Figure II-4. Structures HAWYUZ and JOYHIO [10]

Heteroatom-bridged partial cone calix[4]arenes

The group of *partial cone* heteroatom-bridged calix[4]arenes comprises of a few hits only (9 cif files containing 9 symmetrically tetrasubstituted independent molecules, 3 cif files containing 5 independent molecules with other substitution patterns). Since there are not enough data and therefore no distinct trends could be observed, no division according to the respective substitution patterns was performed. Likewise, complexes are not distinguished because there are only three such structures in this group. The only bridge groups that occur in this group are S and SO; structures containing the SO bridges are emphasized in text.

The α-β plot regarding the group of all *partial cone* heteroatom-bridged calix[4]arenes (Fig. 6) shows two distinct groups. Structures with $\alpha < 110°$ (SEBZEE, YAQKAD and VAVRAM [10]) are 'clathrates' which possess more open 'cavity' (similar effect as in the methylene-bridged *partial cone* group). The more open 'cavity' in these structures is also reflected in higher value of parameter β. In the second group with $\alpha > 120°$ ('cluster' 6-I containing 8 cif files with 9 independent molecules, centered at [121.67; 125.82; 238.77] with standard deviation of [1.09; 10.82; 12.89]), no such effects are involved; these structures have empty 'cavity' and unhindered intramolecular π, π-interaction between two opposite calix[4]arene phenyl rings.
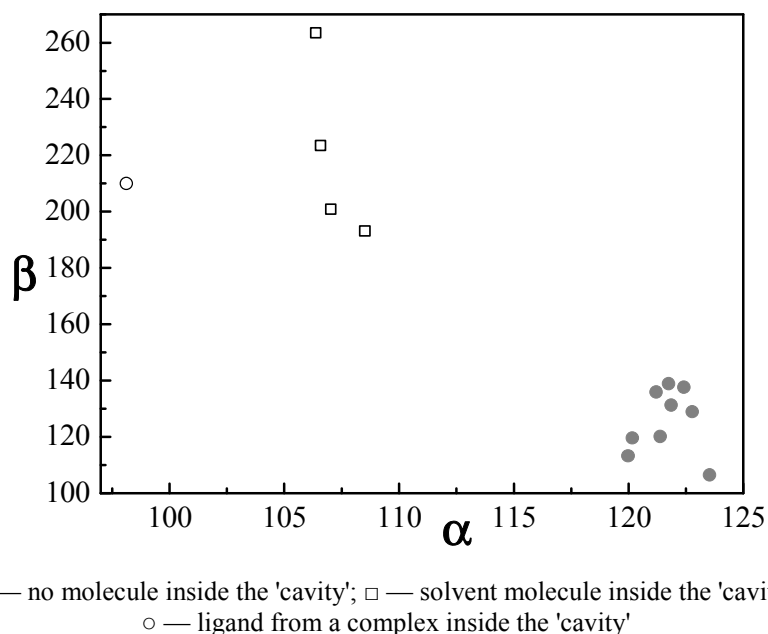

● — no molecule inside the 'cavity'; □ — solvent molecule inside the 'cavity';
○ — ligand from a complex inside the 'cavity'

Figure 6. The α-β plot displaying the group of all partial cone heteroatom-bridged calix[4]arenes

Structure VAVRAM [10] which displays intramolecular π,π-interaction between one calixarene phenyl ring and an aromatic ligand from a complex is depicted in Figure II-5.
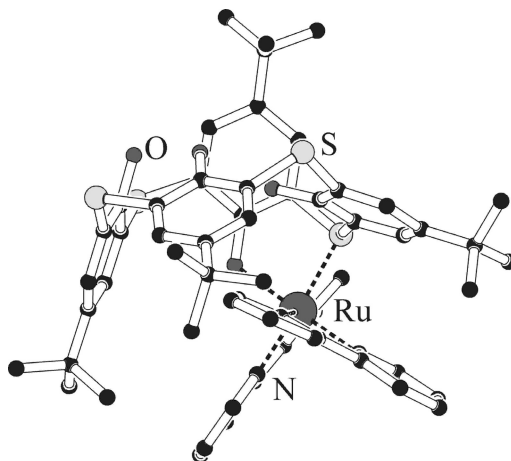

Figure II-5. Structure VAVRAM [10]

In the group of structures with empty 'cavity', the structures are distributed in the δ parameter. It is very difficult to find dependences of the distorsion parameters on the substitution of the calixarene platform because of a small number of structures in this group. However, the only upper rim unsubstituted structure in this group YANBUL [10] has the lowest β (~ 106°) probably because of π, π-interaction between two opposite calixarene phenyl rings unhindered by any upper rim substituents (Fig. II-6). Other structures contain bulky *t*-butyl groups at the upper rim and the resulting sterical hindrance leads to a somewhat more open 'cavity' and slightly increased β. This effect is very similar to that observed in the methylene-bridged group.
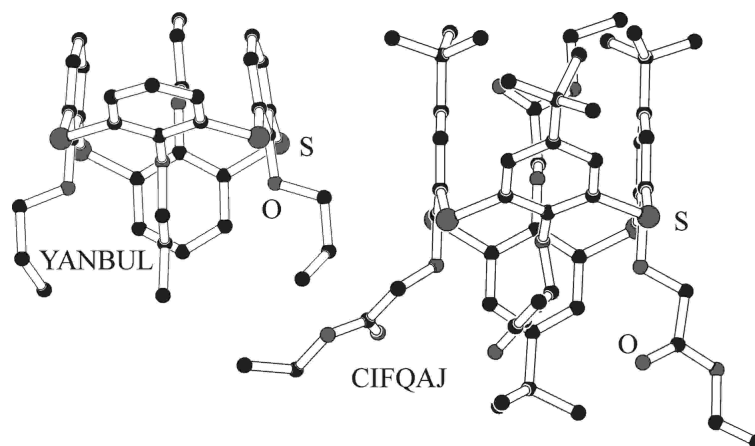

Figure II-6. Structures YANBUL and CIFQAJ [10]

Since there are only a few structures in this group, The values of the parameter **δ** are not discussed. There are four SO-bridged structures with empty 'cavity': trimeric lower rim tetragonally coordinated SUWNAZ [10] (β ~ 120°) and uncomplexed structures LUXYEI, LUXYIM and LUXXUX [10] (two proximal SO and two S bridges) with β > 130°. Structure LUXYEI [10] is depicted on Figure II-7. One interesting feature of the SO-bridged structures is the arrangement of the sulfinyl bridge groups. The structure LUXYEI has these bridges arranged in a *down-*, *up-*, *up-*, *up-* fashion (aeee in clockwise direction beginning at the bridge adjacent to the '*partial cone*' phenyl ring), LUXYIM in a *down-*, *up-*, *up-*, *down-* fashion (aeea), SUWNAZ in a *down-*, *up-*, *down-*, *up-* fashion (aeae) and LUXXUX has its two SO groups arranged in a *up-*, *up-* (ee) fashion (compare to *cone* SO-bridged structures LUXYAE, MAZNEG(01) and OKUKOU (eeee) and the complex RAWLIL (aaaa) [10]).
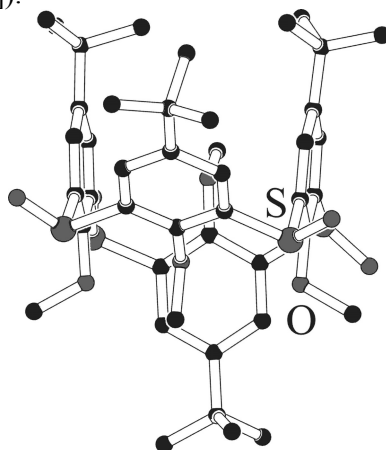

Figure II-7. Structure LUXYEI [10]

Unlike the methylene-bridged structures, there are no single atom 'triple-bridged' structures in this group. Unlike the methylene-bridged structures, there are also quite a number of structures containing hydroxyl groups at the lower rim in this group (4 out of 9 structures). The arrangement of hydrogen bonds at the lower rim therefore seems to be somewhat weaker than in the methylene-bridged group, the reason being probably larger cavity in heteroatom-bridged calix[4]arenes.

Since this group contains only a few structures, no conclusions regarding the effect of substitution and/or coordination beyond those already mentioned in the text were made.

Conclusion — partial cone structures

The arrangement of the *partial cone* base frame is best reflected in parameter β. Very open structures (single atom 'triple-bridged' at the lower rim, 'clathrates') tend to have high β whereas structures with unhindered π, π-interaction between two calixarene opposite phenyl rings have closed 'cavity' and low β. Because of the forced opening of the structure imposed by tetrahedral arrangement of bonds on the heteroatom, single atom 'triple-bridged' structures also have low α. The vast majority of *partial cone* structures are uniform in δ; the role of this parameter is therefore not discussed.

To sum up, the best way to deform the base frame of *partial cone* methylene-bridged molecules seems to be direct substitution of the calix[4]arene phenolic oxygen atoms either by a single atom 'triple bridge' or by lower rim *cis*-coordination by a transition metal ion. (there have been observed no molecules with this substitution or coordination patterns in the heteroatom-bridged group). Substitution at the upper rim significantly affects the *partial cone* calix[4]arene geometry only in the case when one pair of opposite phenyl rings is brought to a close proximity (e.g. upper rim polar substituents capable of some type of interaction).

Compared to *cone* structures, *partial cone* methylene-bridged structures which contain four lower rim hydroxyl groups are rare. Cyclic hydrogen bond arrangement at the lower rim is known to stabilize *cone* conformation (see e.g. [1–3]); *partial cone* conformation is therefore favored by molecules containing alkylated or acylated lower rim hydroxyl groups. On the other hand, heteroatom-bridged *partial cone* calix[4]arenes contain a relatively large number of structures which have four hydroxyl groups at the lower rim; the reason behind this behavior is probably larger cavity and therefore weakening of the hydrogen bonds present at the lower rim.

1,2-alternate structures

Methylene-bridged 1,2-alternate calix[4]arenes

The group of *1,2-alternate* conformers of calix[4]arenes with methylene bridge groups contains relatively few hits (56 complete cif files with 65 independent molecules, 5 incomplete cif files) compared to other groups (especially *cone*, see Part I [7]). Similarly to *partial cone* conformers, the molecules of these entries are also less symmetrically substituted than the *cone* group; the percentage of symmetrically tetrasubstituted molecules is less than 30 % compared to almost 50 % of symmetrically tetrasubstituted molecules in the *cone* conformation. The substitution patterns and the corresponding percentages of the *1,2-alternate* group are given in Table 2.

Since there is a large number of complexes in this group (41 % of cif files belong to metal-coordinated structures), these structures are distinguished.

T a b l e 2

The substitution patterns and the corresponding percentages of the 1,2-alternate group

Type	No. of cif files	%	No. of independent molecules	%
Symmetrically tetrasubstituted	16	26.2	17	26.1
Single atom proximal bridge	17	27.9	19	29.2
Other	28	45.9	29	44.7
Total	61	100	65	100

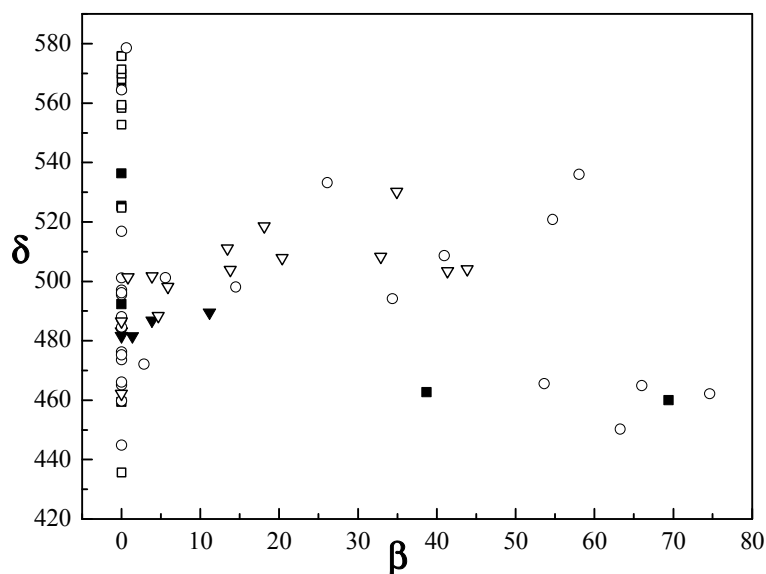The distribution of important groups of *1,2-alternate* calix[4]arenes is given in Figure 7 (α-β plot). The vast majority of symmetrically tetrasubstituted *1,2-alternate* calix[4]arenes falls to the point [180, 0]. The *1,2-alternate* calix[4]arenes with a single atom proximal bridge at the lower rim form a diffuse group. Other substitution patterns contain only a few molecules each and do not form distinct groups.
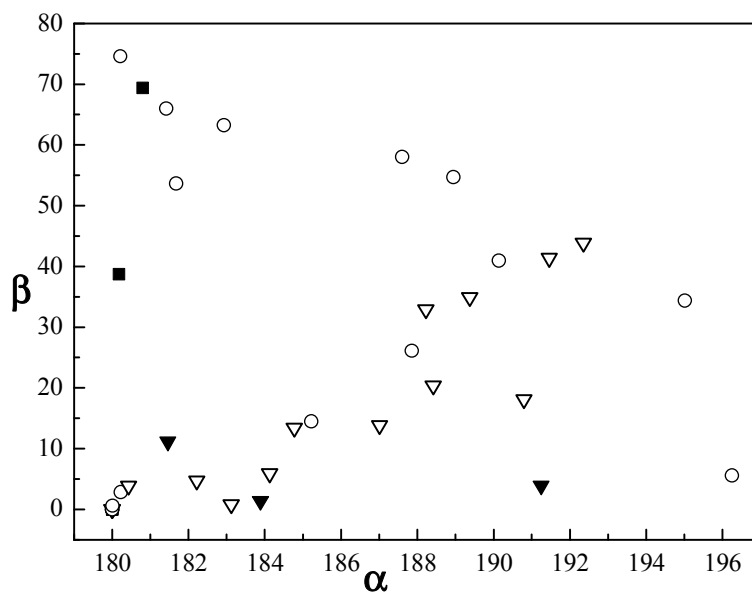
α-β plot; ■ — symmetrically tetrasubstituted — uncomplexed; □ — symmetrically tetrasubstituted — complex;
▼ — single atom proximally bridged lower rim — uncomplexed; ▽ — single atom proximally bridged
lower rim — complex; ○ — other substitution patterns — complexes not distinguished

Figure 7. The distribution of important groups of 1,2-alternate methylene-bridged calix[4]arenes

The β-δ plot (Fig. 8) depicts more closely the group of symmetrically tetrasubstituted molecules. *1,2-alternate* calix[4]arenes with a single atom proximal bridge at the lower rim form again quite a distinct group. Other substitution patterns do not have such a significant distribution and do not form distinct groups. α-δ plot is very similar to the β-δ one and is therefore not reported.

β-δ plot; ■ — symmetrically tetrasubstituted — uncomplexed; □ — symmetrically tetrasubstituted — complex;
▼ — single atom proximally bridged lower rim — uncomplexed; ▽ — single atom proximally bridged
lower rim — complex; ○ — other substitution patterns — complexes not distinguished

Figure 8. The distribution of important groups of 1,2-alternate methylene-bridged calix[4]arenes

In the group of symmetrically tetrasubstituted molecules, there are two distinct 'clusters' (see Fig. 8): 'cluster' 8-I at δ < 500° (5 cif files, 5 independent molecules) formed mostly by uncomplexed molecules and 'cluster' 8-II (9 cif files, 12 independent molecules) at δ > 500° formed mostly by complexes. 'Cluster' 8-I is

centered at [180.20; 21.62; 462.01] with a standard deviation of [0.31; 28.20; 18.02], 'cluster' 8-II is centered at [180.00; 0.00; 556.88] with a standard deviation of [0.00; 0.00; 17.70]. Two symmetrically tetrasubstituted molecules with $\beta > 30°$ were not included in these groups.

In the group of single atom proximally bridged molecules in Figure 8, there are two clusters observable: 'cluster' 8-III with $\beta < 10°$ containing both complexes and uncomplexed molecules and 'cluster' 8-IV formed mainly by complexes with $\beta > 10°$. 'Cluster' 8-III contains 10 cif files with 10 independent molecules, is centered at [182.50; 2.06; 487.17] with a standard deviation of [3.33; 2.17; 11.14]. 'Cluster' 9-IV contains 8 cif files with 9 independent molecules, is centered at [188.21; 25.55; 508.53] with a standard deviation of [3.24; 12.02; 10.56].

In the group of single atom proximally bridged *1,2-alternate* calix[4]arenes, there are 5 uncomplexed structures and 12 complexes. The group of single atom (X) proximally bridged *1,2-alternate* calix[4]arenes is relatively uniform in parameter δ; however, its structures differ significantly in α, β. This behavior probably reflects the rigidity of the lower rim O-X-O frame which depends on bond lengths between atom X and calix[4]arene phenolic oxygen atom and on bond angle on atom X. Smaller atoms (especially B, to a lesser extent Si, P) with short X-O bond lengths and relatively rigid bond angles tend to warp the calix[4]arene base frame more than «coordinated metaloid» atoms (see Fig. II-8). Because this deformation reflects both the rigidity of bond length and angle and because a large number of structures from this group contain mixed metal/non-metal bridges at the lower rim, no correlation and explanation of the two 'clusters' 8-III and 8-IV was attempted. However, structures with larger β from 'cluster' 8-IV are mostly structures with nonsymmetrical proximal substitution (e.g one metal ion and one heteroatom, usually Si). The changes in the calix[4]arene base frame in dependence on atom X seem to be less significant than those in the case of lower rim single atom 'triple-bridged' structures (see *cone* [7] and *partial cone* structures).
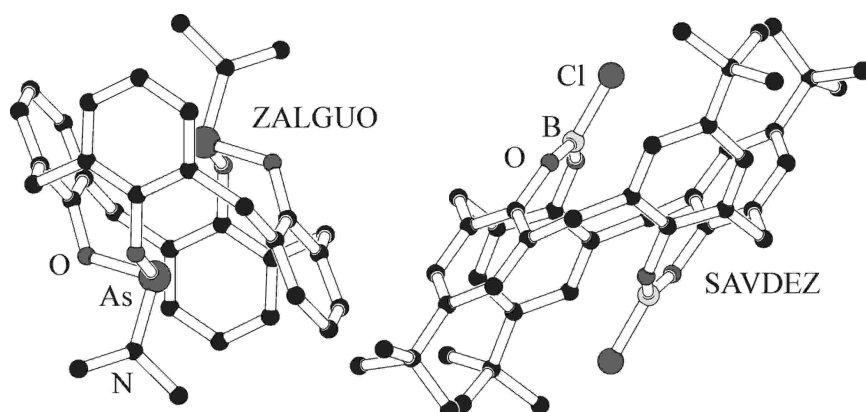

Figure II-8. Single atom proximally bridged 1,2-alternate calix[4]arenes ZALGUO, SAVDEZ [10]

The rigidity of the single atom proximal bridge can be further demonstrated on the values of β and δ parameters of this group and a group of *1,2-alternate* calix[4]arenes which contain longer proximal bridges. Single atom proximally bridged structures have relatively high δ parameter and low β ($\beta < 40°$, $\delta \sim 500°$) whereas in the group with longer proximal bridges (four structures) where the calix[4]arene base frame is less restrained the situation is exactly the opposite ($\beta \sim 60°$, $\delta \sim 460°$). The values of the β and δ parameters can therefore serve as a rough estimation of the rigidity of proximally bridged structures.

The group of symmetrically tetrasubstituted *1,2-alternate* calix[4]arenes (8 uncomplexed structures, 8 complexes) is uniform in α and β parameters with the exception of two structures with $\beta > 30°$. Since no significant intra- or intermolecular interactions exist in the crystal structures of these compounds (beyond relatively weak CH-π interactions), this behavior remains unexplained.

However, the group of symmetrically tetrasubstituted structures varies significantly in the δ parameter. As a rule, structures with one or more lower rim phenolic oxygen atoms missing tend to have higher δ parameter because of the lack of sterical hindrance at the lower rim (structure YIRGAH [10], Fig. II-9); the resulting arrangement of the calix[4]arene moiety is very similar to the *chair* arrangement of resorcinarenes [1–3]. Sterical hindrance stemming from larger substituents at the lower rim is reflected in lower δ because of less open structure as in the case of structure CAZSEC with four carboxymethoxy groups at the lower rim [10].
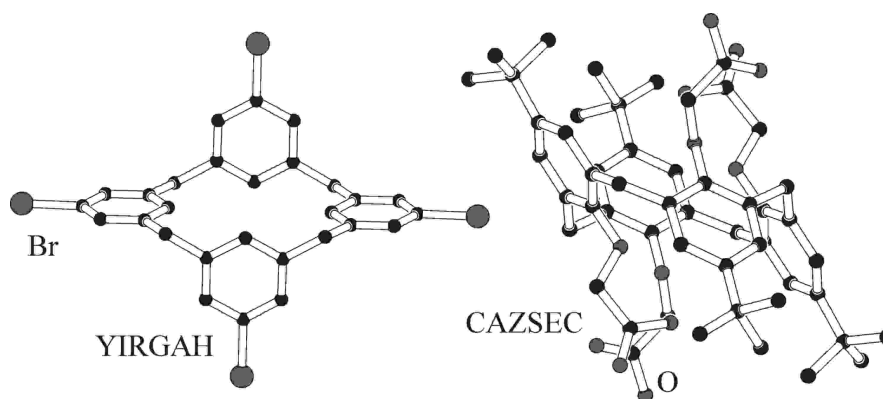
Figure II-9. Structures YIRGAH and CAZSEC [10]

Other substitution patterns with the notable exception of lower rim distally disubstituted structures (16 hits including three complexes) contain each a few molecules only and are therefore not discussed. The only interesting structures within this group are three lower rim single atom 'triple-bridged' structures (3 hits) which have very high value of δ parameter. The influence of this motif on the calixarene base frame is similar to *partial cone* structures described in previous chapter; these structures essentially form the transition between *partial cone* and *1,2-alternate* groups. Representative example is structure POSJUC [10] (Fig. II-10).
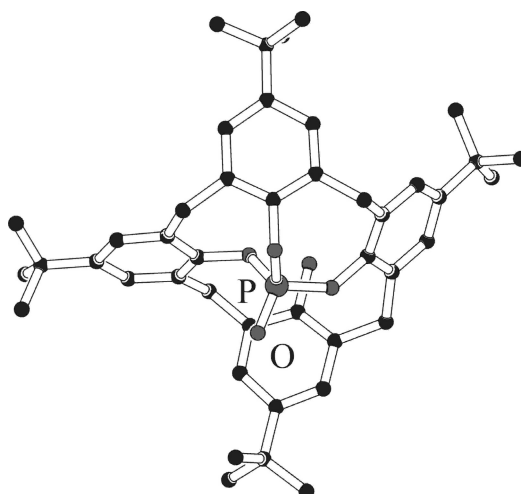

Figure II-10. Single atom 'triple-bridged' 1,2-alternate calix[4]arene POSJUC [10]
(the fourth lower rim substituent has been omitted for clarity)

Since the *1,2-alternate* calix[4]arenes lack cavity, clathrates cannot be defined. However, quite a large variety of inter/intramolecular interactions can be observed in this group. CH-π; π,π- and van der Waals interaction exist between lower rim substituents, ligands from complex or solvent molecules and the calixarene 'half-cavity' in almost all these structures. In addition, structures lacking lower rim hydroxyl groups tend to stack in a chair-like fashion in solid state (intermolecular π, π-interactions between calixarene molecules). Since the structures in this group are few and the effects are usually mixed, no clear dependence of parameters α, β, δ on the type of interaction has been observed. Similarly, because there are only a few structures and these structures vary widely in substitution, no dependence of the calix[4]arene geometry on the type of upper rim substituent was observed.

Complexes of *1,2-alternate* calix[4]arenes generally fall into two categories: metal ion(s) coordinated in a single atom proximal bridge fashion or metal ion(s) coordinated in a single atom 'triple bridge' fashion (Fig. II-11). These structures tend to have high δ because of the forced opening of the calixarene base frame. For comparison, see previous chapter on similar (both coordinated and uncomplexed) *partial cone* structures.
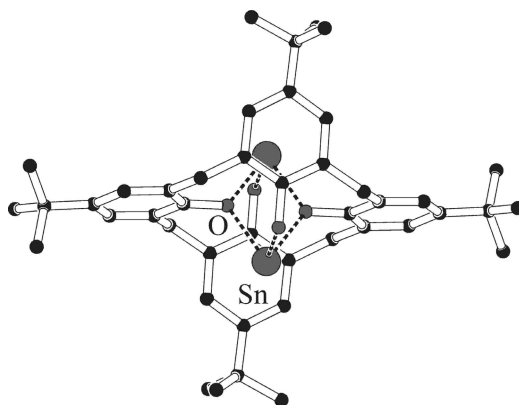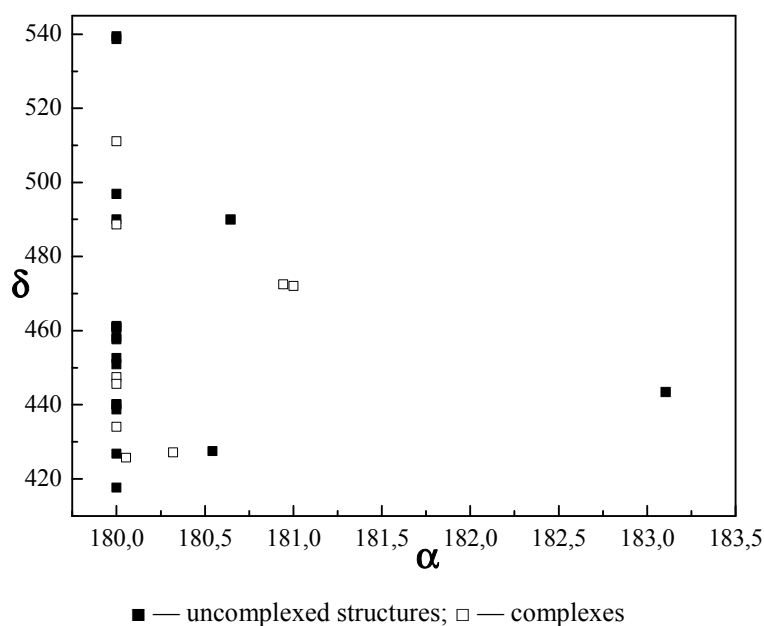
Figure II-11. Structure JOQBEW [10]

Heteroatom-bridged 1,2-alternate calix[4]arenes

The group of *1,2-alternate* heteroatom-bridged calix[4]arenes consists of relatively few hits (23 cif files containing 23 symmetrically tetrasubstituted independent molecules, 6 cif files containing 6 independent molecules with other substitution patterns). Since there are only a few molecules of other substitution patterns than the symmetrically tetrasubstituted one, separation according to substitution patterns was not performed. This group contains a relatively large number of complexes (9 complete cif files, all of them belong to the symmetrically tetrasubstituted group) which are distinguished. Moreover, there are only two structures containing complete cif files with bridge groups other than S (oxygen-bridged ACUNAO and SO_2-bridged OCUFUO [10]; discussed in text below).

Figures 9, 10 show α-δ and β-δ plots of this group. α-β plot is the least informative one (as in the group of methylene-bridged *1,2-alternate* calix[4]arenes, the majority of structures fall to the point [180, 0]) and is therefore not displayed.

In Figures 9, 10, no distinct 'clusters' can be observed. As in the group of methylene-bridged *1,2-alternate* calix[4]arenes, structures are distributed in the δ parameter. Likewise, there is quite a large number of inter/intramolecular interactions between calixarene molecules, upper or lower rim substituents and calixarene phenyl rings or solvent molecules and the calixarene 'half-cavity'. No distinct dependence of the calix[4]arene symmetry on the type of interaction has been observed, however. Similarly, no dependence on the type of upper/lower rim substituents was observed in this group.

■ — uncomplexed structures; □ — complexes

Figure 9. The α-δ plot of the group of 1,2-alternate heteroatom-bridged calix[4]arenes

■ — uncomplexed structures; □ — complexes
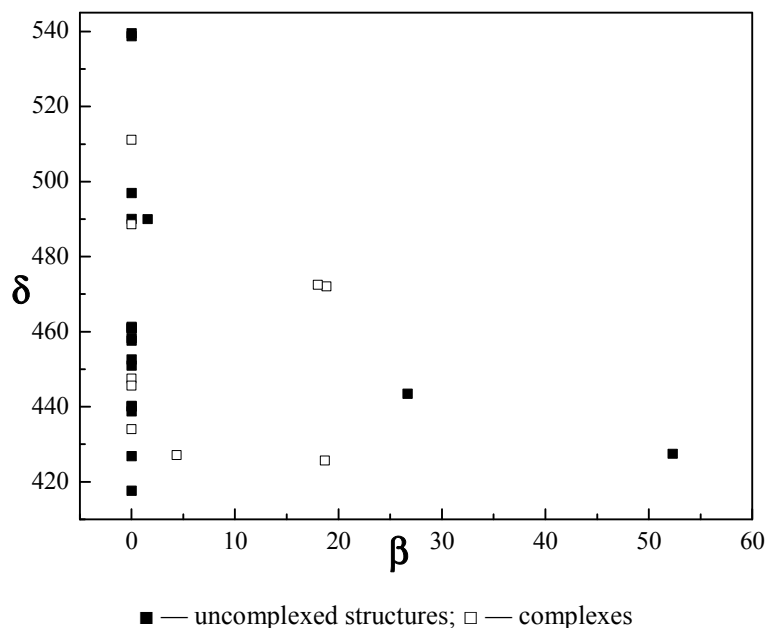
Figure 10. The β-δ plot of the group of 1,2-alternate heteroatom-bridged calix[4]arenes

There are two deviating hits in Figure 11 with δ > 520°. One of them is structure ACUNAO [10], a unique structure containing oxygen bridges, *m*-substituted phenyl rings, two hydrogen atoms and two carbon atom substituents at the lower rim. The geometry of this structure is close to that of *chair* resorcinarenes. The other deviating hit in Figure 11 is structure FUDXAD (Fig. II-12), which contains very short one atom proximal bridges at the lower rim and therefore a very open structure. The only other proximally bridged lower rim structure in this group is structure BALNOS (two crown-5 bridges) with significantly more average geometry owing to longer and more flexible lower rim substituents. Figure II-12 depicts structures FUDXAD and BALNOS [10] showing the dependence of the calixarene geometry on the length of the proximal bridge. Structure BALNOS has very low δ (426°) which reflects a relatively closed 'cavity' in this case. Similar effects have been observed previously in the group of methylene-bridged *1,2-alternate* structures.
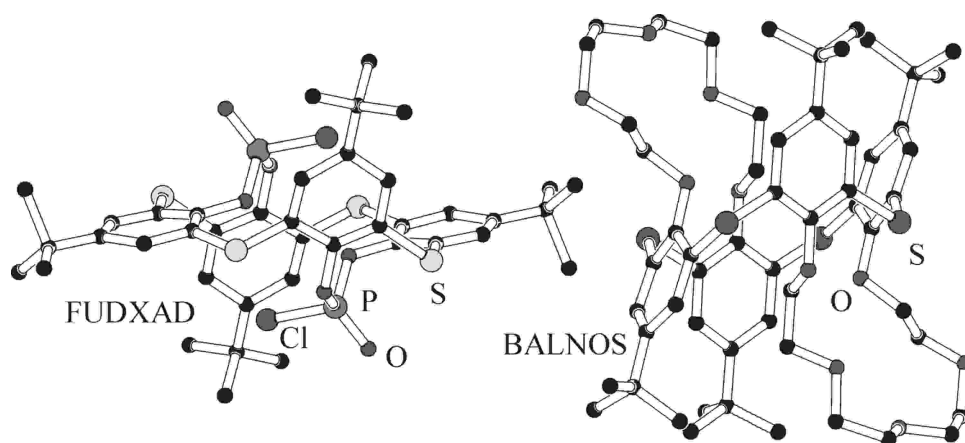

Figure II-12. Structures FUDXAD and BALNOS [10]

The deviating hit in Figures 9, 10 with α > 183° and β ~ 27° is structure ETUQAL [10]. The hit with β ~ 52° in Figure 10 is a similar tetrasubstituted structure ETUQOZ [10]. Bulky lower rim substituents (three in ETUQAL, four in ETUQOZ) cause deformation of the base calixarene skeleton mostly because of sterical hindrance; both structures possess CH-π interaction between upper rim *t*-butyl substituent and one calixarene phenyl ring from different calixarene molecule which is probably behind increased β. Both structures have low δ (430–440°) which indicates a relatively closed structure (Fig. II-13).
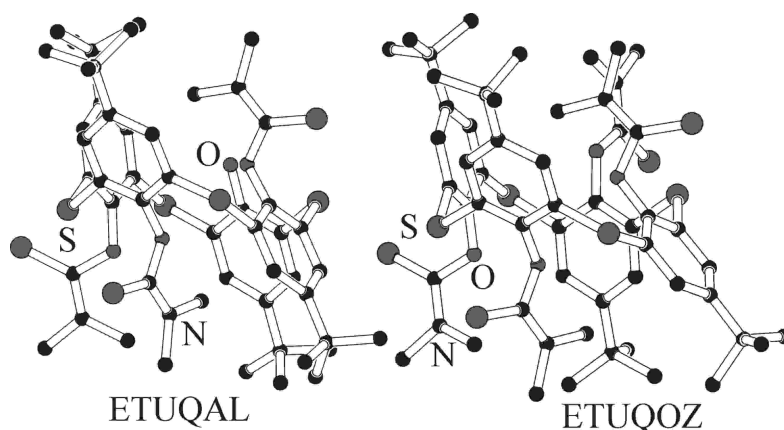
Figure II-13: Structures ETUQAL, ETUQOZ [10]

It is obvious that the geometry of the calix[4]arene base frame regarding opening of the structure is dependent on the substitution of the calixarene skeleton and is reflected by parameter δ as in the group of methylene-bridged *1,2-alternate* structures. This dependence is demonstrated on a group of symmetrically tetrasubstituted uncomplexed *1,2-alternate* heteroatom-bridged calix[4]arenes with upper rim *t*-butyl substituents with $\alpha \sim 180°$, $\beta \sim 0°$ (the main group in Figures 9, 10 with δ between 410–460°).

The dependence of the geometry of these molecules on the size of lower rim substituents (and henceforth the sterical hindrance) is depicted in Figure 11; it shows the plot of the δ parameter against the 'length' of the lower rim substituents expressed as a number of atoms in chain from the calixarene phenyl oxygen (included) to the most distant atom on the substituent (also included).
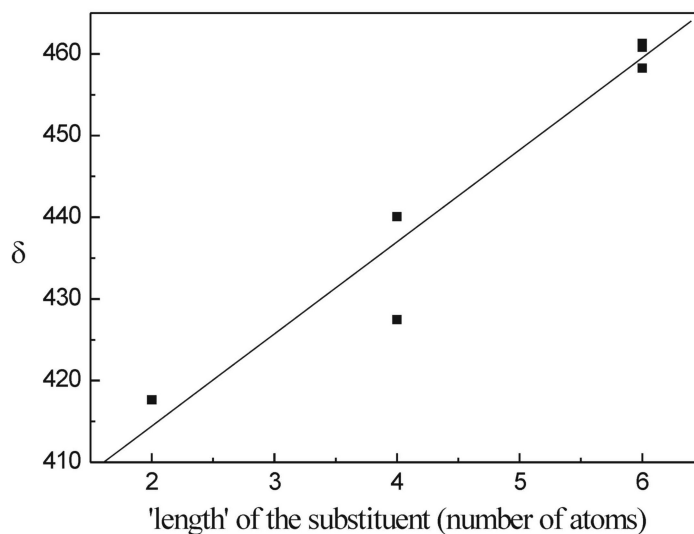
Figure 11. Dependence of the δ parameter on the 'length' of the lower rim substituents

The group of *1,2-alternate* heteroatom-bridged calix[4]arenes contains relatively large number of complexes (compared to the *partial cone* group). All complexes are derived from symmetrically tetrasubstituted calixarenes, which simplifies evaluation of inter- and/or intramolecular interactions on their geometry.

The two deviating hits with $\beta \sim 18°$ and $\delta \sim 470°$ in Figure 11 (β-δ plot) are structures containing proximally coordinated two oxygen atoms at the lower rim (and the bridge between them) compared to other structures in this chapter with none or all lower rim oxygen atoms coordinated. This type of coordination forces the structures more open as demonstrated by higher δ value; nonsymmetrical coordination at the lower rim is probably behind slightly increased β. The representative structure MOTMUD [10] is shown on Figure II-14.
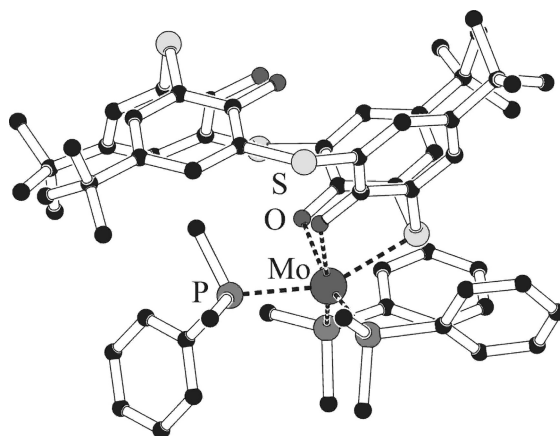
Figure II-14. Structure MOTMUD [10]

The two deviating hits with β = 0° and δ > 480° in Figure 11 are structures OCUFUO and TARFIC [10] (Fig. II-15). Structure OCUFUO is the only structure among *1,2-alternate* calix[4]arenes which contains sulfone bridges, one oxygen atom from each of two distal bridges participates on the octahedral coordination of two Cu(II) ions. The coordination is similar to the proximal coordination mentioned above and the value of the δ parameter is therefore larger. The structure TARFIC contains four proximally Rh(III) complexed thiolato groups at the lower rim; there is a structure with the same coordination pattern (TARFAU, Ir(III) complex) possessing an average geometry (δ ~ 445°). These structures show only weak intermolecular CH-π interactions; the difference in δ therefore seems to arise from different ionic radii of Rh and Ir. The size of the calixarene lower rim is obviously better suited for larger Ir(III), the coordination polyhedron is therefore less strained and the influence on the calixarene base frame not so profound. On the other hand, smaller Rh(III) forces the lower rim oxygen atoms closer and the structure is therefore more open as confirmed by higher δ.

The coordination of all mentioned lower rim complexes (two proximal oxygen atoms and the bridge between them) is very close to one of coordination patterns occurring in the *cone* group (see Part I, [7]).
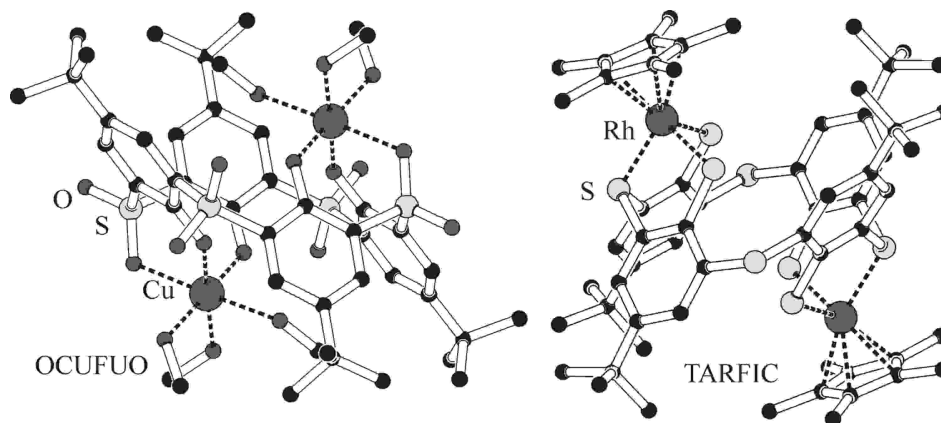

Figure II-15. Structures OCUFUO and TARFIC [10]

Other complexes from the average group with δ ~ 440° in Figure 11 belong to polymeric upper rim coordinated sulfonato calix[4]arenes. In conclusion, upper rim complexation does not seem to affect the geometry of the calixarene base frame as significantly as the lower rim and/or bridge coordination.

Conclusion — 1,2-alternate structures

Calix[4]arenes lacking lower rim substituents tend to have their base frame deformed towards that of *chair* calix[4]resorcinarenes (average α, β; δ ~ 500° and more). On the other hand, structures with very large lower rim substituents tend to have low δ because of a more closed structure caused by sterical hindrance at the lower rim. The parameter δ can therefore serve as an indicator for the degree of opening of the structure.

Single atom proximally or 'triple-bridged' structures have also very open structures as reflected by high δ along with somewhat increased α and β.

To sum up, the best way to immobilize and 'open' the *1,2-alternate* calix[4]arene base frame is to proximally bridge the lower rim by a single atom (preferably from the second period) or to form a single atom 'triple bridge' as in the *partial cone* group. A variety of atoms and cations can be utilized for this purpose; the single atom 'triple bridge' appears to be the more efficient way to open structures. Another method of opening the calixarene base frame is removal of lower rim phenolic oxygen atoms and the resulting decrease of sterical hindrance at the lower rim. On the other hand, large substituents on the lower rim phenolic oxygen atoms tend to produce more closed structures (opposite effect). Direct coordination at the lower rim phenolic oxygen atoms can also significantly affect the calixarene geometry; little influence has been observed in the case of coordination at the upper rim substituents.

As in the group of *partial cone* structures, *1,2-alternate* methylene-bridged calix[4]arenes which contain four lower rim hydroxyl groups are uncommon. On the other hand, in the group of heteroatom-bridged structures there is quite a number of structures with lower rim hydroxyl groups in this group which confirms that the hydrogen bonds at the lower rim in heteroatom-bridged structures are weaker than in their methylene-bridged counterparts.

1,3-alternate structures

Methylene-bridged 1,3-alternate calix[4]arenes

This group contains relatively small number of symmetrically tetrasubstituted structures (42 out of 184 cif files, which correspond to about 23 %). On the other hand, the number of lower rim distally bridged structures in this conformation is the largest of all methylene-bridged calix[4]arenes (81 from the total of 184 cif files, 44 %). For further details, see Table 3.

There are also quite a large number of complexes in this group (30 %); the complexes are therefore distinguished.

Table 3

1,3-alternate methylene-bridged calix[4]arenes from [10]

| Type	No. of cif files	%	No. of independent molecules	%
Symmetrically tetrasubstituted	42	22.8	43	22.4
Distally bridged lower rim	81	44.0	84	43.8
Other	61	33.2	65	33.9
Total	184	100	192	100

α-β plot (Fig. 12) and β-δ plot (Fig. 13) depict almost continuous distribution of all substitution patterns; no pattern forms a distinct group and only little amounts of trends can be deducted. First, symmetrically tetrasubstituted structures are all uniform in α parameter, differing significantly in β. No distinct 'clusters' can be observed in this group.

On the other hand, lower rim distally bridged structures form a small group at $\beta < 350°$ ('cluster' 12-I) and a significantly larger group at higher β ('cluster' 12-II). 'Cluster' 12-I contains 10 cif files with 11 independent molecules; this cluster is centered at [180.92; 326.75; 4.54] with a standard deviation of [0.86; 4.98; 3.45]. 'Cluster' 12-II contains 58 cif files with 67 independent molecules; this 'cluster' is centered at [181.54; 424.64; 11.20] with a standard deviation of [1.48; 21.18; 9.15].

Several trends can be observed within the β-δ plot. The group of symmetrically tetrasubstituted molecules remains uniform even in the δ parameter; only a few structures have $\delta > 10°$. The two distinct groups at lower/higher β ('clusters' 13-I, 13-II) of molecules with distally bridged lower rim remain even in this plot. However, the group of other substitution patterns distributed almost evenly in the δ parameter.
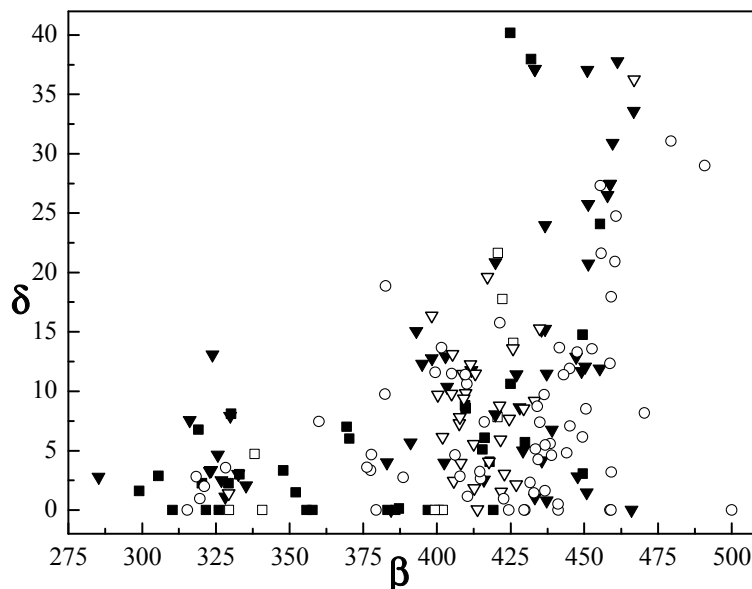
In the group of symmetrically tetrasubstituted structures in Fig. 13, several hits deviate from the main group. Some of the structures with $\delta > 15°$ contain large and flexible lower rim substituents one of which reaches into the 'cavity' formed by the two opposite phenyl rings (CH-π interactions; structure AFEFUM [10], Fig. II-16). Since the substituents are large, it is impossible for both distal substituents to be inside the 'cavity' and the structure is therefore deformed in the δ parameter. Deformation in the δ parameter may also arise from sterical hindrance by four bulky lower rim substituents; the substituents are simply too large to fit

inside the 'cavity'. In the case of complexes, the deformation in the δ parameter is caused by nonsymmetrical proximal coordination of the lower rim by two metal ions (structure FUTKAG [10], Fig. II-18). The effect of the proximal coordination can be demonstrated on the fact that other complexes of this group which contain more symmetrical distal lower or upper rim coordination have low δ. Other structures in the symmetrically tetrasubstituted group have more symmetrical arrangement with δ < 15°.
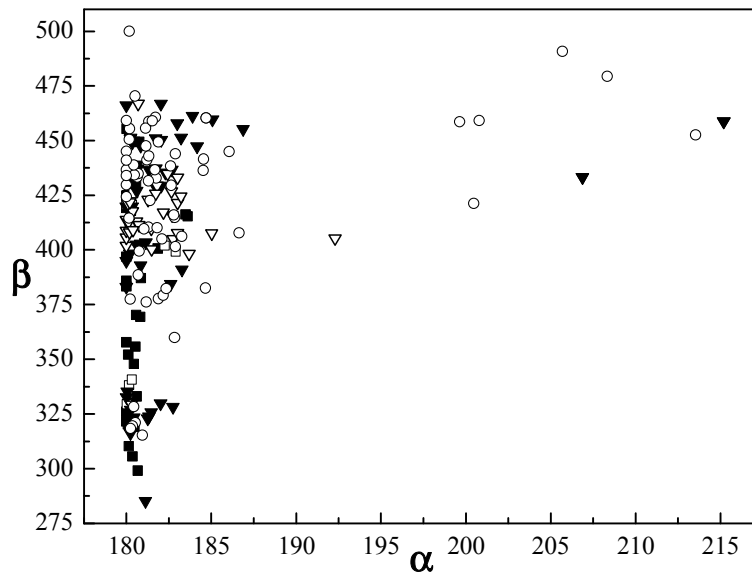
■ — symmetrically tetrasubstituted — uncomplexed; □ — symmetrically tetrasubstituted — complex;
▼ — distally bridged lower rim — uncomplexed; ▽ — distally bridged lower rim — complex;
○ — other substitution patterns — complexes not distinguished

Figure 12. The α-β plot of the group of 1,3-alternate methylene-bridged calix[4]arenes

■ — symmetrically tetrasubstituted — uncomplexed; □ — symmetrically tetrasubstituted — complex;
▼ — distally bridged lower rim — uncomplexed; ▽ — distally bridged lower rim — complex;
○ — other substitution patterns — complexes not distinguished

Figure 13. The β-δ plot of the group of 1,3-alternate methylene-bridged calix[4]arenes

The β parameter reflects the degree of opening of the calix[4]arene 'cavity' (see Fig. II-16, II-17) and can be therefore used to describe the geometry of uncomplexed calix[4]arenes from this group. As a rule, structures with low β parameter have more closed 'cavities' which corresponds to the presence of π, π-interactions between the opposite calix[4]arene phenyl rings (e.g. structure FAZFAO [10], Fig. II-16). Bringing of the calixarene opposite phenyl rings to close proximity is often facilitated by lower rim sterical hindrance caused by presence of bulky lower rim substituents in these structures. On the other hand, if the lower rim substituent (AFEFUM [10], Fig. II-16) or other molecule (GOTHAY [10], Fig. II-16) enters the calixarene 'cavity', π, π-interaction between the opposite rings is disrupted and as a result the structure is more open as reflected by higher value of the β parameter (see Fig. II-16). Similar effect has been already observed in *partial cone* structures.
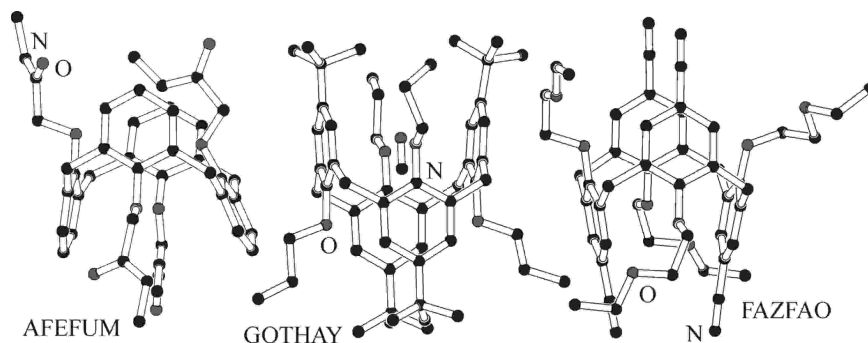

Figure II-16. Structures AFEFUM (β ~ 425°), GOTHAY (β ~ 370°) and FAZFAO (β ~ 320°) [10] demonstrating effects of a filled and empty 'cavity' on the geometry of the calix[4]arene base frame

The type of the upper rim substituent plays less transparent role; structures with nonpolar bulky upper rim substituent (*t*-butyl) tend to have more open structures with larger β parameter probably because of the sterical hindrance at the upper rim. On the other hand, in structures which contain upper rim polar substituents capable of π, π- and/or dipolar interaction the β parameter differs in dependence whether the π, π-interaction takes place between the calixarene opposite phenyl rings bearing these substituents or whether there is an interaction between the upper rim substituents and some other molecule inserted into the calixarene 'cavity' (this molecule may be even similar substituent from another calixarene molecule). An example of these three effects is the trio of structures KARNEX, KARNIB, KARNUN [10] (Fig. II-17).

Structure KARNEX contains phenyl groups at the upper rim; however, the π, π-interaction of the calixarene opposite phenyl rings is disrupted by interfence of lower rim substituents and phenyl group from another calixarene molecule (not depicted, β ~ 449°). Structure KARNIB contains bromine atoms at the upper rim; nothing prevents π, π-interaction of the calixarene opposite phenyl rings in this case (β ~ 329°). Structure KARNUN with bulky *t*-butyl groups at the upper rim adopts less deformed conformation because of sterical hindrance at the upper rim and the contribution of lower rim substituents which partially reach into the 'cavity' (β ~ 449°).
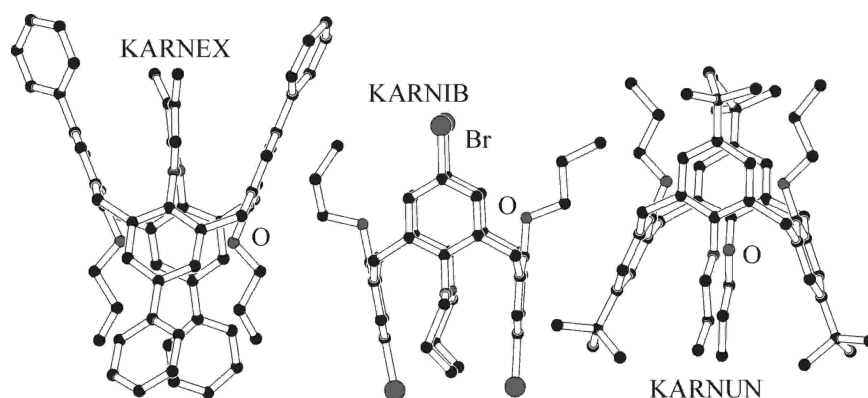

Figure II-17: Structures KARNEX, KARNIB and KARNUN [10]

There are several possible modes of metal ion coordination within the symmetrically tetrasubstituted group: lower rim phenolic oxygen or sulfur atoms as in structures FUTKAG, HELYAY [10] (proximal or distal coordination, Fig. II-18), lower rim phenolic oxygen atoms combined with donor atoms from the corresponding lower rim substituent (distal coordination), lower rim substituents (distal coordination), upper rim distal coordination (AHUCEL [10]) or distal coordination on a rigid upper rim substituent. Since there are only a few structures of coordinated calix[4]arenes in this group, drawing extensive conclusions is impossible. However, the upper rim coordinated structures have all very low β parameter which is caused by bringing of the opposite phenyl rings to close proximity by their distal coordination; lower rim coordinated structures where this restraint is absent have all more open structures as demonstrated by higher values of the β parameter.
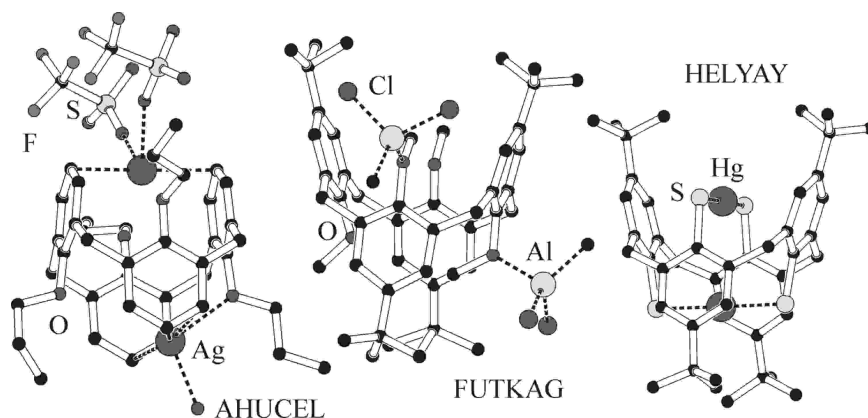

Figure II-18. Structures of the Ag(I) complex AHUCEL (β ~ 338°), Al(III) complex FUTKAG (β ~ 422°) and Hg(II) complex HELYAY (β ~ 426°) [10] demonstrating the influence of different types of upper/lower rim coordination on the geometry of the calix[4]arene

Lower rim bridged structures (49 uncomplexed, 32 complexes) in the group of *1,3-alternate* calix[4]arenes have a few unique specifics. First, proximal bridges are impossible within this group unless these bridges were very large. Single atom proximal or 'triple-bridging' at the lower rim described in the groups of *partial cone* or *1,2-alternate* calix[4]arenes which can significantly affect the geometry of the calix[4]arene base frame is impossible from sterical reasons. The remaining possibility is distal lower rim bridge; according to Table 3, this form of lower rim substitution is very popular within this group. For the most part, flexible lower rim bridges with insignificant sterical demands have been utilized in the vast majority of these structures and the length of these lower rim bridges (number of atoms in the bridge) has little effect on the geometry of the calix[4]arene base frame. In the case of more rigid lower rim bridges, some effect on the geometry of the calix[4]arene moiety has been observed (see next paragraph).

The group of lower rim distally bridged *1,3-alternate* calix[4]arenes formed two distinct groups in parameter β ('clusters' 13-I, 13-II; Fig. 12, 13). The larger/lower β seems to reflect the same effects as in the group of symmetrically tetrasubstituted molecules (namely reaching of lower rim substituent into the calixarene cavity). The group with lower β also contains more molecules with more rigid lower rim bridges compared to the group with larger β.

Complexes of the lower rim bridged *1,3-alternate* calix[4]arenes form a uniform group because the coordination takes place at the lower rim substituent and mostly even at lower rim phenolic oxygen atoms; the resulting cation-π interaction between this metal ion and two opposite calixarene phenyl rings ensures a relatively open structure and therefore higher β (see structure AVERUO, Fig. II-19). As a rule, the coordination at the lower rim does not significantly affect the geometry of the calix[4]arene base frame as described by relatively uniform values of the β parameter; all these structures belong to 'cluster' 13-II. The only notable exception within this group is one structure coordinated distally at the rigid upper rim substituents; this structure falls into the 'cluster' 13-I. The low value of β in this case reflects the π, π-interaction present between the calix[4]arene opposite phenyl rings and the resulting deformation of the calix[4]arene moiety towards a more closed structure.
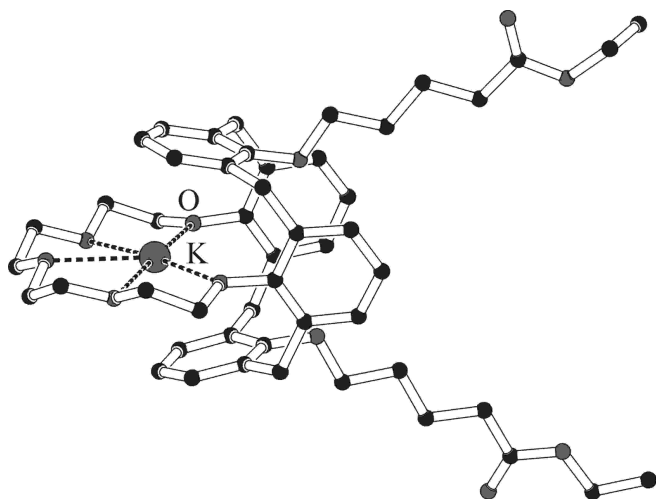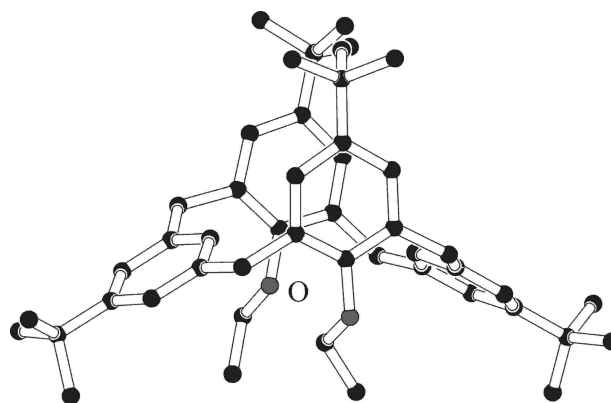
Figure II-19. Structure AVERUO [10]

Figure II-20. Structure YUYYOG [10]

Among *1,3-alternate* calix[4]arenes with other substitution patterns, the only relatively numerous group is the group of lower rim distally disubstituted structures (19 hits including 6 complexes). The values of the β in the calix[4]arenes with other substitution patterns generally seem to follow the same rules as those for the symmetrically tetrasubstituted group. However, there are several structures with relatively high α parameter. Structures with $\alpha > 200°$ (e.g. YUYYOG [10], Fig. II-20) lack lower rim phenolic oxygen atoms and, because of missing sterical hindrance at the lower rim, their conformation is similar to that of *saddle* conformers of calix[4]resorcinarenes (for comparison, see the effect of missing phenolic oxygen atoms in the *1,2-alternate* group). Slightly increased α parameter is also present in the structures of calix[4]quinones.

Effect of a filled/empty 'cavity' in the group of *1,3-alternate* methylene-bridged calix[4]arenes is depicted in Fig. 14 and 15. The main difference from the *cone* and *partial cone* conformers is that *1,3-alternate* calix[4]arenes have two 'cavities'; each of these may be filled or empty.
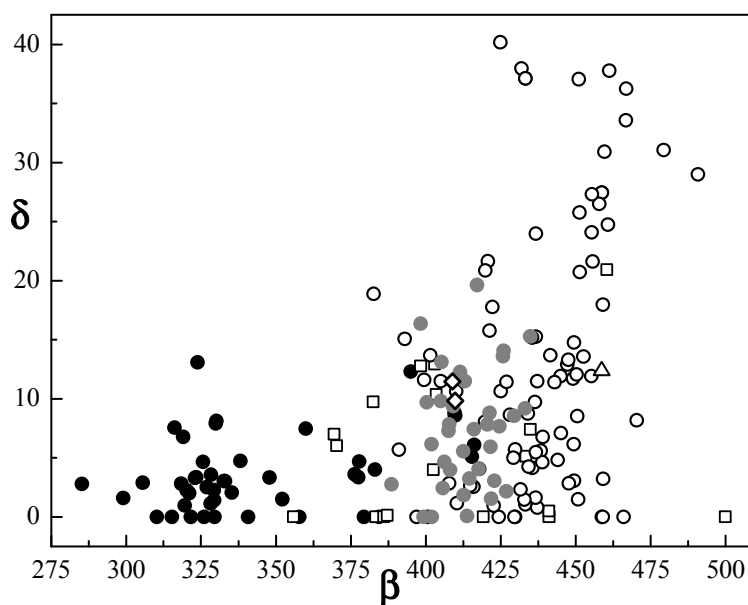
β-δ plot; ● — no molecule inside any 'cavity'; ● — metal ion inside at least one 'cavity'; □ — solvent molecule inside at least one 'cavity'; ○ — lower rim substituent inside at least one 'cavity'; Δ — upper rim substituent from another molecule inside the 'cavity'; ◊ — ligand from a complex inside the 'cavity'

Figure 14. Dependence of the geometry of 1,3-alternate methylene-bridged calix[4]arenes on the type of clathrate

From Figure 14, it is obvious that structures with empty 'cavities' have low β whereas for clathrates the reverse is true. Empty 'cavities' allow undisturbed π, π-interaction between two opposite calix[4]arene phenyl

rings; the structure is therefore more closed and the parameter β lies below 400° (see similar effect in *partial cone* structures). Filled 'cavities' result in more open structures. Uncomplexed structures with both 'cavities' filled have β usually above 430°; when only one 'cavity' is filled this parameter drops to about 400°. These effects are depicted in Fig. 15. The group of complexes with one or two metal ions inside the 'cavities' is relatively uniform; the number of encapsulated metal ions does not seem to matter.

A large number of structures with lower rim substituent inside the 'cavity/ies' have δ > 20° (Fig. 14). The reason for this behavior is probably that in case of bulky lower rim substituents only one of these distal substituents can be encapsulated; the other one lies necessarily outside the 'cavity' because of sterical reasons. This arrangement at the lower rim may lead to deformations in δ.
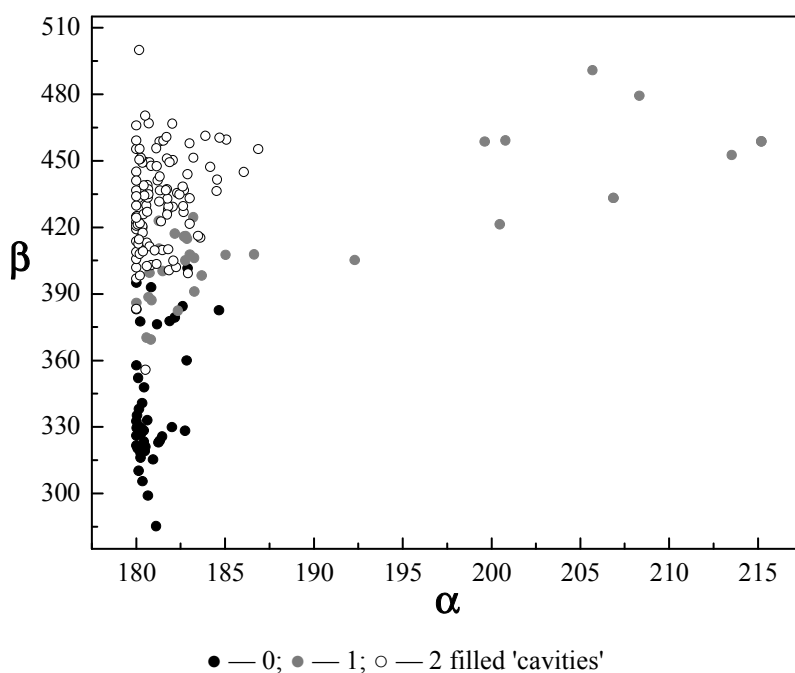

● — 0; ● — 1; ○ — 2 filled 'cavities'

Figure 15. Effect of the number of filled 'cavities' on the geometry of 1,3-alternate methylene-bridged calix[4]arenes

There are three 'clusters' in Figure 15: the first one ('cluster' 15-I, 44 cif files with 47 independent molecules) centered at [180.80; 344.34; 4.48] with a standard deviation of [1.00; 32.13; 4.50] which contains molecules with empty 'cavities'; the second one ('cluster' 15-II, 21 cif files with 24 independent molecules) centered at [182.16; 402.86; 7.27] with a standard deviation of [1.60; 15.55; 5.45] containing molecules with one 'cavity' filled and α < 190° and the third 'cluster' ('cluster' 15-III, 99 cif files with 110 independent molecules) centered at [181.33; 432.16; 10.00] with a standard deviation of [1.46; 21.30; 9.72] containing molecules with both 'cavities' filled.

Heteroatom-bridged 1,3-alternate calix[4]arenes

The group of *1,3-alternate* heteroatom-bridged calix[4]arenes contains 63 cif files with 73 independent molecules (significantly more than the *partial cone* and *1,2-alternate* groups). However, complexes are scarce (4 complete cif files with 5 independent molecules, 2 incomplete cif files compared to its methylene-bridged counterpart). The complexes are therefore not distinguished. In addition, all types of bridges (S, SO, SO$_2$, N, Si, O) were observed in this group (compared to the *cone*, *partial cone* and *1,2-alternate* groups).

Figure 16 depicts α-β plot of all calixarenes from this group divided according to their substitution patterns. No distinct groups among the symmetrically tetrasubstituted structures can be observed. On the other hand, lower rim distally substituted, upper rim symmetrically tetrasubstituted structures form a distinct group at β ~ 440° with several structures located at lower β. Other substitution patterns apart from these two ones contain only a few structures each and are therefore not distinguished.

The main group of lower rim distally substituted, upper rim symmetrically tetrasubstituted structures ('cluster' 16-I) with β > 400° contains 6 cif files with 8 independent molecules and is centered at [182.11; 437.39; 10.92] with a standard deviation of [2.54; 15.98; 6.96]. Structures from 'cluster' 16-I are lower rim

bridged with crown 5 bridge(s). There are three structures with $\beta < 400°$ which do not fall into this group; these structures are either not bridged at the lower rim or are bridged with longer crown ether chain (e.g. crown 6).
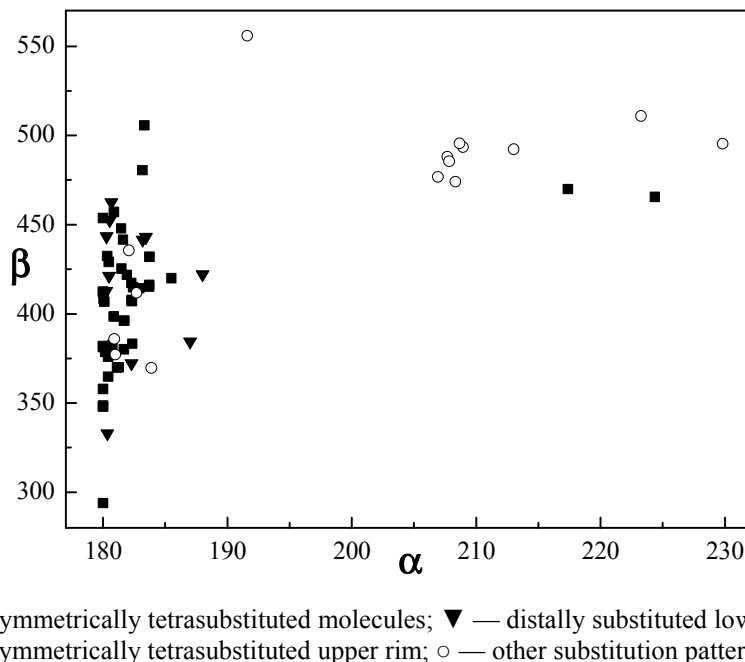

■ — symmetrically tetrasubstituted molecules; ▼ — distally substituted lower rim, symmetrically tetrasubstituted upper rim; ○ — other substitution patterns

Figure 16. The α-β plot of all 1,3-alternate heteroatom-bridged calix[4]arenes

Figures 17, 18 (α-β plots) depict dependence of the calix[4]arene symmetry on the type of clathrate. Similar effects have been already observed for the methylene-bridged group.
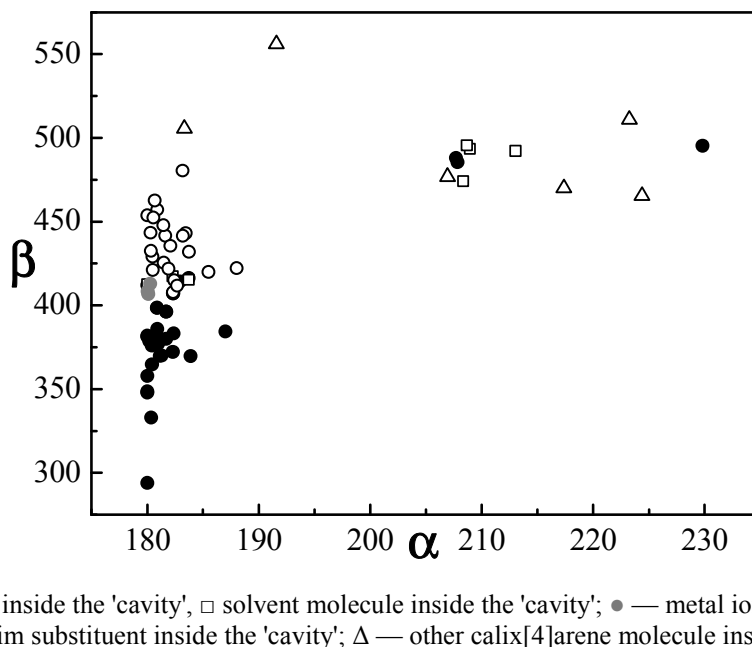

● — no molecule inside the 'cavity', □ solvent molecule inside the 'cavity'; ● — metal ion inside the 'cavity'; ○ — lower rim substituent inside the 'cavity'; Δ — other calix[4]arene molecule inside the 'cavity'

Figure 17. Dependence of the symmetry of the calix[4]arene scaffold on the type of the clathrate

As *1,3-alternate* calixarenes have two 'cavities', only one or both of them can be filled or empty. Structures which have both 'cavities' empty have $\beta < 400°$; or $\alpha > 200°$ and large β if they lack substituents at the lower rim. Structures with only one 'cavity' filled have generally $\beta \sim 410°$, structures with both 'cavities' filled have larger β because of a more open structure (see Fig. 18). Similar effect has been observed within

the methylene-bridged group. Since there are only a few molecules in each group, calculation of 'clusters' was not performed.
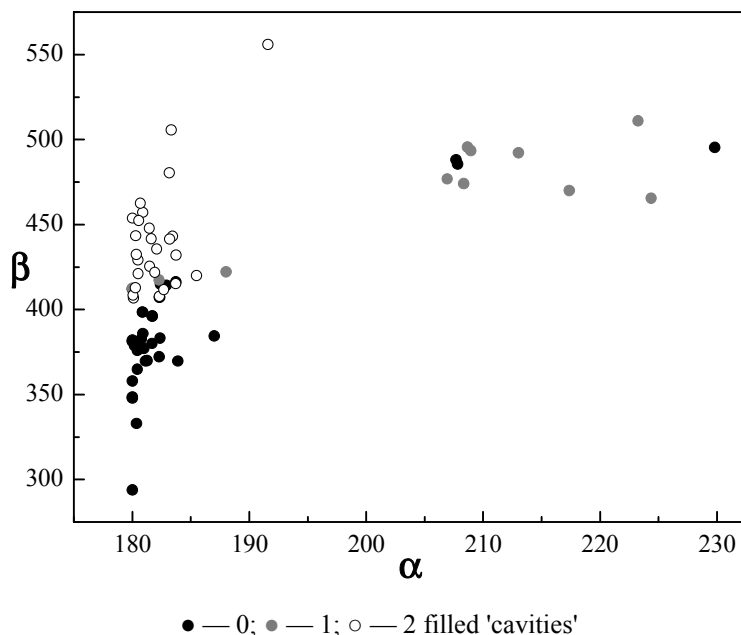

● — 0; ● — 1; ○ — 2 filled 'cavities'

Figure 18. Effect of a filled 'cavity' on the geometry of 1,3-alternate heteroatom-bridged calix[4]arenes

Figure 19 shows effects of upper/lower rim substitution on the geometry of the calix[4]arene scaffold. From Figure 19, it can be seen that structures which contain alkylated or acylated lower rim hydroxyl groups are all relatively uniform. Unlike other previously described groups, there are a large number of structures with missing hydroxyl groups at the lower rim in the *1,3-alternate* heteroatom-bridged group; these structures have α > 200° and/or β > 500° in Figure 19.

■ — nonpolar substituent at the upper rim, hydroxyl or no substituent at the lower rim;
● — polar substituent at the upper rim, hydroxyl or no substituent at the lower rim;
▲ — no substituent at the upper rim, hydroxyl or no substituent at the lower rim;
□ — nonpolar substituent at the upper rim, substituted lower rim hydroxyl groups;
○ — polar substituent at the upper rim, substituted lower rim hydroxyl groups;
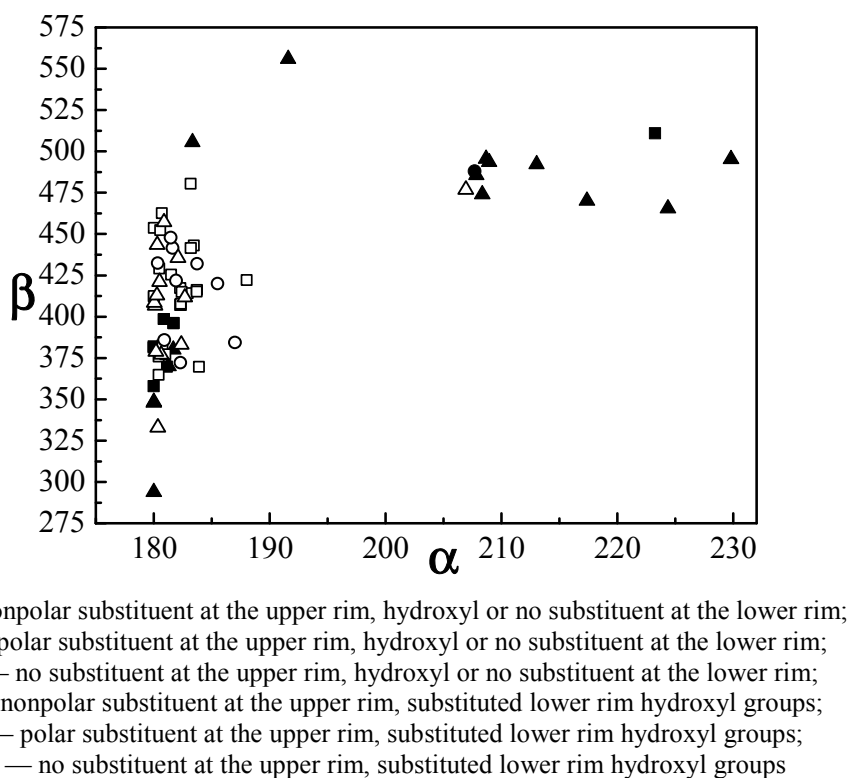Δ — no substituent at the upper rim, substituted lower rim hydroxyl groups

Figure 19. Dependence of the symmetry of the calix[4]arene scaffold on the type of the substitution

Since there are altogether six possible types of bridge in the group of *1,3-alternate* heteroatom-bridged calix[4]arenes, Figure 20 depicts this group divided according to the type of the bridge.
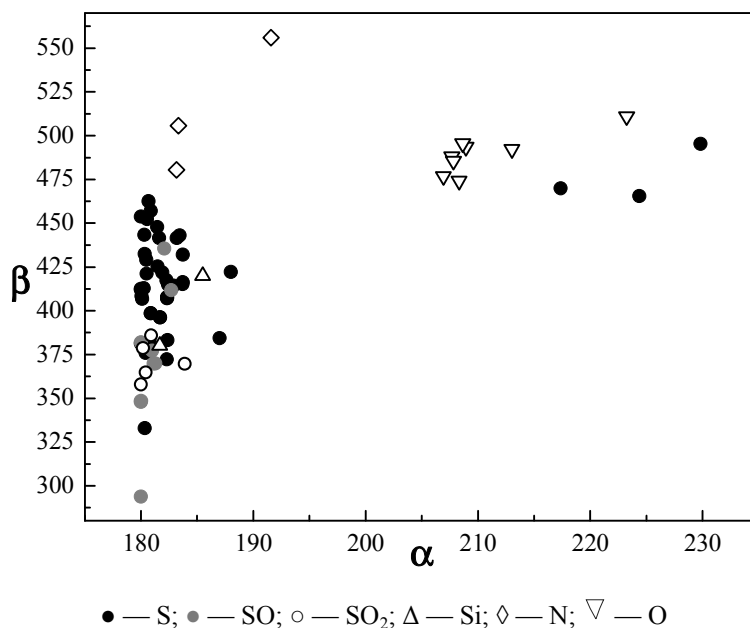

● — S; ● — SO; ○ — SO$_2$; Δ — Si; ◊ — N; ▽ — O

Figure 20. The α-β plot of all 1,3-alternate heteroatom-bridged calix[4]arenes divided according to the type of the bridge

The type of the bridge seems to have some effect on the calixarene stereochemistry (Fig. 20). It can be clearly seen that the nitrogen- and oxygen-bridged calix[4]arenes form distinct groups. Likewise, all sulfone-bridged calix[4]arenes are very close to each other. Thanks to the symmetrical SO$_2$ bridge, these structures are very symmetrical with all phenyl ring angles to the reference plane of about 90° (the opposite calixarene phenyl rings are almost parallel in all these structures, see Fig. II-21). These values of the phenyl ring angles account for the relatively low β value. The sulfone-bridged group is uniform in α and β and differs slightly in δ ('cluster' 20-I; 5 cif files with 5 independent molecules; center at [181.08; 371.41; 9.85], standard deviation [1.44; 9.93; 7.91]); no dependence of the δ parameter in the sulfone group on the size and type of substituents was observed.
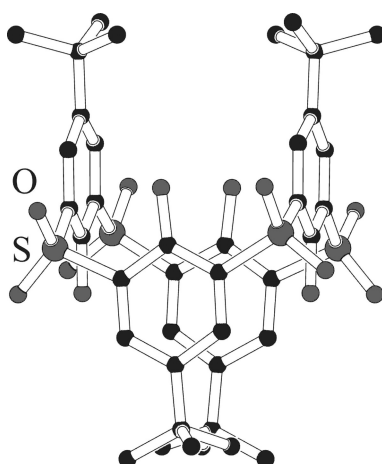

Figure II-21. Structure NUHFOL [10]

The group of SO-bridged calix[4]arenes is relatively uniform in parameter α; however, in the β parameter there are significant differences. No correlations between this parameter and the substitution and/or size of the upper and lower rim substituents were found. The hit with β < 300° is structure LEQMID [10], a structure with SO bridges and unsubstituted upper rim. All structures possessing SO bridges in this group (includ-

ing the structure LEQMID) have these bridges arranged in an *up-*, *down-*, *up-*, *down-* (aeae) fashion but only the structure LEQMID has unsubstituted upper rim which allows for a more efficient π, π — stacking of two opposite calixarene rings (and CH-π interaction between upper rims from different molecules) and has therefore lower β (Fig. II-22).
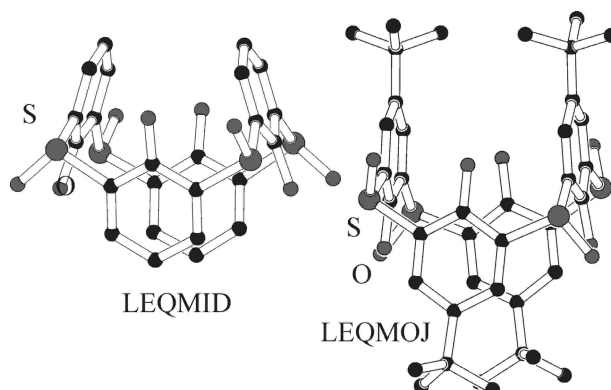

Figure II-22. Structures LEQMID and LEQMOJ [10]

The oxygen-bridged group is likewise uniform in α, β and varies in δ; because of the complexity of the substitution patterns in this group, no conclusions concerning dependence of the δ parameter on the type and size of the substituents could be made. This group contains 6 cif files with 8 independent molecules ('cluster' 20-II) and is centered at [210.58; 489.59; 11.50] with a standard deviation of [5.09; 10.82; 9.11]. The conformation of these structures is very similar to those of *saddle* resorcinarenes. An example of an oxygen-bridged structure shows Figure II-23.

Nitrogen-bridged structures are NANREA, SUDMOT and TAZMEN [10], Figure II-24. Structure TAZMEN is a clathrate with *m-* substituted phenyl rings (the lonely hit with α ~ 190° and β ~ 550°). The common feature of all these structures is a very open cavity (no intramolecular π, π-stacking). The factors affecting the calixarene stereochemistry coming into play are numerous: substitution of N bridges, filled or empty cavity, intermolecular π, π- and CH-π interaction and substitution of the upper and lower rim and possible *m*-substitution. Because of too few structures of this type, these stereochemical factors are very difficult to evaluate.
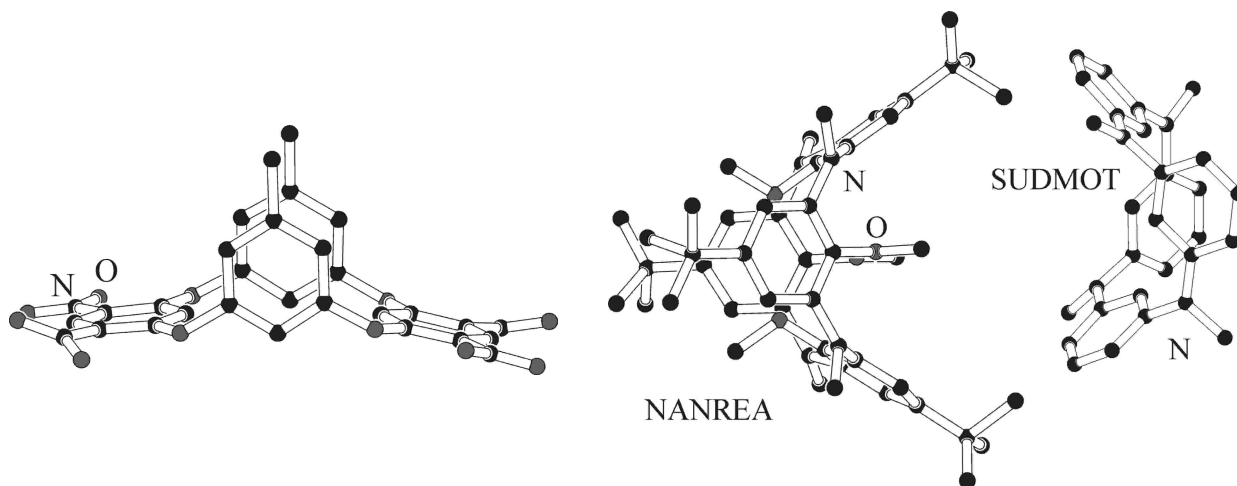

Figure II-23. Structure FEZZIU [10]

Figure II-24. Structures NANREA, SUDMOT [10]

Since in the silicon-bridged group there are only two structures it is difficult to draw any conclusions here. Conformations of these structures are similar to those of the sulfone-bridged group.

Dependence of the β parameter on the type of the bridge can be shown on the example of lower rim methoxy, upper rim *t*-butyl tetrasubstituted *1,3-alternate* calix[4]arenes with different bridge groups (all these structures are uncomplexed). The α-β plot is given in Figure 21. The majority of relevant structures are

discussed elsewhere in this chapter. No similar uncomplexed methylene-bridged structure was found in the CSD [10] for comparison.
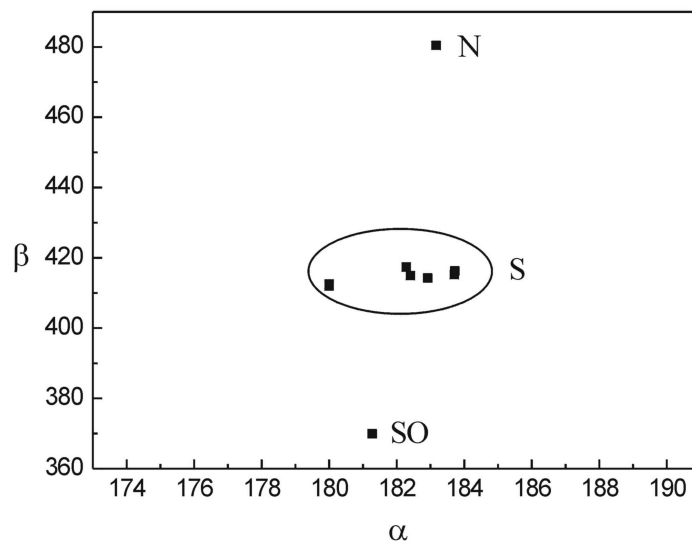

Figure 21: α-β plot showing dependence on the bridge

By far the most common bridge among *1,3-alternate* heteroatom-bridged calix[4]arenes is the sulfur one. The following text will deal exclusively with these structures.

In the group of symmetrically tetrasubstituted molecules, several hits deviate from the main group. The two hits from the symmetrically tetrasubstituted group with $\alpha > 210°$ are structures SAXJEG(01) [10]. These structures lack substituents on both upper and lower rim and their conformation is similar to that of *saddle* resorcinarenes. There is intramolecular π,π-stacking (Fig. II-25) present in these structures and intermolecular CH-π interaction between calixarene phenyl rings. The intramolecular π,π-stacking is not present in similar structure SUDMOT (Fig. II-24) because there is another calixarene molecule positioned inside the cavity in this structure; the intramolecular π,π–stacking cannot be therefore present.
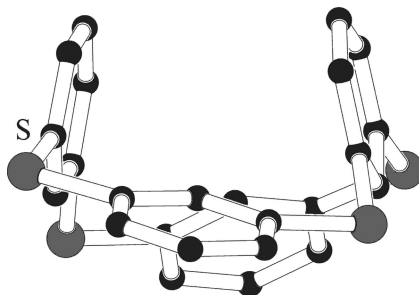

Figure II-25. Structure SAXJEG [10]

The remaining hit with $\alpha > 205°$ belongs to structure NODJOF [10], long chain *m-* substituted, S-bridged structure with missing lower rim substituents. Because of the lack of sterical hindrance at the lower rim, the conformation of this structure is similar to that of *saddle* resorcinarenes.

The rest of the sulfur-bridged group ('cluster' 20-III, 28 cif files, 41 independent molecules, centered at [181.70; 413.64; 5.92], standard deviation [1.75; 26.70; 8.41]) is relatively uniform with regard to both α and β. Structures with two identical crown ether bridges at the lower rim have been included in the lower rim distally substituted group, therefore there are no lower rim distally bridged structures within the symmetrically tetrasubstituted group. The trends within this group are similar to those observed within the methylene-bridged group.

For example, structure ALETUG01 [10] similar to the structure ALETEQ (β = 377°) is substituted by *t-*butyl groups at the upper rim and has a more open structure (β ~ 415°) which reflects sterical hindrance caused by bulky upper rim substituents. Structures ALETEQ, ALETUG01 are depicted in Fig. II-26. Four

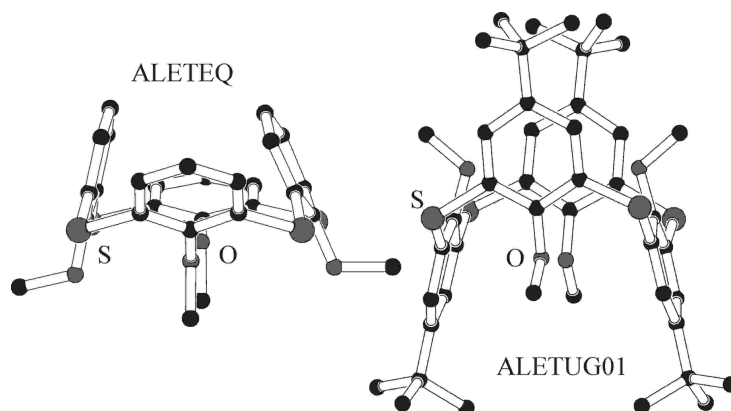other lower rim methoxy, upper rim *t*-butyl-substituted structures are very similar to the structure ALETUG01 (β ~ 415°).

Figure II-26. Structures ALETEQ, ALETUG01 [10]

Upper rim ethynyl-substituted structure HAGVAN (β ~ 430°) has a relatively open structure because of coordination of the ethynyl groups and bulky phosphine ligands on Pt(II). On the other hand, similar structure HAGTUF with 4-pentylphenylethynyl substituents at the upper rim is not so open because there is hydrophobic interaction between two 1-pentyl chains on the upper rim substituents on the opposite calixarene rings and CH-π interaction between upper and lower rim substituents (Fig. II-27). Therefore, the β value for this structure lies beneath 410°.
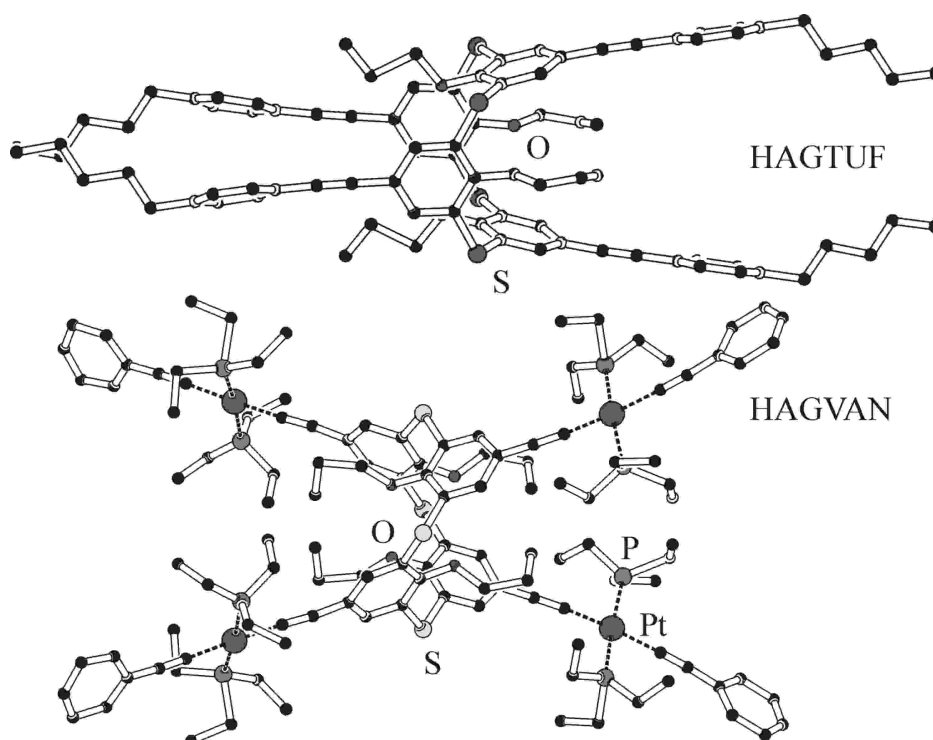

Figure II-27. Structures HAGTUF and HAGVAN [10]

The only interesting structures in the group of lower rim distally substituted heteroatom-bridged *1,3-alternate* calix[4]arenes are crown-6 bridged BOXWEQ and ERUWET01 [10], its Cs(I) complex (the only complex in this group). The long crown-6 chain allows for π, π-interaction between the opposite calixarene rings in the structure BOXWEQ but this interaction is broken in the structure ERUWET01 because of Cs(I) complexation and the resulting cation-π interaction with the two opposite calixarene rings. The structure ERUWET01 is therefore more open (Fig. II-28) and has larger β value.
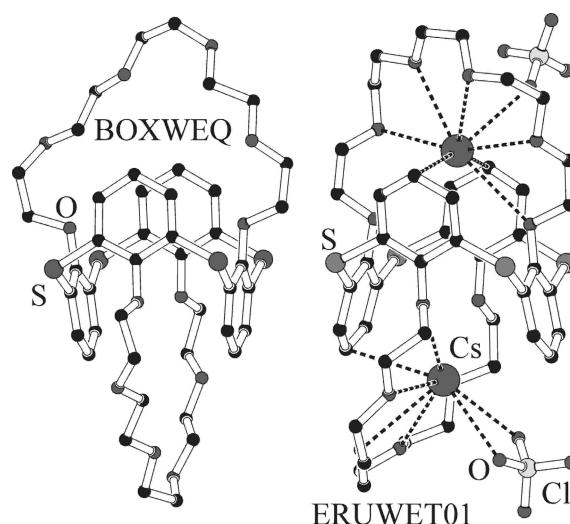
Figure II-28. Structures BOXWEQ and ERUWET01 [10]

Crown-5 bridged calixarenes from this group tend to have larger β value (more open cavities) because of shorter bridge which partially reaches into the ′cavities′; these structures are therefore not able to form intramolecular π, π-interaction like the crown-6 bridged structure BOXWEQ [10]. Representative example is structure BOXQUA (Fig. II-29; compare to structures BOXWEQ and ERUWET01 on Fig. II-28).
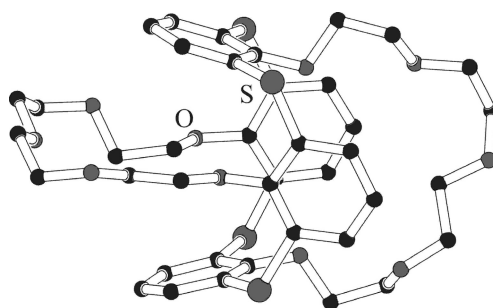

Figure II-29. Structure BOXQUA [10]

Conclusion — 1,3-alternate structures

The parameter β seems to be the best one to describe the base frame geometry of *1,3-alternate* calix[4]arenes. Structures with parallel or closer opposite calixarene rings (more closed cavities) have low β whereas structures with more open cavities have high β. Structures lacking lower rim substituents and therefore deformed towards the *saddle* geometry common among *saddle* resorcinarenes also have higher β but this type of deformation affects predominantly α (> 200°). Because the δ parameter is below 15° in the vast majority of *1,3-alternate* structures, it is relatively insignificant for this group. Heteroatom-bridged calix[4]arenes containing oxygen bridge substituents are also deformed towards the *saddle* geometry common among *saddle* resorcinarenes (short C-O bond length 1.43 Å compared to C-C 1.54 Å).

To sum up, the best way to significantly influence the geometry of the *1,3-alternate* methylene-bridged calix[4]arenes seems to be distal upper rim coordination which leads invariably to more closed structures. Removal of lower rim phenolic oxygen atoms also has significant impact on the calix[4]arene geometry. Other effects (filled/empty cavity; effects of upper rim substitution and lower rim coordination; length, flexibility or rigidity of the lower rim bridge) do not seem to affect the geometry of the calix[4]arene moiety so significantly and/or the result cannot be reasonably foreseen by the chemist.

The best way to immobilize the *1,3-alternate* conformation in heteroatom-bridged calix[4]arenes is a double distal bridge at the lower rim. The length of the bridge seems to affect the geometry of the calixarene base frame; shorter bridges tend to produce more open structures with higher β whereas longer ones do not disrupt intramolecular π,π-interaction between the opposite calixarene phenyl rings and therefore tend to produce more closed cavities with lower β.

As in the group of *partial cone* structures, *1,3-alternate* methylene-bridged calix[4]arenes which contain four lower rim hydroxyl groups are few. Unlike the groups of *partial cone* and *1,2-alternate* structures, there are not so many structures containing unsubstituted lower rim hydroxyl groups among the *1,3-alternate* heteroatom-bridged structures.

Conclusion

To sum up, the parameters α, β, δ are very useful in describing the geometry of the base frame of methylene- and heteroatom-bridged calix[4]arenes. The values of these parameters reflect not only the base conformation (e.g. *cone*, *partial cone*, *1,2-alternate* or *1,3-alternate*) of the calix[4]arene base frame but react to inter- and/or intramolecular interactions present in the structure as well (see discussions at the end of each chapter). Dependence of the parameters α, β, δ on several types of inter- and/or intramolecular interactions has been demonstrated. However, as these results were obtained from solid state data, no conclusion concerning conformations and behavior of calix[4]arene molecules in solution can be stated.

Acknowledgements

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Каликс[4]арендердің конформациялары — CSD мәліметтеріне негізделген зерттеу. II-бөлім. Бөлшектік конус, метиленді және гетероатомды каликс[4]арендердің 1,2-альтернантты және 1,3-альтернантты конформерлері

Бұл зерттеудің бірінші бөлімінде Кембридж құрылымдық мәліметтер базасы (CSD) негізінде метиленді және гетероатомды көпірлері бар каликс[4]арендердің конустық конформерлері зерттелді. Ертерек енгізілген α, β және δ параметрлері жоғарыда келтірілген қосылыстардың көмірсутекті негізі қаңқасының конформациясын сипаттағанда қолданылды. Бұл бөлімде метиленді және гетероатомды каликс[4]арендердің бөлшектік конустық, 1,2-альтернантты және 1,3-альтернантты конформерлері зерттеліп, бұл қосылыстардың конформацияларында молекулааралық және -ішілік әрекеттесулердің әсері бағаланды.

Кілт сөздер: каликс[4]арен, кристалды құрылымдар, конформациялар, бұрау бұрышы, бұрмалау параметрі.

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Конформации каликс[4]аренов — исследование, основанное на данных CSD. Часть II. Частичный конус, 1,2-альтернантные и 1,3-альтернантные конформеры метиленовых и гетероатомных каликс[4]аренов

В первой части нашего исследования были рассмотрены конические конформеры каликс[4]-аренов с метиленовыми и гетероатомными мостиками из Кембриджской структурной базы данных (CSD). Ранее вводимые параметры α, β и δ использовались при описании конформаций каркаса углеводородного основания указанных выше соединений. Во второй части исследования изучены частичные конические, 1,2- и 1,3-альтернативные конформеры метилен- и гетероатомно-мостиковых каликс[4]-аренов и оценено влияние меж- и внутримолекулярных взаимодействий на конформации этих соединений.

Ключевые слова: каликс[4]арен, кристаллические структуры, конформация, угол скручивания, параметр искажения.