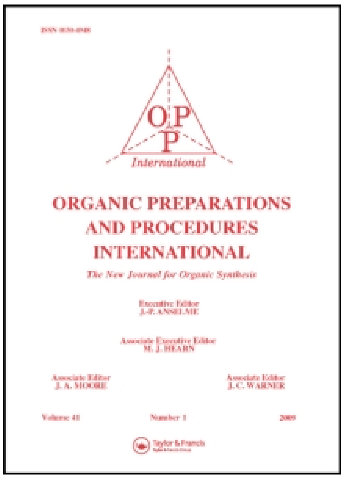

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article van Loon, J. -D. , Verboom, W. and Reinhoudt, D. N.(1992) 'SELECTIVE FUNCTIONALIZATION AND CONFORMATIONAL PROPERTIES OF CALIX[4]ARENES, A REVIEW', Organic Preparations and Procedures International, 24: 4, 437 — 462

To link to this Article: DOI: 10.1080/00304949209356227

URL: http://dx.doi.org/10.1080/00304949209356227

ORGANIC PREPARATIONS AND PROCEDURES INT., 24 (4), 437-462 (1992)

SELECTIVE FUNCTIONALIZATION AND CONFORMATIONAL PROPERTIES OF CALIX[4]ARENES. A REVIEW

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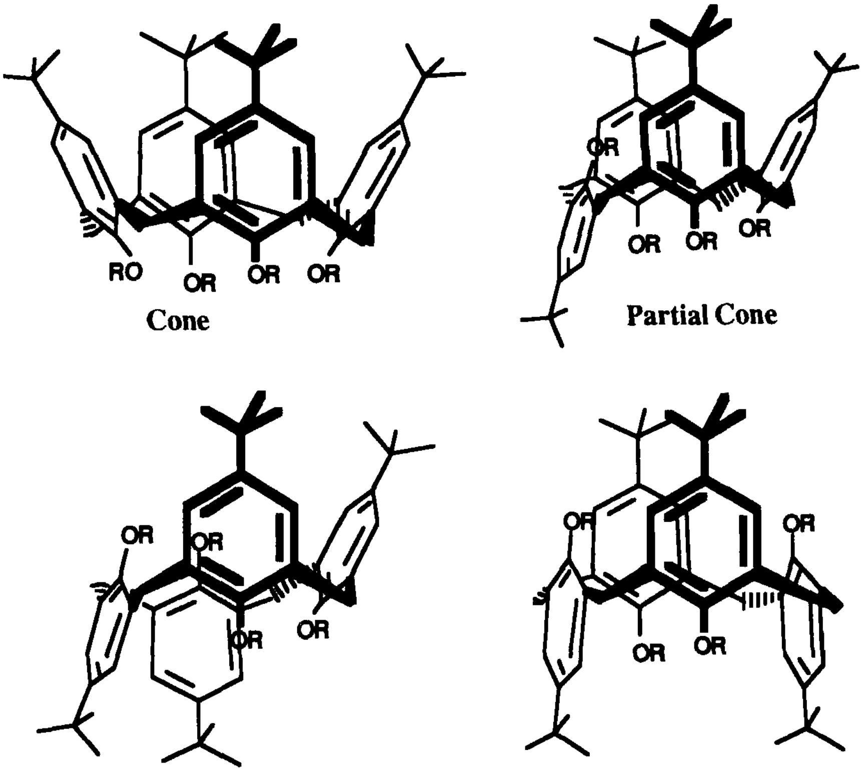
INTRODUCTION

The mimicry of natural recognition processes is one of the challenging research topics of today. Biological receptors consist of large linear molecules that form three dimensional structures by specific intramolecular interactions. The recognition sites offer a precise stereochemistry and exhibit very efficient recognition processes. However, this is achieved at the expense of a high molecular weight. A possible strategy for *synthetic* receptors comprises combination of medium-sized organic building blocks to which functional groups for molecular recognition can be attached. In this respect, calix[4]arenes (CHART 1) are very promising building blocks, because they provide a cavity and can be prepared on large scale. In addition they have different positions that can be selectively functionalized, *viz.* the phenolic oxygens at the *lower rim* and the aromatic para positions at the *upper rim.* Calix[4]arenes can adopt four different extreme conformations, *viz.* the cone, partial cone, 1,2-alternate and 1,3-alternate conformation (CHART 1), and this enlarges the number of potentially useful geometries of these molecules as building blocks. The chemistry of calix[4]arenes is well established, and recently two excellent books have appeared.[1] This review deals with recent developments concerning functionalization of the individual phenol rings of calix[4]arene at the lower and upper rim, functionalization by bridging of calix[4]arenes, and with conformational properties of calix[4]arenes. The literature cited includes 1991.

I. SELECTIVE FUNCTIONALIZATION OF THE LOWER RIM

Until recently functionalization of calix[4]arenes at the lower rim was restricted to tetrasubstituted compounds in which all phenol rings bear the same substituents. In some of the reactions that were aimed at tetrasubstituted calix[4]arenes, products were isolated, that turned out to be partly substituted calix[4]arenes. In some cases these reactions have led to general methods for the synthesis of partly O-substituted calix[4]arenes.

CHART 1



Cone

Partial Cone

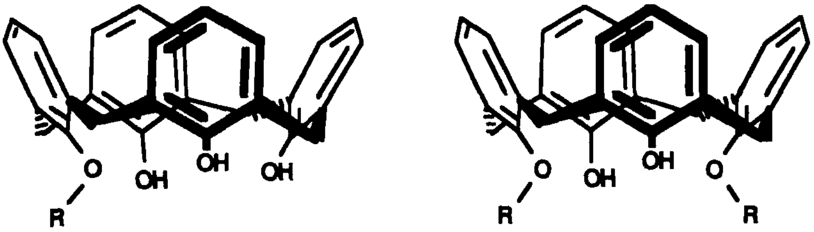
1,2-Alternate

1,3-Alternate

1. Monosubstitution

There are two general methods for the synthesis of monosubstituted calix[4]arenes **1** (CHART 2). The first method is indirect and comprises selective removal[2] of functional groups at the lower rim of

CHART 2



1 R = Me, Et, allyl
CH_2COOEt

2 R = Me, Et, Bn, allyl
CH_2COOR_1
CH_2CN, $CH_2CON(R_1)_2$

1,3-di- (*vide infra*) or tetrasubstituted calix[4]arenes.[3] In this way calix[4]arene monoalkyl ethers could be prepared in reasonable yields by the use of one or three equivalents of iodotrimethylsilane as a dealkylating reagent, respectively.[4] Monoesters have been obtained by reaction of a 1,3-diester with ten equivalents of imidazole.[5] The second method for selective monosubstitution comprises direct alkylation of calix[4]arenetetrol with excess of alkylating agent in the presence of 1.2 equivalents of the very weak base CsF[6] in DMF in yields varying between 37 and 88%.[7] The use of 0.6 equivalents of K_2CO_3 in CH_3CN also afforded reasonable amounts of monoalkylated products, but 1,3-disubstituted products were always formed as side products.[7] Alkylations with weak base proceed *via* the monoanion of calix[4]arene, which is stabilized by two H-bonds from adjacent phenolic groups. However, also one monoanion of the monoalkylated calix[4]arene can be stabilized by two H-bonds and consequently there is only a small difference in basicity[8] and reactivity of these two monoanions. The use of a very weak base is necessary to distinguish between the two anions. Apparently, K_2CO_3 and $KHCO_3$, which is formed during the reaction, are too strong bases to effect selective monoalkylation.

2. 1,3-Disubstitution

Calix[4]arenes can be alkylated selectively at two opposite phenol rings by reaction with two equivalents of an alkylating agent in the presence of one equivalent of K_2CO_3.[9] Yields are generally excellent and the products **2** (CHART 2) exist in the cone conformation. Under the conditions used, this reaction is very selective, because further alkylation requires deprotonation of **2**, which is less favorable since the resulting anion can only be stabilized by one very weak H-bond from the diametrically positioned phenol ring.[10]

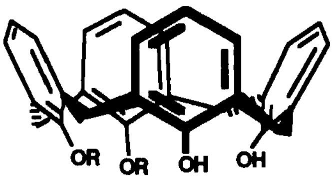
3. 1,2-Disubstitution

The selectivity of alkylation can be completely altered by the use of the strong base NaH in DMF. The first example was reported by Pappalardo *et al.*,[11] who reacted *p-tert*-butylcalix[4]arenetetrol with (2-chloromethyl)pyridine to afford a 1,2-disubstituted product **3** (CHART 3) in the cone conformation. The regioselectivity of the reaction was first explained by the ability of the pyridine pendant group in the monoalkylated intermediate to activate the adjacent phenol group by H-bonding. The reaction was found to be more general by using excess of NaH and 2.2 equivalents of alkylating agent.[12] The formation of 1,2-disubstituted calix[4]arene can be rationalized by assuming that the dianion of the monoalkylated calix[4]arene (**4**) is an intermediate. This will have the structure as shown because of the minimization of the repulsion between the two oxyanions and the stabilizing effect of a H-bond of a hydroxyl group. As an alternative the 1,2-dimethyl ether of *p-tert*-butylcalix[4]arene has been obtained by selective demethylation of the tetamethoxy derivative with $TiBr_4$.[13] Gutsche *et al.* reported the synthesis of *p-tert*-butylcalix[4]arene 1,2-bis(3,5-dinitrobenzoate) in the cone conformation by rearrangement of the corresponding 1,3-diester with imidazole.[5b]

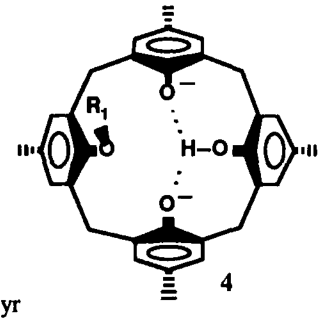
4. Trisubstitution

Reaction of calix[4]arenetetrol with MeI in DMF with $BaO/Ba(OH)_2$ as a base afforded the

CHART 3



3 R = Me, Et, Bn, allyl
CH_2CH_2OEt, 2-CH_2-pyr



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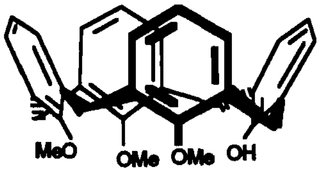

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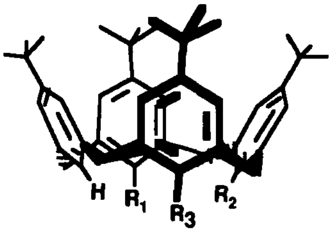
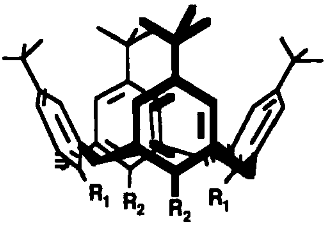


6 a $R_1 = R_2 = R_3 = OH$
b $R_1 = R_3 = OH, R_2 = H$
c $R_1 = OH, R_2 = R_3 = H$
d $R_1 = R_2 = R_3 = H$



7 a $R_1 = OMe, R_2 = OH$
b $R_1 = OMe, R_2 = SMe$
c $R_1 = H, R_2 = SH$

trimethoxycalix[4]arene **5**,[14] which is flexible but exists mainly in the cone conformation at room temperature.[14] The applied reaction conditions were later exploited for the selective synthesis of other trialkylated calix[4]arenes in the cone conformation.[15,16] A few triacylated calix[4]arenes have been isolated in the partial cone conformation by the use of pyridine as a base,[2,17] and in the cone conformation by the use of 1-methylimidazole in CH_3CN.[5b]

5. Replacement of the Phenolic OH Groups

The phenolic OH groups of *p-tert*-butylcalix[4]arenetetrol can be removed by reductive cleavage (K in liquid NH_3) of the corresponding tetrakis(diethylphosphate) ester to give metacyclophane **6a**.[18] Starting from 1,3-di- and tetraphosphate esters also the partly dehydroxylated calix[4]arenes **6a-d** could be isolated.[19] The first thiocalix[4]arenes **7b** and **7c** were synthesized by the Newman-Kwart rearrangement of the *O*-dimethylthiocarbamates of **7a** and **6b** to the corresponding *S*-dimethylthiocarbamates, followed by reduction of the carbamate moieties.[19a]

6. Mechanism of Tetrasubstitution

Tetrasubstitution of calix[4]arenes with large substituents at the lower rim (*vide infra*) generally leads to products in a fixed conformation, or a mixture of different fixed conformations, which can be separated.[20] What factors actually determine the conformation of the products is one of the

TABLE 1. Conformations of Tetralkylated *p-tert*-Butylcalix[4]arenes.

#	Electrophile	Reaction Conditions^a			Isolated Conformations (%)^b				Ref
		Base	Solvent	t(h)	cone	paco	1,2-alt	1,3-alt	
1	Me-I	NaH	THF/DMF	1	-^{c}	-^{c}	-^{c}	-^{c}	59
2	Et-I	NaH	THF/DMF	1		?			59
3	Et-I	NaH	THF/DMF	2	(11)	(89)		(<1)	21f
4	Pr^n-I	NaH	THF/DMF	2	(15)	(81)		(4)	21f
5	Pr^n-Br	NaH	THF/DMF	2	(42)	(55)		(3)	21f
6	Pr^n-Br	Cs_2CO_3	DMF^d	3		(34)		(57)	21f
7	Bu^n-Br	NaH	THF/DMF	2	(50)	(47)		(3)	21f
8	Allyl-Br	NaH	THF/DMF	1	75				59
9	$PhCH_2$-Cl	NaH	THF/DMF	1	65				59
10	(2-pyr)CH_2-Cl	NaH	DMF^e	24	80				11
11	$Et(OCH_2CH_2)_2$-Br	NaH	DMF^f	2	85				66
12	$Me(OCH_2CH_2)_2$-OTos	KOtBu	benzene	3		80			22
13	$(O_2S(CH_2)_3O)$	NaH	THF^g	24	80				30
14	$EtO(O)CCH_2$-Br	NaH	DMF^e	2	72				66
15	$EtO(O)CCH_2$-Br	Li_2CO_3	DMF^d	45	22				21c
16	$EtO(O)CCH_2$-Br	Na_2CO_3	DMF^d	6	(88)	(12)			21c
17	$EtO(O)CCH_2$-Br	K_2CO_3	DMF^d	8	(84)	(16)			21c
18	$EtO(O)CCH_2$-Br	Cs_2CO_3	DMF^d	3	(27)	(73)			21c
19	$EtO(O)CCH_2$-Br	Na_2CO_3	acetone	22	59				21c
20	$EtO(O)CCH_2$-Br	K_2CO_3	acetone	72	88				68
21	$EtO(O)CCH_2$-Br	K_2CO_3	acetone	22	(96)	(3)			21c
22	$EtO(O)CCH_2$-Br	Cs_2CO_3	acetone	1		(100)			21c
23	$Bu^tO(O)CCH_2$-Br	NaH	THF/DMF	3	70				69
24	$C_6H_{11}O(O)CCH_2$-Br	NaH	THF/DMF	3	31				70
25	$C_{10}H_{21}O(O)CCH_2$-Br	NaH	THF/DMF	3	30				70
26	$Et_2N(O)CCH_2$-Cl	NaH	THF/DMF	3	95				71
27	$Bu^n_2NO(O)CCH_2$-Cl	NaH	THF/DMF	3	41				70
28	$R(O)CCH_2$-Cl	K_2CO_3	acetone	5-48	27-28				68

a) If not stated otherwise, reactions were carried out at reflux temperature. b) "?" indicates that the yield has not been reported "( )" indicates a relative yield that was determined by HPLC analysis. c) Product is flexible at room temperature. d) 70°. e) 60°. f) 80°. g) Room temperature.

challenging problems in calix[4]arene chemistry.[21,15b] A selected number of alkylations are summarized in TABLE 1. It should be emphasized here that definite conclusions can be drawn only if *the mechanism of tetrasubstitution via different partly substituted calix[4]arenes* is taken into account! Groenen in our group[22] studied the tetraethylation of *p-tert*-butylcalix[4]arenetetrol with EtI at room temperature as a function of base and solvent (TABLE 2). The intermediates were identified by the partial ethylation of the monoethyl ether of **1** (R = Et) with 1.1 equivalent of EtI. The results are summarized in TABLE 3. As an example tetraalkylation of *p-tert*-butylcalix[4]arenetetrol with NaH as a base in DMF proceeds *via* a 1,2-dialkylated intermediate.[12] The reactions with KH and KOtBu proceed *via* at least two different disubstituted intermediates, which demonstrated the influence of the counterion of the base on the conformational outcome. Furthermore, the mechanism of substitution will depend on the strength of the base. With weak bases a sequence of alternating deprotonation and

TABLE 2. Results of Tetraethylation of *p-tert*-Butylcalix[4]arene (EtI, RT, 24 hrs).

Reaction Conditions		Relative yields of conformation (%)			
base	solvent	cone	partial cone	1,2-alternative	1,3-alternative
NaH	DMF	100	[a]	[a]	[a]
NaH	MeCN	100	[a]	[a]	[a]
NaH	THF/DMF 10:1	62	28	10	[a]
NaH	THF	[b]	[b]	[b]	[b]
KH	DMF	2	64	17	17
KH	THF	[a]	64	5	31
KOtBu	MeCN	5	84	2	9
KOtBu	DMF	[a]	77	[a]	23

a) Not detected in the ^{1}H NMR spectrum. b) No product had been formed after 34 hrs.

TABLE 2. Results of Tetraethylation of *p-tert*-Butylcalix[4]arene (EtI, RT, 24 hrs).

Reaction conditions		Products after Reaction with 1.1 equivalent of EtI (RT, 16 hrs)
base	solvent	
NaH	DMF	*syn*-1,2-di (*syn*-1,2,3-tri, tetra)
NaH	MeCN	*syn*-1,2-di (*syn*-1,2,3-tri, tetra)
NaH	THF/DMF 10:1	*syn*-1,2-di (*syn*-1,2,3-di, tetra)
NaH	THF	no reaction
KH	DMF	*anti*-1,2-di, *syn*-1,2-di (*syn*-1,2-*anti*-3-tri)
KH	THF	*syn*-1,2-di, *anti*-1,2-di
KOtBu	MeCN	*syn*-1,3-di, *anti*-1,2-di, *syn*-1,2-di (*syn*-1,2-*anti*-3-tri)
KOtBu	DMF	no reaction

alkylation steps will occur,[9a,b] whereas strong bases will effect multiple deprotonation (*vide supra*). Whether the reaction can be stopped at the mono, 1,3-di-, or tetrasubstituted products can partly be controlled by the amount of base used, but depends also on the reactivity of the electrophile and of the calix[4]arene monoanion.

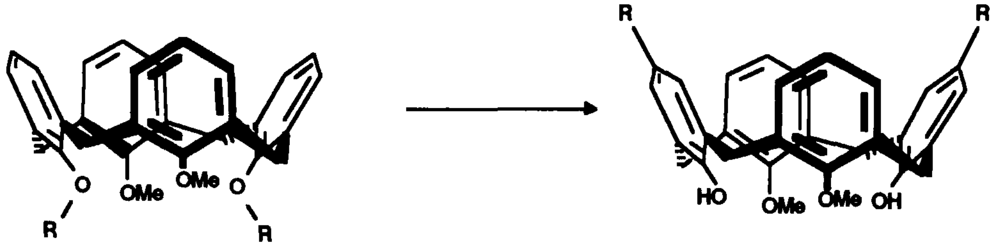
II. SELECTIVE FUNCTIONALIZATION OF THE UPPER RIM

A prerequisite for the application of calix[4]arenes as building blocks in supramolecular chemistry is the ability to control the functionalization at each individual phenol ring of calix[4]arene. For a long time stepwise methods developed by Kämmerer and Böhmer[23] (and extended by de Mendoza)[24] were the only methods available. However, with the synthesis of partly substituted calix[4]arenes at the lower rim discrimination between the phenol rings of the parent calix[4]arenetetrol can be accomplished, and this can be applied for selective introduction of substituents at the upper rim of calix[4]arene. This has been demonstrated for the selective functionalization of calix[4]arene 1,3-dialkyl ethers.[9a,b] Several methods can be distinguished.

1. Transfer of Functionality

The first method to obtain difunctionalized calix[4]arenes at the upper rim comprises selective transfer of substituents from the lower rim to the upper rim *via* a rearrangement reaction. As an example the Claisen rearrangement of diallyldimethyl ether **8a** affords diallyl calix[4]arene **9a** in 99% yield (SCHEME 1). The *p*-allyl groups could be transformed into other functional groups (like CH_2X, CH=O, COOH). No *et al.* have performed a Fries rearrangement of the diacetyl ester **8b** with $AlCl_3$ to afford *p*-acetyl calix[4]arene **9b** in 63% yield.[25] Direct Friedel-Crafts acylation of **2** (R = Me) with acetyl chloride resulted in the formation of a *p*-disubstituted compound with acetyl moieties at the para positions of the anisole rings (*vide infra*).[25b]

SCHEME 1



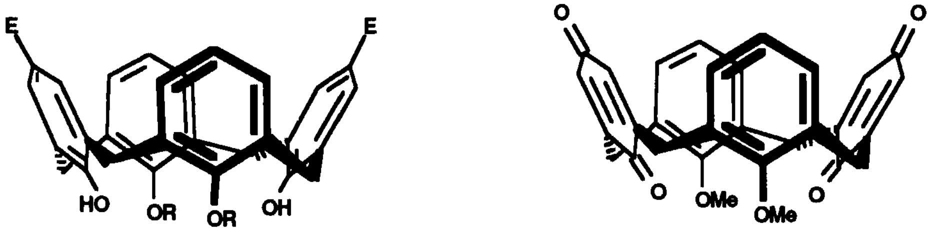
8 a R = allyl
b R = C(=O)Me

9 a R = allyl
b R = C(=O)Me

2. Direct Substitution

The second method[9a,b] takes advantage of the fact that electrophilic aromatic substitutions are much faster on phenols than on alkylated phenols. Therefore, a variety of substituents (Br, NO_2, CHO, CH_2NMe_2, HgOTFA) can be introduced selectively at the para positions of dialkylated calix[4]arenes (**10**) in yields > 80% (CHART 4). A special case comprises oxidation of the phenol

CHART 4



10 E = Br, NO_2, CH_2NMe_2, CH=O
COOH, HgOTFA

11

rings of **10** (R = H) with thallium nitrate to afford the first calix[4]diquinone **11**, which is an interesting candidate for the formation of charge transfer complexes.[9b]

The presence of a selectively functionalized lower rim is not an absolute prerequisite for selective functionalization of the upper rim. Pochini *et al.* have reported that mono-, 1,3-di-, tri-, and tetraformylated calix[4]arenes **12b-e** (CHART 5) could be prepared by selective Gross formylation[26] of calix[4]arene tetrakis(ethoxyethyl) ether in reasonable yields.[26] Compound **12a** can also be selectively 1,3-dinitrated in 30-40% yield. The 1,2-dinitrated product was not observed in this reaction.[27]

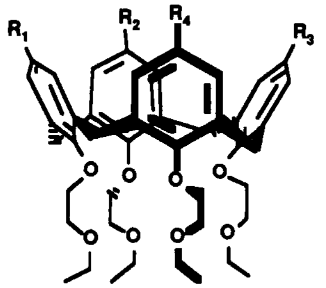
3. Selective De-*tert*-butylation

The third approach for selective introduction of functional groups at the upper rim comprises selective removal of two *p-tert*-butyl groups from the phenolic nuclei of a dialkoxy-tetra-*p-tert*-butylcalix[4]arene (**13**) by a Friedel-Crafts transalkylation under mild conditions ($AlCl_3$ in toluene at room temperature). The para positions of the phenol rings are now available for further substitution by methods described above, while the remaining two para positions are protected. An example comprises the Gross formylation of di-*p-tert*-butyldimethoxycalix[4]arene **14a**. Diformyl derivative **14b** could be prepared by reaction of **14a** with 10 equivalents of Cl_2CHOCH_3 in the presence of 10 equivalents of $TiCl_4$. By changing the ratio **14a**/Cl_2CHOCH_3/$TiCl_4$ to 1:10:5 in combination with a shorter reaction time monoformyl calix[4]arene **15** could be prepared in 95% yield.[28] Gutsche has reported that selective removal of *p-tert*-butyl groups of calix[4]arene diesters is also possible.[5b]

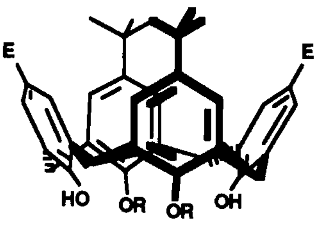
The *tert*-butyl groups of tetrasubstituted calix[4]arenes can also be replaced directly by nitro groups (*ipso*-nitration).[27] When this reaction was performed with 100% HNO_3 in CH_2Cl_2/AcOH tetranitrocalix[4]arenes (e.g. **16d**) were formed, but under milder conditions (65% HNO_3) each of the four partly nitrated calix[4]arenes **16a-c** could be isolated. Nitrated calix[4]arenes are very interesting in non-linear optics because they combine four donor-π system-acceptor moieties in one molecule.[29]

We applied selectively functionalized calix[4]arene **17** with pyridone moieties at the upper rim for the construction of supramolecular assemblies of calix[4]arenes (FIGURE 1).[30] A 10 mM solution of **17** shows a number averaged molecular mass M_N = 5100 and a weight averaged molecular mass

CHART 5

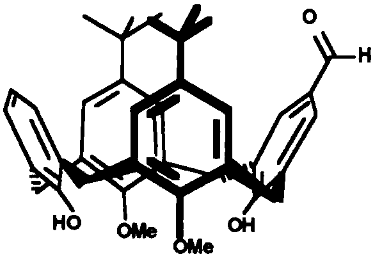


12 a $R_1 = R_2 = R_3 = R_4 = H$
b $R_1 = R_2 = R_3 = H, R_4 = CHO$
c $R_1 = R_3 = H, R_2 = R_4 = CHO$
d $R_1 = R_2 = R_3 = CHO, R_4 = H$
e $R_1 = R_2 = R_3 = R_4 = CHO$



13 E = *t*-Bu

14 a R = Me, E = H
b R = Me, E = CH=O



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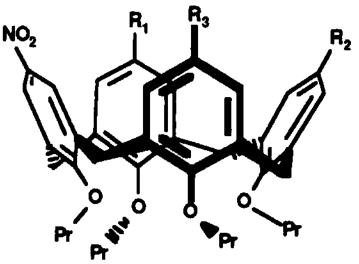


16 a $R_1 = R_2 = R_3 = H$
b $R_1 = R_3 = H, R_2 = NO_2$
c $R_1 = H, R_2 = R_3 = NO_2$
d $R_1 = R_2 = R_3 = NO_2$

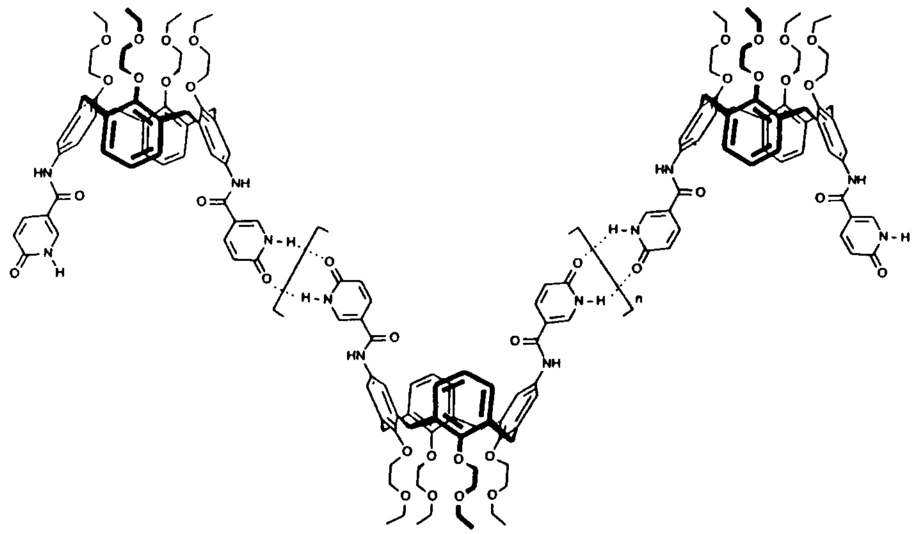
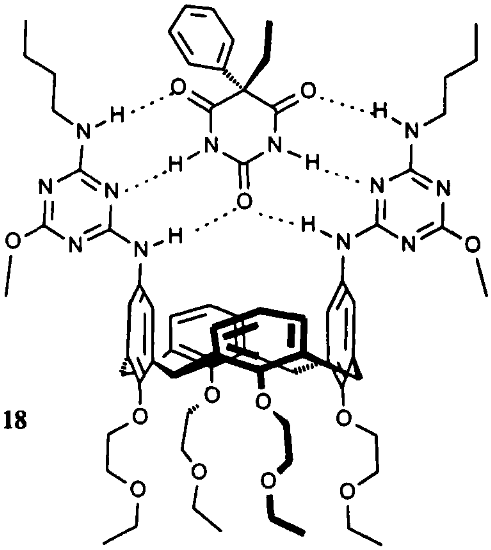


FIGURE 1. Supramolecular Assemblies of 17. Circular Structures also possible.

CHART 6



M_W = 70000. The polydispersity index M_W/M_N indicates a broad oligomer distribution. A receptor for barbiturates was synthesized based on tetrakis(ethoxyethyl) ether **18** (CHART 6) in a distorted cone conformation,[31] bearing diaminotriazine moieties at the upper rim, in order to demonstrate that in solution calix[4]arenes are useful molecular platforms rather than cavity-containing hosts.[32]

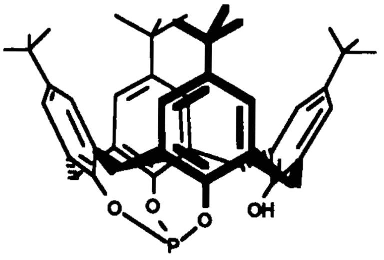
III. BRIDGED CALIX[4]ARENES

A special class of selectively functionalized calix[4]arenes comprises bridged calix[4]arenes, in which two phenol rings are connected by a cap. Since the report of the first calix[4]crown (*vide infra*) by Ungaro and Andreetti *et al.*[33] in 1983 many different bridged calix[4]arenes have been synthesized.

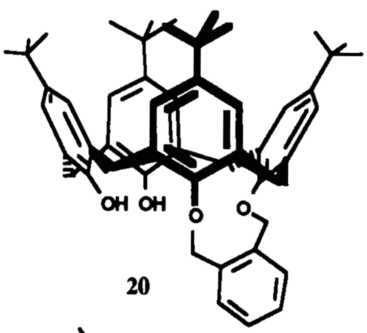
1. Calix[4]arenes Bridged at the Lower Rim

The first class of bridged calix[4]arenes comprises compounds in which the oxygen atoms of at least two phenol rings are capped. The smallest cap reported by Lattman, Gutsche *et al.* consists of one phosphorus atom that forms a three-coordinate calix[4]arene derivative **19** (CHART 7).[34] Gutsche *et al.* reported that two adjacent phenolic OH groups of *p*-*tert*-butylcalix[4]arene can be capped with a one-atom sulfur oxyde bridge by reaction with $SOCl_2$.[5b] Proximally bridged calix[4]arenes have also been obtained by reaction of *p*-*tert*-butylcalix[4]arene with ortho-disubstituted benzenes like phthaloyl dichloride.[35] Reaction of *o*-bis(bromomethyl)benzene with *p*-*tert*-butylcalix[4]arene with K_2CO_3 in CH_3CN not only afforded 1,2-bridged calix[4]arene **20** in 16% yield, but also a double calix[4]arene **21**, of which the crystal structure could be solved (FIGURE 2).[36] A proximally bridged bis-calix[4]crown has also been reported.[13]

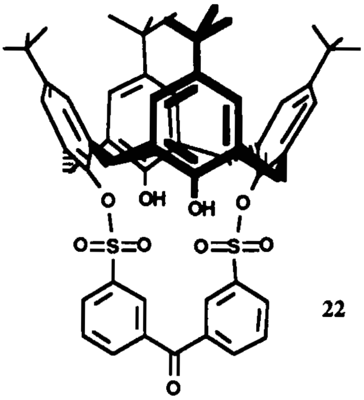
CHART 7



19

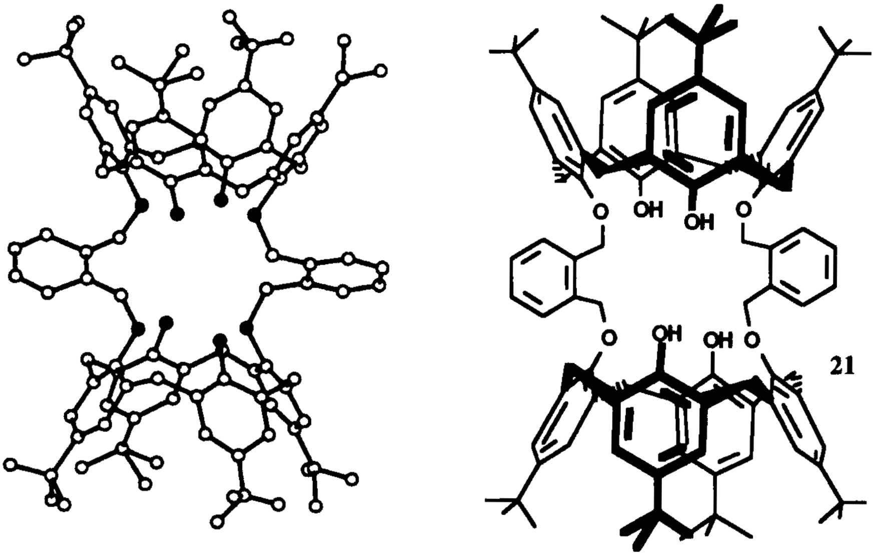


20



22

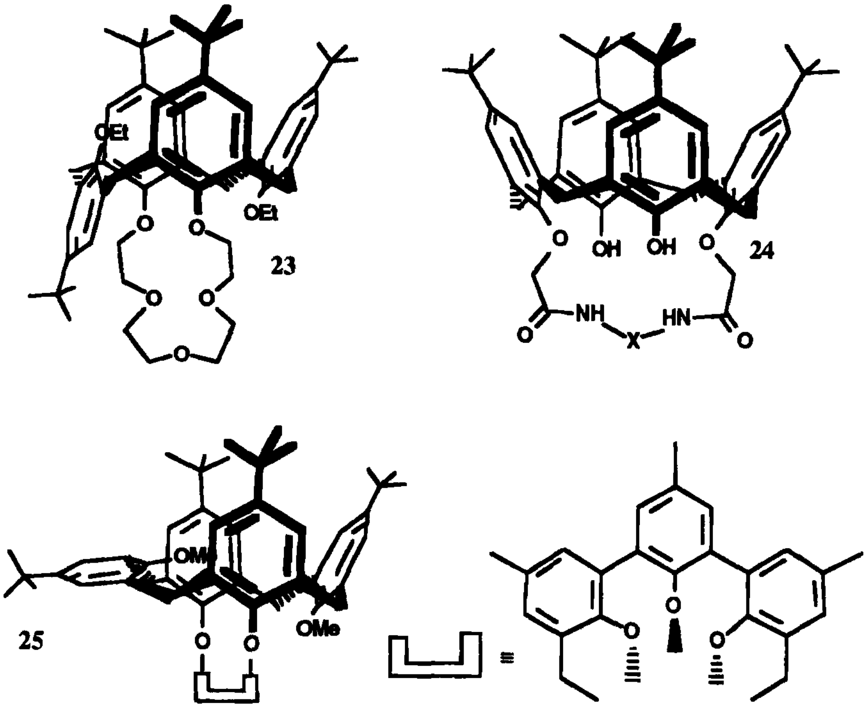
FIGURE 2. Crystal structure of double calix[4]arenes (21).



21

If the reaction centers of the bridge are put further apart, like in 3,3'-benzophenone disulphonyl dichloride, usually two opposite phenol rings are capped (22).[35] In some cases also double calix[4]arenes like **21** are formed as side-products. Special classes of diametrically bridged calix[4]arenes comprise calix[4]crowns **23**,[37] calix[4]azacrowns **24**,[38] and calixspherands **25**,[39] since they form a cavity for the binding of metal ions (CHART 8). Calix[4]crown **23** in the partial cone

CHART 8



forms thermodynamically stable complexes with potassium with a very high K^+/Na^+ selectivity of 1.18×10^4.[37] Azacrowns **24** can be used for complexation of trivalent cations like Sc^{3+}, Y^{3+} and Gd^{3+}.[38] Calixspherands **25** form kinetically stable complexes with Na^+, K^+, and Rb^+.[39]

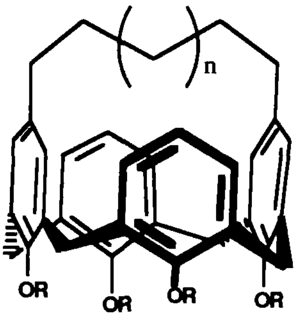
Double calix[4]arenes[40] can be designed by the use of 'bridging reagents' that are unable to form either proximally or diametrically intra-bridged calix[4]arenes, like terephthaloyl dichloride.[41] In the case of 4,4'-biphenyl disulphonyl dichloride also a triple calix[4]arene was isolated.[41] Double and triple calix[4]arenes are also reported for metallocene bridges.[42]

2. Calix[4]arenes Bridged at the Upper Rim

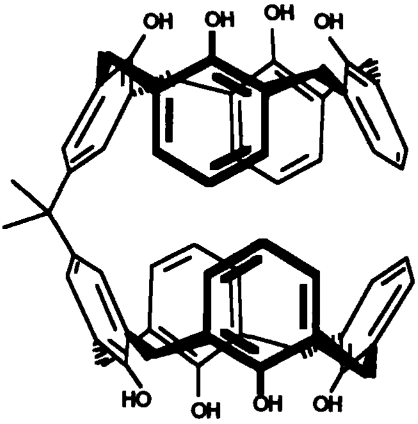
The second class of bridged calix[4]arenes comprises compounds of which two *para* positions of the phenolic groups are connected by a cap. Böhmer *et al.* reported the stepwise synthesis of a series of calix[4]arenes **26**, in which the bridges consist of methylene chains of different length (CHART 9).[43] In the case of a short chain (n ≥ 2) the calix[4]arene cannot adopt a symmetrical cone conformation, and as a consequence the affinity of tetraesters **27** for sodium ions decreases substantially.[44]

Tetramethoxycalix[4]arenes have been bridged with poly(oxyethylene) chains at the upper rim to give upper rim calix[4]crowns (*vide infra*)[45] and Pochini *et al.* have prepared calix[4]arenes that

CHART 9



26 R = H
27 R = CH_2COOEt



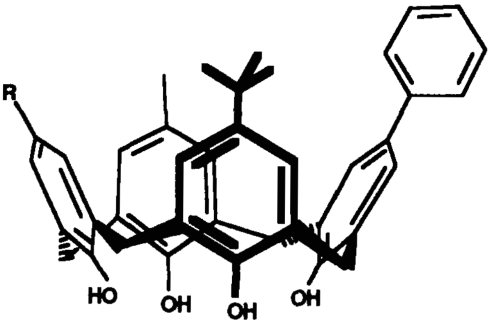
28

are bridged at the upper rim with aromatic capping reagents like α,α'-dibromo-*p*-xylene.[26] They also reported a double calix[4]arene in which two calix[4]arene moieties have been connected *via* two opposite para positions with a $-CH_2OCH_2-$ bridge.[26] Similar double calix[4]arenes have been reported by Böhmer *et al.* in which two calix[4]arenes are connected by one, two, and four alkyl chains (*e. g.* **28**).[46,47]

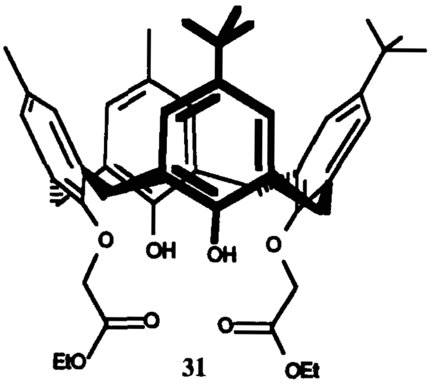
IV. CHIRAL CALIX[4]ARENES

Böhmer recognized that calix[4]arenes with four different *p*-substituted phenol rings like **29** (CHART 10) are chiral, because calix[4]arene is not planar, but cone shaped.[48] Similarly, calix[4]arenes with a substitution pattern 'AABC', like **30**, are asymmetric.[49] The problem, however, is that the enantiomers can not be separated, because a rapid racemization occurs due to the conformational inversion process. Böhmer *et al.* reported the synthesis of a rigid calix[4]arene **31**, of which both enantiomers could be observed in the ^1H NMR spectrum in the presence of a chiral shift reagent.[50] The substitution pattern at the lower rim of **31** requires only an AABB-type substitution at the upper rim to render the molecule chiral. Chiral but not asymmetric calix[4]arenes can be obtained by clockwise introduction of meta substituents in a symmetrical calix[4]arene (**32**).[51] The first optical resolution of a calix[4]arene that is asymmetrically substituted at the upper rim by the use of a chiral column was reported by Shinkai *et al.*[52] Chiral calix[4]arenes in the cone conformation were reported with an asymmetric substitution pattern at the lower rim of type 'AABC'.[53] Calix[4]arenes that show an 'AABB' substitution pattern become also chiral when they adopt a rigid partial cone conformation.[54]

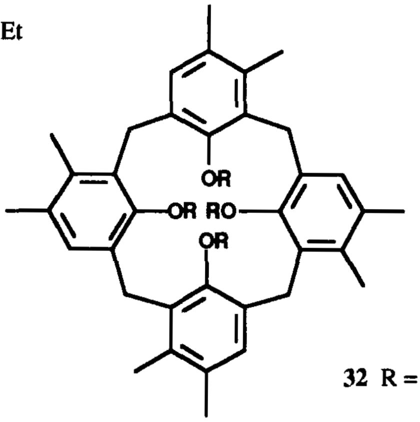
CHART 10



29 R = COOEt
30 R = CH_3



31



32 R = CH_2COOEt

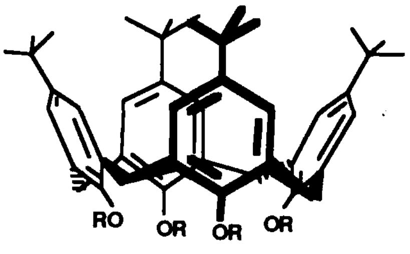
V. CONFORMATIONAL PROPERTIES OF CALIX[4]ARENES

One of the most important properties of calix[4]arenes is the ability to adopt four different extreme conformations (*vide supra*). When the substituents at the lower rim are small, in principle interconversion between different conformers is possible. The ratio of different conformations of these compounds is determined by the relative free energies.

1. Calix[4]arenetetrols

The 'unsubstituted' calix[4]arenetetrols (e.g. **33**, CHART 11) are flexible and show only a rigid cone conformation[55] (at the ^1H NMR time scale) upon lowering of the temperature, due to intramolecular H-bonding.[56] From temperature-dependent ^1H NMR spectra activation parameters of the conformational inversion process (cone to cone) were determined using lineshape analysis[56,57,58] and coalescence temperatures,[59] but there is still no general agreement on the *mechanism* of conformational interconversion. Kämmerer *et al.*[56] suggested a 1,3-alternate conformation as an intermediate, which can revert either to the original cone conformation or to its mirror image (i.e. the 'inverted cone'). Since the 'broken chain' mechanism of Kämmerer requires unfavorable disruption of all the H-bonds in the circular array of the initial cone conformation, Gutsche *et al.*[59] proposed a continuous-chain pathway, in which the aryl groups swing through the annulus in sequence. Based on space-filling model studies they suggested a skewed 1,2-alternate conformation as the activated complex, that would allow an almost continuous H-bonded system throughout the process. No experimental evidence, however, was presented. Shinkai *et al.*[58] have determined activation parameters, ΔH^* and ΔS^* by lineshape analysis, and they concluded from the continuity of the Arrhenius plot that a direct cone to cone interconversion occurs, and that a cone to alternate transition does not exist. Grootenhuis *et al.*[60] suggested a partial cone conformation as a key intermediate for the interconversion of tetra-*p*-methylcalix[4]arene on basis of molecular dynamics studies. Royer *et al.*[61] reported on basis of MMP2 calculations that most of the energy barrier to inversion is to disrupt the circular H-bonding going from the cone to the partial cone conformation. Finally, Keller *et al.*[62] observed that the infrared OH stretching frequency shows a much smaller temperature dependence than is expected for a ring inversion process. Together with the small temperature dependence of the dipole moment of calix[4]arene this leads to their suggestion that no ring inversion takes place at all, but only a loss of the methylene symmetry by an increased rocking motion. This hypothesis is not likely, since upper rim bridged calix[4]arenes **26** (n > 2) allow a rocking motion but no interconversion.[43] The ^{1}H NMR spectra of **26**, however, do not show coalescence at higher temperatures,[43] which points at an inversion process in unrestricted tetrols.

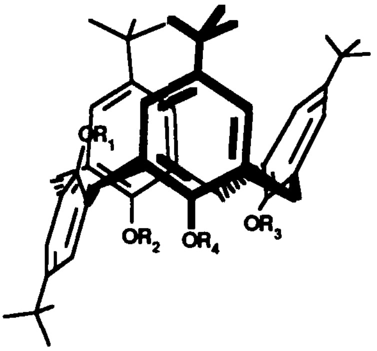
CHART 11



33 R = H

34 R = Me

35 R = Et



37 **a** $R_1 = R_2 = Me, R_3 = R_4 = Et$
b $R_1 = R_3 = Me, R_2 = R_4 = Et$
c $R_2 = R_3 = Me, R_1 = R_4 = Et$
d $R_2 = R_4 = Me, R_1 = R_4 = Et$

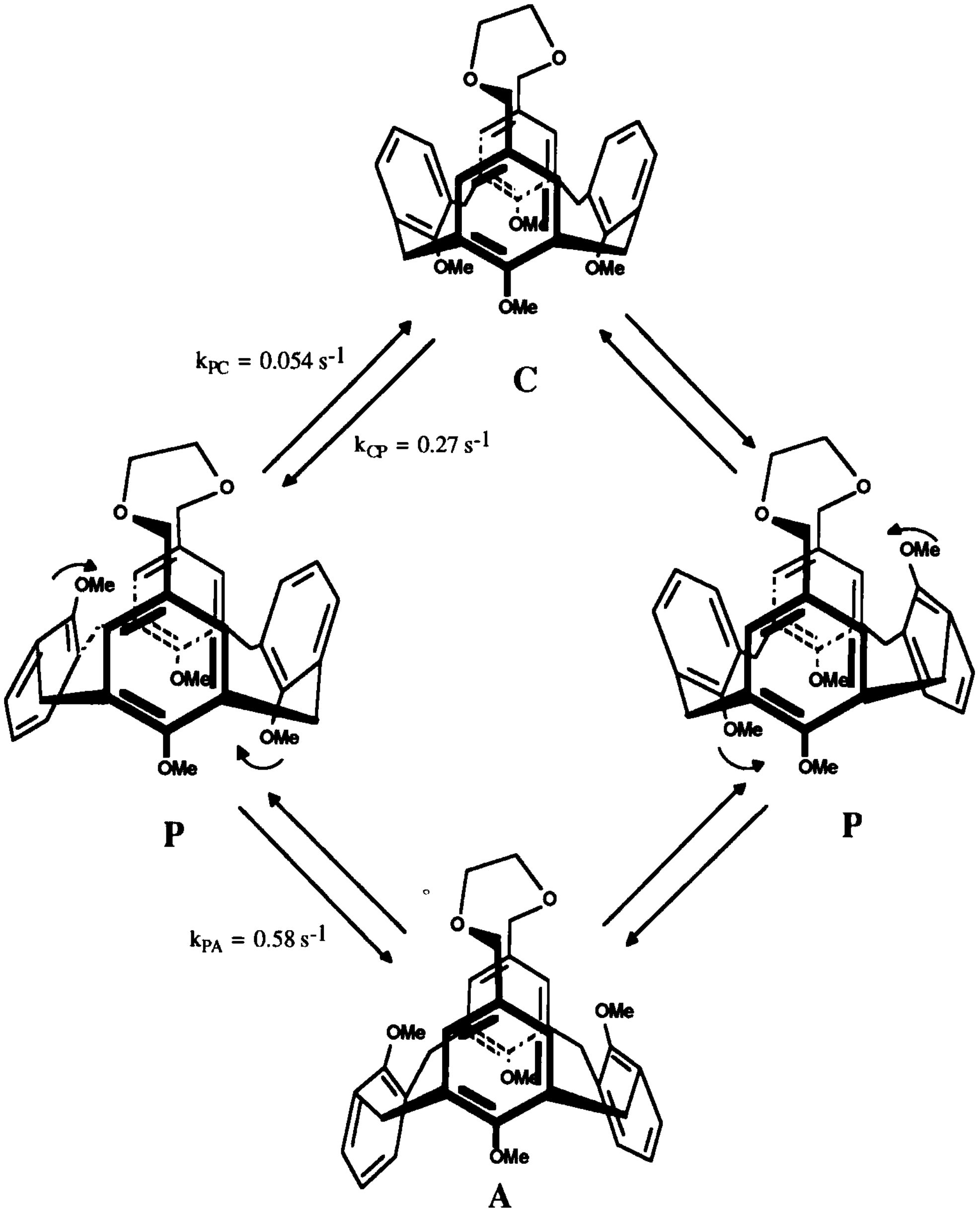
On the basis of NMR experiments it is not possible to exclude any of the proposed pathways, since *intermediates involved* may have such a high energy compared with the cone conformation that they cannot be detected by ^{1}H NMR spectroscopy, which has only an energy window of about 3 kcal mol^{-1}. Although no direct evidence exists for the mechanism of inversion of calix[4]arenetetrols, one can get some information by comparing with other flexible systems. Calix[4]arenes bearing four methoxy groups (*e. g.* **34**) are flexible molecules,[63] which means that methoxy groups are small enough to rotate through the calix[4]arene annulus. However, partly methylated calix[4]arenes show very different conformational properties. Monomethyl ethers (*e. g.* **1**, R = Me) and 1,3-dimethyl ethers (*e. g.* **2**, R = Me) exhibit a rigid cone conformation according to ^{1}H NMR spectroscopy,[7,63] and they show no coalescence at higher temperatures. The trimethyl ether is flexible (on the NMR time scale) only at higher temperatures. These observations indicate that calix[4]arenetetrols and tetramethoxy calix[4]arenes interconvert according to *different mechanisms*. The latter interconvert by rotation of one anisole ring at the time (*vide infra*) and as a consequence this is probably not the case with calix[4]arenetetrols. A continuous-chain mechanism, in which no H-bonds are broken, seems likely in these systems, but experimental evidence is hard to provide.

2. Tetramethoxycalix[4]arenes

The mechanism of conformational interconversion has been elucidated of tetramethoxycalix[4]arenes, in which the conformation is not determined by H-bonding. The first study was directed towards tetramethoxycalix[4]arenes, of which two opposite anisole rings are rigidified by means of a poly(oxyethylene) bridge at the upper rim (upper-rim-calix[4]crowns **36**, FIGURE 3).[45] This has the advantage that one of the four possible conformations, *viz.* the 1,2-alternate conformation is eliminated as an intermediate. Furthermore, conformational transitions are confined to rotation of the two free anisole rings. In $CDCl_3$ solution at -20° these compounds exist as a mixture of *two conformations*, *viz.* partial cone (P) and cone (C). The P/C ratio varies between 4.0 and 1.7 depending on the length of the bridge. Upper rim calix[4]crowns are flexible molecules according to temperature dependent ^{1}H NMR spectroscopy. The mechanism of conformational interconversion of calix[4]crown-2 and calix[4]crown-3, containing 6 and 9 bridge atoms, respectively, was elucidated by quantitative 2-D EXSY NMR spectroscopy. It proves that there are *two different pathways* (a slow and a fast process) by which two P conformational topomers can interconvert (FIGURE 3). One interconversion proceeds *via* C (slow process), and the other process proceeds most likely *via* a short-lived 1,3-alternate (A) intermediate (fast process). The overall rate diminishes dramatically going from a 9-atom bridge to a 6-atom bridge. Furthermore, shortening of the bridge has a much larger decelerating effect on the P→A than on the P→C process.

As a consequence of the results obtained for upper rim calixcrowns the conformational properties of the conformationally unrestricted tetra-*p*-*tert*-butyl-tetramethoxycalix[4]arene **34** were reinvestigated,[64] and evidence was provided that in $CHCl_3$ at -30° this compound exists as a mixture of all four possible conformers, including the rare 1,2-alternate conformation. (For ratios see TABLE 4). Temperature-dependent ^{1}H- and 2-D EXSY NMR experiments indicate that the interconversion involving the 1,2-alternate conformation is much slower than the interconversion between cone,

FIGURE 3. Mechanism of Conformational Interconversion of Calix[4]crown-2 (**36**).



partial cone and 1,3-alternate. The *1,2-alternate is the kinetically most stable conformation.* The ratio of conformations is dependent on the solvent (TABLE 4). In $CDCl_3$, CH_2Cl_2 and toluene-d_8 the partial cone is the thermodynamically most stable conformation. Shinkai *et al.* reported that the cone conformation becomes more stable in $CDCl_3$ containing polar solvents like CD_3CN and DMF-d_7.[65] Molecular mechanics calculations with AMBER and MM2 force fields in MACROMODEL of isolated molecules in the gas-phase predict the 1,3-alternate conformation to be the most stable, whereas both the MM2P(85) and the QUANTA/CHARMm program calculate the partial cone to be the conformation with the lowest energy (TABLE 5).[60]

TABLE 4. Relative Equilibrium Concentrations of the Tetramethyl, Diethyl and Tetraethyl Ethers of *p-tert*-Butylcalix[4]arene. (Measured in $CDCl_3$ at -30°, in %)

	cone	partial cone	1,2-alternate	1,3-alternate
32	4	85	8	3
32[e]	18	74	8	—[a]
32[f]	20	73	7	—[a]
35a	<5[a]	76	24	—[b]
35b	20	80	—[b]	<5[a]
35c	—[b]	64	25	11
35d[c]	—[b]	35	65	—[b]
33[d]	7	47	43	3

a) This conformation could not be ruled out because of the low resolution of the ^1H NMR. b) Precluded confromation for this compound. c) Measured at room temperature. d) Measured in $CDCl_2CDCl_2$ at 132°. e) CD_2Cl_2. f) Toluene-d_8.

In order to obtain more information about the factors that influence the ratios of conformations and the interconversion process the properties of a series of mixed diethyldimethyl ethers (**37**) were investigated, that are partly rigidified because of the presence of ethoxy groups.[64] In **37b** the 1,2-alternate is precluded and the ^1H NMR spectrum at room temperature shows only broad peaks, indicating a fast interconversion between cone, partial cone and 1,3-alternate. For **37a** and **37c** sharp peaks of the 1,2-alternate are visible beside broad signals of the other conformations, showing that the 1,2-alternate is also in these compounds a kinetically stable conformation. In **37d** the two fast interconversion pathways are precluded, since the 1,3-alternate and the cone conformation are not possible. As a consequence the ^1H NMR spectrum only exhibits sharp peaks. The 1,2-alternate conformation is also thermodynamically the most stable conformation for this compound.

Shinkai *et al.*[66,21f] reported that the tetraethyl ether of *p-tert*-butylcalix[4]arene is flexible at temperatures higher than 100°. They reported that the partial cone conformation slowly isomerizes to the 1,2-alternate, resulting in a nearly 1:1 mixture of partial cone and 1,2-alternate.[66] However, it was shown that also this compound adopts all four conformations (TABLE 4).[64] A kinetic investigation of the conversion of the partial cone to the other three conformations confirmed the relative rates of the three processes.

TABLE 5. Comparison of Several Force Fields for Calculations on *p*-Methylcalix[4]arene.

Force Field	Conformation	E_{bonded}	E_{VDW}	E_{elec}	E_{total}
AMBER 3.0	cone	25.5	1.4	-130.0	-103.2
	partial cone	24.9	1.7	-134.9	-108.3
	1,2-alternate	26.2	1.5	-136.0	108.3
	1,2-alternate	24.0	0.5	-137.2	-112.6
MACROMODEL AMBER	cone	19.0	0.7	+ 2.5	22.2
	partial cone	18.2	0.0	- 0.5	17.7
	1,2-alternate	18.8	2.8	+ 1.1	22.7
	1,2-alternate	17.8	0.1	- 1.1	16.8
MACROMODEL MM2	cone	28.0	9.2	+ 6.9	30.3
	partial cone	17.7	7.8	- 7.0	28.5
	1,2-alternate	28.5	9.4	+ 6.8	31.1
	1,2-alternate	27.4	7.8	- 6.8	28.4
MM2P(85)	cone	- 7.3	15.0	+ 1.3	19.0
	partial cone	- 8.0	14.4	- 0.7	16.2
	1,2-alternate	- 6.1	16.4	+ 2.0	21.4
	1,2-alternate	- 8.3	14.9	- 1.0	19.1
QUANTA CHARMm	cone	32.2	-4.2	+ 0.2	27.8
	partial cone	31.2	-5.3	- 1.2	24.7
	1,2-alternate	35.3	-0.5	+ 3.5	38.1
	1,2-alternate	33.2	-5.5	- 0.9	26.8

a) Energies are in kcal mol^{-1}

CONCLUDING REMARKS

The present review demonstrates that selective functionalization of calix[4]arenes at both lower and upper rim is now well established. At the same time, knowledge of the conformational properties of calix[4]arenes gives a better insight in the potential applicability of functionalized calix[4]arene as building blocks for the construction of receptor molecules for organic guests in solution. With the recent developments in calix[4]arene chemistry, the role of this building block in supramolecular chemistry can be looked upon with confidence.

Acknowledgments.- This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO), and the EEC Twinning Project No. ST2J-0215. We kindly acknowledge Prof. R. Ungaro, Prof. A. Pochini, Prof. L. Mandolini, Dr. V. Böhmer, Prof. M. A. McKervey, and Dr. L. C. Groenen for their contributions and stimulating discussions.

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(Received on March 5, 1992; in revised form April 30, 1992)