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Calix[4]arenes as building blocks for molecular receptors

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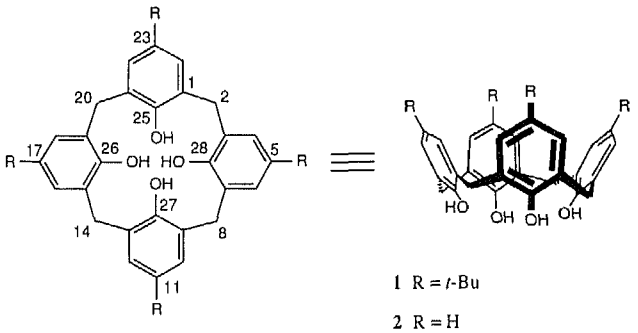
Abstract. Molecular receptors for organic molecules are described in which calix[4]arene is used as a *molecular platform* rather than for its *cavity*. This is illustrated by the synthesis of a receptor for barbiturates, a calix[4]arene in a cone conformation containing two diaminotriazine moieties at the upper rim. This receptor (**9**) forms a molecular cleft in which phenobarbital complexes by hydrogen bonding both triazine rings. The association constant K is $520\,M^{-1}$, when the self-association of the barbiturate is taken into account.

Introduction

Calix[4]arenes (Chart 1) have received increasing attention in the field of supramolecular chemistry[1]. *Gutsche* recognized the potential application of calix[4]arenes as molecular receptors or even as enzyme mimics at an early stage because the aromatic walls of calix[4]arene enclose a molecular cavity in which a substrate may be complexed[2].



1 R = *t*-Bu

2 R = H

3 R = SO_3Na

Chart 1

The first evidence for their binding properties was provided by *Andreetti* et al. in 1979[3], who reported the crystal structure of a toluene complex of *p-tert*-butylcalix[4]arene **1** in which the methyl group of toluene is embedded in the calix[4]arene cavity. This result triggered further research in the calix[4]arene field and several adducts with neutral molecules have been reported. In the solid state, *p-tert*-butylcalix[4]arene forms complexes with aromatic molecules, such as benzene[4], xylene[4], phenol[5], and anisole[6]. *Vicens* et al.[7] recently demonstrated the selective complexation of *p*-xylene with *p*-isopropylcalix[4]arene by crystallization from a 1 : 1 : 1 mixture of the three xylene isomers. Calix[4]arene tetrasulphonate **3** forms an inclusion complex with water in the solid state by aromatic π-electron hydrogen bonding[8].

Calix[4]arenes that are *functionalized at the lower rim* are also able to complex organic molecules in the solid state[9]. Despite these solid-state complexes, evidence for complexation of organic molecules in solution is rare. So far, only two examples are known: both concern the complexation of organic ammonium cations, in CD_3CN and D_2O, respectively. *Gutsche* et al.[10] reported the complexation of aliphatic amines by *p*-alkylcalix[4]arenes in CD_3CN. They suggested[11] a two-step process for the formation of the complex, *viz.*, proton transfer from the calix[4]arene to the amine followed by association of the two ions to form an *endo* complex, with association constants in the order of $10^4\,M^{-1}$. Very recently, *Shinkai* et al.[12] provided evidence for the complexation of the trimethylanilinium cation by a water-soluble calix[4]arene tetrasulphonate. Hydrophobic as well as electrostatic forces play an important role in the binding of the "guest" molecules. In studies that compare the complexation properties of calix[4]arenes with the higher homologues, calix[5–8]arenes, calix[4]arenes are reported as poor complexing agents[12b,13].

Several reasons may be responsible for the fact that complexation of organic molecules by calix[4]arene in solution has not been very successful. Firstly, the cavity is too small to encapsulate the "guest", and the stabilizing forces (mostly van der Waals interactions) are not sufficiently strong to overcome competition by the solvent. Secondly, the cavity of the parent calix[4]arenes is not rigid and is continuously disrupted by fast conformational inversion processes in solution. This problem might be overcome by stiffening the skeleton by substitution at the lower rim, but this will have a significant effect on the shape of the cone conformation. In the course of our studies on the conformational properties of calix[4]arene derivatives[14], it appeared *that the symmetrical cone conformation of calix[4]arene is probably more an exception than a rule.* In fact, the symmetrical cone conformation is stabilized only by extraneous forces, *viz.*, by hydrogen bonding in the unsubstituted calix[4]arenes, by

electrostatic forces in the Na^+ or K^+ complexes of calix[4]arenetetraacetamides[9f], or by formation of a transition metal complex, such as the oxomolybdenum complex[9d]. If these stabilizing forces are lacking, the cavity will collapse, because a distorted cone conformation with two parallel and two perpendicular aromatic rings is more stable[15,16]. Evidence for a distorted cone conformation is provided by the X-ray structures of tetraalkylated calix[4]-arenes[15]. In solution, the short NMR-T_1-relaxation times of the aromatic protons prove that calix[4]arenetetraacetic ester performs a "seesaw" motion between two distorted cone topomers, that is frozen only by complexation of a Na^+ cation in the lower rim cavity[16,17].

In this paper, a new approach is presented for the design of molecular receptors for organic molecules in solution on the basis of calix[4]arenes. According to our concept, the calix[4]arene *is applied not for its cavity but as a platform* on which a molecular cleft is constructed by selective functionalization. The concept will be illustrated by the synthesis of a receptor for barbiturates, which are known to form complexes with diaminopyridines and diaminotriazines by hydrogen bonding[18,19].

Results and discussion

Synthesis

CPK models suggested that, by linking two 2,4-diaminotriazine moieties to the parallel aromatic rings of a calix[4]arene (**9**) in a distorted cone conformation, a molecular cleft is formed that can be used for the complexation of barbiturates (Chart 2) via six hydrogen bonds. Reaction of calix[4]arene **2** with excess 2-ethoxyethyl tosylate and NaH as a base in DMF gave the tetrakis(2-ethoxyethyl) ether **4** in 72% yield (Chart 3)[20]. This compound shows a typical

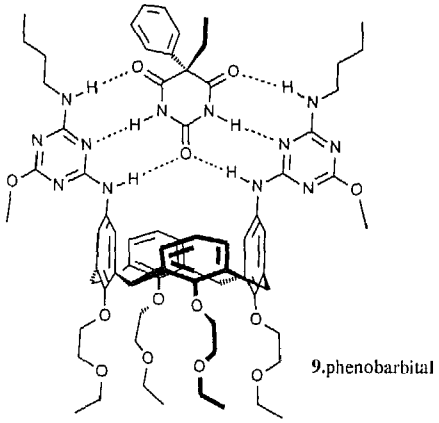


Chart 2

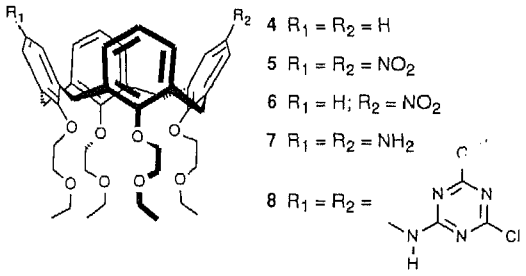


Chart 3

AB pattern for the methylene bridge protons (δ 4.50 and 3.14, J 13.4 Hz) in the ^{1}H NMR spectrum. The selective formation of the cone conformation is in agreement with the observation of *Groenen* et al.[21] that alkylations with NaH in DMF generally yield calix[4]arenes in a rigid cone conformation. Nitration of compound **4** under carefully controlled conditions with acetyl nitrate in CH_2Cl_2 at room temperature gave the diametrically substituted dinitrocalix[4]arene **5** in 30–40% yield, together with 20% of mononitrated product **6**. Remarkably, no proximally 1,2-dinitrated products could be isolated. The reason for the regioselectivity is not known, but the result is in agreement with the observation of *Pochini* et al.[20] that the Gross formylation of **4** also occurs with diametrical 1,3 selectivity. Reduction of dinitrocalix[4]arene **5** with hydrazine and Raney Nickel as catalyst gave the diaminocalix[4]arene **7** in 98% yield. This compound shows a singlet at δ 5.97 in the ^{1}H NMR spectrum for the aromatic aniline protons. It was observed that the reduction only proceeds if the starting material is very pure, otherwise poisoning of the catalyst takes place. Reaction of compound **7** with two equivalents of 2,4-dichloro-6-methoxy-1,3,5-triazine in dioxane with NaOH as a base at room temperature resulted in the selective substitution of one of the chlorine atoms to give **8** in 80% yield. The substitution of the second chlorine was accomplished by reaction of **8** with excess *n*-butylamine in refluxing dioxane to give the receptor **9** in 50% yield after recrystallization from THF/heptane. The butyl groups were introduced to increase the solubility of the receptor. As a reference compound, the [(*p*-methoxyphenyl)amino]triazine **10** (Chart 4) was prepared in 93% overall yield by reaction

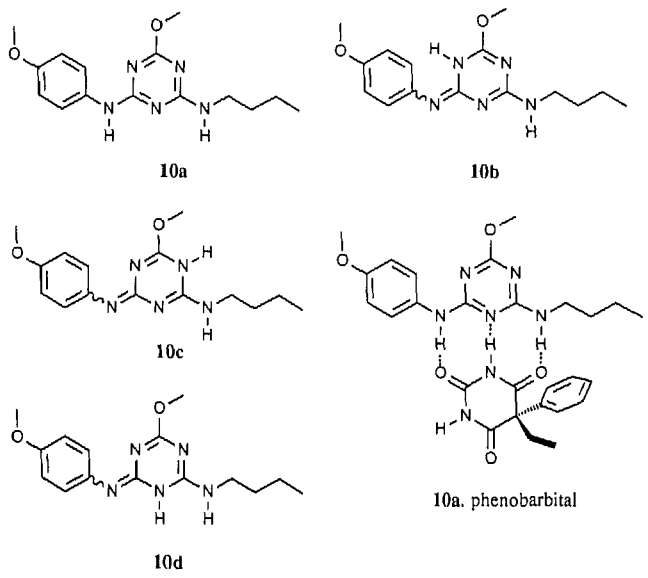


Chart 4

of 4,6-dichloro-*N*-(4-methoxyphenyl)-1,3,5-triazin-2-amine with 2 equivalents of *n*-butylamine in dioxane at room temperature and subsequent reaction with sodium methoxide in refluxing methanol.

Complexation properties

The ^{1}H NMR spectrum of **10** in $CDCl_3$ is more complex than would be expected, since it exhibits two signals for the methoxy groups on the triazine ring in a ratio of 1 : 1, each corresponding to 1.5 protons. Similarly, the protons of the anisole ring *ortho* to the amino group show two doublets in a 1 : 1 ratio, and two broad signals of equal intensity were detected for each NH group. In DSMO-d_6, the ^{1}H NMR

spectrum is similar, but the ratio between the signals is 1 : 2. This can be interpreted as a mixture of two tautomeric forms, the ratio of which depends on the solvent. Although no definite conclusions can be drawn on the structure of the tautomers, the ^{1}H- and ^{13}C-NMR spectra indicate that the anilino NH proton shifts to form **10b**, **10c** or **10d** (Chart 4). Some examples of tautomerism in triazinyl CH acids are known[22], but no systematic study on the tautomerism of these heterocycles has been reported[23]. Upon addition of increasing amounts of phenobarbital [5-ethyl-5-phenyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione] to a solution of **10** in $CDCl_3$ the NH signals of both the guest and the host shift downfield and the tautomeric equilibrium is shifted almost completely to **10a** (Figure 1). This can be attributed to the formation of complex **10a** · phenobarbital, in which only tautomer **10a** can form the complementary hydrogen bonds with the barbiturate.

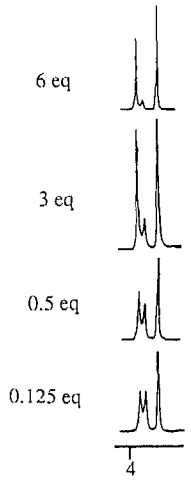


Figure 1. Shift of tautomeric equilibrium of **10** *upon complexation with phenobarbital.*

The calix[4]arene receptor **9** has two triazine moieties at the upper rim. The ^{1}H NMR spectrum in $CDCl_3$ shows a broad and complex pattern, reflecting a mixture of tautomers. Upon addition of phenobarbital, a 1 : 1 complex (*vide infra*) is formed and the ^{1}H NMR spectrum becomes sharp and unambiguous (Figure 2). The NH signal of the barbiturate shifts downfield by more than 3 ppm and the protons of the aryl group become non-equivalent, showing a

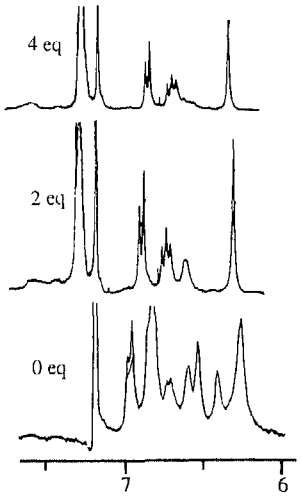


Figure 2. Complexation of **9** *with phenobarbital.*

multiplet instead of a singlet, as in the free guest[24]. In the ^{1}H NMR spectrum of the host, the broad signals of the 2-ethoxyethyl substituents are sharper, and the signals of the methyl groups exhibit two triplets. This may be attributed to a small conformational change in the calix[4]-arene conformation.

Determination of the complexation constant

The association constant K_{HG} of a complexation process is usually determined from the chemical shift of a signal of the host or the guest at different host/guest ratios[25]. Since the calix[4]arene receptor **9** exists as a mixture of tautomers in $CDCl_3$, the NH of the barbiturate is the only NMR signal suitable to obtain an association constant of the complex. However, applying the standard curve-fitting procedure[26] to the experimental data gave very poor fits. The reason for this is that the curve-fitting procedure only takes into account the association between host and guest (Eqn. 1).

$$H + G \leftrightarrows HG \qquad K_{HG} = [HG]/([H] \cdot [G]) \tag{1}$$

However, especially in hydrogen-bonded systems, two other equilibria may play a significant role, *viz.*, self-association of the host and/or the guest.

$$H + H \leftrightarrows H_2 \qquad K_{H2} = [H_2]/[H]^2 \tag{2}$$

$$G + G \leftrightarrows D \qquad K_D = [D]/[G]^2 \tag{3}$$

Barbiturates (2,4,6-pyrimidinetriones) are known to dimerize[27] and it proved to be important to take this equilibrium into account. The host showed no detectable dimerization in $CDCl_3$, according to vapour-pressure osmometric-weight determinations. For the determination of association constants, self-association phenomena have been largely neglected[28], and it was, therefore, necessary to develop a procedure that takes into account self-association of the guest. From equilibria 1 and 3 and the boundary conditions $[G]_0 = [G] + 2 \cdot [D] + [HG]$ and $[H]_0 = [H] + [HG]$, in which $[G]_0$ and $[H]_0$ are the initial concentrations of guest and host, respectively, Eqn. 4 can be derived:

$$[G]^3 + \frac{K_{GH} + 2 \cdot K_D}{2 \cdot K_D \cdot K_{HG}} \cdot [G]^2 + \frac{K_{HG} \cdot ([H]_0 - [G]_0) + 1}{2 \cdot K_D \cdot K_{HG}} \cdot [G] - \frac{[G]_0}{2 \cdot K_D \cdot K_{HG}} = 0 \tag{4}$$

This equation can be solved analytically and provides a value for [G] (and thus for [H], [D], and [HG]) at given values of K_D, K_{HG}, $[G]_0$ and $[H]_0$.

If the signal of the guest is measured by NMR spectroscopy, the observed chemical shift is given by Eqn. 5:

$$\delta_{obs} = \delta_0 + f_D \cdot (\delta_{D,max} - \delta_0) + f_{HG} \cdot (\delta_{HG,max} - \delta_0) = \delta_0 + \frac{2 \cdot [D]}{[G] + 2 \cdot [D] + [HG]} \cdot \Delta\delta_{D,max} + \frac{[HG]}{[G] + 2 \cdot [D] + [HG]} \cdot \Delta\delta_{HG,max} \tag{5}$$

where δ_0 is the chemical shift of the pure monomeric guest, f_D and f_{HG} are the fractions of guest dimer and complex, and $\Delta\delta_{D,max}$ and $\Delta\delta_{HG,max}$ are the maximum chemical shifts caused by dimerization and complexation, respectively.

The values for δ_0, K_D and $\Delta\delta_{D,max}$ can be determined in a separate experiment, in which the dimerization of the guest is derived from the concentration dependent chemical shift of the guest NH[29]. The only unknown parameters are K_{HG}

and $\Delta\delta_{HG,max}$. These can be obtained by the simultaneous fitting of both parameters, with Eqns. 4 and 5. An estimated value of K_{HG} provides values for f_D and f_{HG} by means of Eqn. 4 and, together with an estimated value of $\Delta\delta_{HG,max}$ and Eqn. 5, the chemical shifts can be calculated. Minimization of the difference between calculated and observed chemical shifts by systematic variation of K_{HG} and $\Delta\delta_{HG,max}$, with least-square methods provides optimal values for both parameters. A LOTUS-1-2-3 program was written to facilitate the iteration process.

The self-association of phenobarbital was determined independently by the method of *Horman* and *Dreux*[29] to give a dimerization constant $K_D = 8.5 M^{-1}$ and $\delta_0 = 7.84$ and $\Delta\delta_{D,max} = 2.41$ ppm. When this dimerization equilibrium was taken into account, a good fit was obtained for the complexation of phenobarbital by the calix[4]arene receptor **9**, to give an association constant of $520 \pm 50 M^{-1}$ with $\Delta\delta_{HG,max} = 4.99$ ppm (Figure 3). It should be noted that,

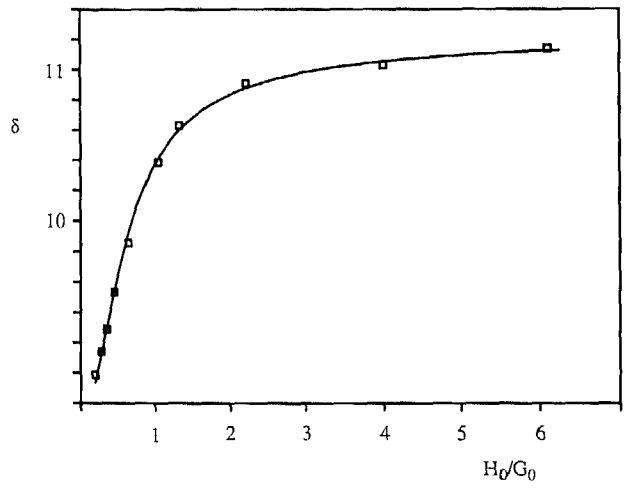


Figure 3. Titration curve of **9** *and phenobarbital.*

although the association constant K_D is very low in comparison with K_{HG}, the dimerization of the guest has a large influence on the observed NMR signal, because the $\Delta\delta_{D,max}$ is comparable to $\Delta\delta_{HG,max}$ and the dimerization equilibrium is shifted considerably as a result of complexation. The association constant for the complexation of phenobarbital with reference compound **10** was determined similarly, to give a $K_{HG} = 200 \pm 20 M^{-1}$, with $\Delta\delta_{HG,max} = 3.66$ ppm.

The good correlation between calculated and observed chemical shifts not only provides evidence for the existence of a 1 : 1 complex, but also indicates that both triazine units are involved in the complexation process, since the calix[4]arene receptor binds phenobarbital 2.6 times better than the reference compound. However, the association constant is low, since a value of $K_{HG} = 520 M^{-1}$ corresponds to a free energy of complexation[30] $\Delta G = 3.7$ kcal · mol^{-1}. It should be noted that the association constant of the reference compound cannot be used to calculate an individual contribution of each triazine unit in the calix[4]arene receptor **9**, since the binding sites of the barbiturate are not independent[31]. This is demonstrated by the fact that the complexation of the reference compound corresponds well to a 1 : 1 complexation, so that the complexation of a second triazine moiety to the free binding site of the complex is apparently very unfavorable.

Several factors may be responsible for the low overall association constant of the calix[4]arene receptor, in which the tautomeric equilibria are included[32]. The pre-organization of the host is a factor that is likely to have a large influence on the free energy of binding. Although the conformation of the calix[4]arene is fixed in the cone conformation, it is still able to interconvert rapidly between two distorted cone conformations of which only one can bind the barbiturate via both triazine rings. In addition to the flexibility of the calix[4]arene skeleton, the triazine moieties can also take different orientations with respect to the calix[4]arene framework, since they are connected by a single bond which will have a large influence on the shape of the cleft. Intramolecular hydrogen bonds between the two triazine rings cannot be ruled out; they should have a decreasing effect on the association constant, because they must be broken before complexation. However, it is likely that the most important factor is the shape of the cleft, which is a function of the angles α and β between the triazine rings and the corresponding phenyl rings of the calix[4]arene (Figure 4).

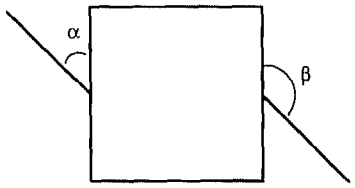
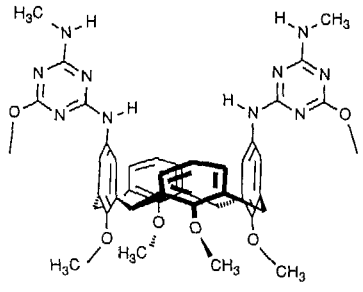


Figure 4. Schematic drawing of receptor **9**.

To get more insight into the geometry of the cleft, molecular modelling studies were performed with the program QUANTA-CHARMm for minimization of the structures. The calculations were performed with a standard parameter set on an isolated molecule in vacuum. Since the 2-ethoxyethyl chains and the *n*-butyl substituents of **9** increase the number of possible conformations substantially, and since they are not likely to have a significant effect on the complexation properties, they were replaced by methyl groups (**11**, Chart 5). Only the complementary tautomer was studied.



11

Chart 5

Minimization of the free host, starting from different geometry all lead to a distorted cone conformation in which the two triazine units stack, and the methoxy groups of the triazine rings point towards the two anisole rings of the calix[4]arene (Figure 5). The total energy is dominated by the electrostatic term. The favorable stacking of the triazine rings can be understood from the fact that in vacuum, all flexible substituents will try to achieve a maximum electrostatic interaction, which is particularly favoured by the large partial charges[33] at the C and N atoms of the triazine rings. In solution, the minimized structure of **11** is not very realistic, since a considerable upfield shift of the protons of the triazine-methoxy groups should be observed due to the

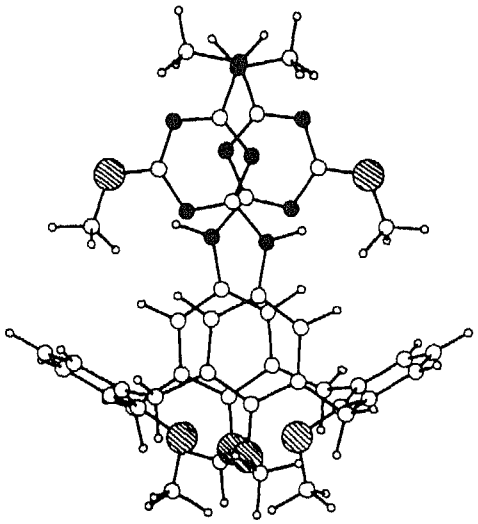


Figure 5. Minimized structure of **11**.

shielding effect of the aromatic rings of the calix[4]arene. Comparison of the ^{1}H NMR spectra of receptor **9** and reference compound **10** showed no measurable chemical-shift difference. To overcome the problem of stacking, which is known to be overestimated in molecular modelling studies[34], the positions of the triazine units were fixed with respect to the calix[4]arene at various angles α and β by the application of a dihedral constraint. For various combinations of α and β, the structure of the host was minimized with and without the presence of phenobarbital. The results are summarized in Table I. The complex at α = β = 90° is the most stable, having 6 hydrogen bonds with bond lengths of 1.8–1.9 Å for all NH...O bonds and 2.1 Å for the NH...N bonds. However, the energy differences with complexes that have other α/β values are very small and they cannot be attributed to one particular energy term. Although the energy differences are small, there are changes in the geometry of the complex. At larger deviations of β 90°, one of the H bonds between the calix[4]arene-NH and O-3 of the barbiturate becomes longer and breaks at β 60 or 120°. A similar effect can be seen for the adjacent NH...N bond. This means that, at deviations larger than 30° from the perpendicular orientation of the triazine units with regard to the calix[4]arene, only four hydrogen bonds can be formed[35]. In all minimized structures, the barbiturate is complexed non-symmetrically. Experimental evidence for a non-symmetric complex is provided by the ^{1}H NMR spectra of the 1 : 1 complexes of phenobarbital with receptor **9** and with the reference compound **10** at −60 °C in $CDCl_3$. They show two singlets of equal intensity for the calix[4]arene-NH, whereas the corresponding NH of the reference compound shows a sharp singlet. The modelling studies indicate that the fit of the guest is dependent on the relative orientation of the triazine rings with regard to the calix[4]arene, but the results should be regarded with scepticism. More reliable results would be obtained if solvent molecules were taken into account.

Conclusions

Experimental evidence is provided in this paper to support the statement that calix[4]arenes in solution should not primarily be regarded as cavity-containing host molecules, such as cyclodextrins, but rather as molecular building blocks that are useful for the positioning of functional groups in space to form a binding site for organic substrates.

Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 250 spectrometer in $CDCl_3$ (unless otherwise indicated) with Me_4Si as an internal standard. FAB mass spectra were obtained with a Finnigan MAT 90 spectrometer with *m*-nitrobenzyl alcohol as a matrix. All chemicals were reagent grade and used without further purification. Compound **2** was prepared according to *Gutsche* and *Lin*[36]. All reactions were carried out in a nitrogen atmosphere. Chromatographic separations were performed on silica gel 60 (SiO_2, E. Merck, particle size 0.040–0.063 mm, 230–240 mesh); preparative TLC was performed on 60 F254 (Al_2O_3) preparative plates (E. Merck, thickness 1.5 mm).

25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene[37] *(cone)* (**4**)

Calix[4]arene (10 g, 23.6 mmol) was added in portions to a suspension of NaH (7.08 g, 236 mmol, 80% in oil, washed with hexane) in dry DMF (300 ml). After hydrogen formation had stopped, 2-ethoxyethyl tosylate[38] (115.2 g, 472 mmol) was added dropwise. The mixture was stirred at room temperature for 1½ h and at 75 °C for an additional 23 h. Excess NaH was decomposed with H_2O (caution!), and after evaporation of the solvent CH_2Cl_2 (300 ml) and H_2O (200 ml) were added. The organic layer was washed with NH_4Cl solution (2 × 100 ml) and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was treated with cold MeOH to give **4** as a white solid; yield 72%; m.p. 122 °C (MeOH). Anal. calcd. for $C_{44}H_{56}O_8$ (712.92): C 74.39, H 7.93; found: C 74.13, H 7.92%. ^{1}H NMR: δ 6.64–6.53 (m, 12H, ArH), 4.50 and 3.14 (ABq, 8H, *J* 13.4 Hz, $ArCH_2Ar$), 4.12 (t, 8H, $ArOCH_2$), 3.85 (t, 8H, Ar OCH_2CH_2), 3.55 (q, 8H, OCH_2CH_3), 1.21 (t, 12H, CH_3). Ms (EI), *m/z* 712.398 (M^+, calcd. 712.398).

25,26,27,28-Tetrakis(2-ethoxyethoxy)-5,17-dinitrocalix[4]arene (cone) (**5**)

HNO_3 (65%, 40 ml) was added to a solution of calix[4]arene **4** (0.85 g, 1.2 mmol) in a mixture of CH_2Cl_2 (40 ml) and glacial acetic

Table I Minimization data of complex **11** · *phenobarbital.*

No.	α	β	E_{tot}	E_{comp}[a]	E_{bond}	E_{angle}	E_{dih}	E_{imp}	E_{LJ}	E_{elec}	NH..O	NH..N
			kcal · mol^{-1}				kcal · mol^{-1}				Å	
1	60	60	−261.2	−21.6	9.7	16.6	53.2	2.8	56.8	−400.3	2.61	2.34
2	70	70	−259.7	−21.5	9.6	16.4	55.7	2.7	59.2	−403.3	2.20	2.20
3	80	80	−258.3	−21.2	9.7	16.4	57.1	2.5	60.7	−405.0	2.01	2.18
4	90	90	−257.0	−22.4	9.8	16.6	57.3	2.5	61.9	−405.2	1.94	2.16
5	80	100	−257.2	−19.5	9.7	16.4	57.1	2.2	61.7	−404.4	1.96	2.16
6	70	110	−258.1	−18.5	9.6	16.3	54.9	2.2	61.1	−402.2	2.11	2.17
7	70	110	−258.1	−18.5	9.7	17.9	49.4	2.1	58.8	−396.3	4.03	3.01
8	60	120	−260.7	−19.1	9.8	18.5	46.3	2.0	59.0	−396.5	4.51	3.20

[a] Energy gain as a result of complexation.

acid (2.4 ml). The mixture was stirred at room temperature and monitored with TLC (SiO_2, petroleum-ether-(b.p. 40–60°C)/EtOAc 7:3). After 2 h, H_2O (25 ml) was added and the organic layer was washed with 5% K_2CO_3 solution until neutral pH. The solvent was dried over $MgSO_4$ and evaporated to give a mixture of products that were separated by column chromatography (SiO_2, petroleum-ether-(b.p. 40–60°C)/EtOAc 7:3) to give **5** as white solid after recrystallization from MeOH; yield 30–40%; m.p. 158–159°C (MeOH). Anal. calcd. for $C_{44}H_{54}N_2O_{12} \cdot 0.5H_2O$ (802.92): C 65.09, H 6.83, N 3.45; found: C 64.86, H 6.68, N 3.31%. ^{1}H NMR: δ 7.65 (s, 4H, ArH), 6.70–6.45 (m, 6H, ArH), 4.59 and 3.25 (ABq, 8H, *J* 13.6 Hz, $ArCH_2Ar$), 4.30, 4.07 (t, 4H, $ArOCH_2$), 3.90–3.70 (m, 8H, CH_2OEt), 3.62–3.41 (m, 8H, OCH_2Me), 1.18 (t, 6H, CH_3), 1.16 (t, 6H, CH_3). Ms (FAB), *m/z* 802.4 (M^+, calcd. 802.4).

25,26,27,28-Tetrakis(2-ethoxyethoxy)-5-nitrocalix[4]arene (cone) (**6**)

Compound **6** was isolated by column chromatography (*vide supra*) as a side-product in the synthesis of **5** as an oil in 20% yield. ^{1}H NMR: δ 6.90–6.70 (m, 9H, ArH), 6.40–6.30 (m, 2H, ArH), 4.57 and 3.16 (ABq, 4H, *J* 13.6 Hz, $ArCH_2Ar$), 4.47 and 3.20 (ABq, 4H, *J* 14.6 Hz, $ArCH_2Ar$), 4.30–4.00 (m, 8H, $ArOCH_2$), 3.90–3.70 (m, 8H, $ArOCH_2CH_2$), 3.60–3.40 (m, 8H, $ArOCH_2Me$), 1.20–1.10 (m, 12H, CH_3). Ms (EI), *m/z* 757.355 (M^+, calcd. for $C_{44}H_{53}NO_{10}$ 757.355).

5,17-Diamino-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (cone) (**7**)

Hydrazine hydrate (1 ml) was added dropwise to a suspension of **5** (1.0 g, 1.2 mmol) and a catalytic amount of Raney Ni in MeOH (25 ml). After 1-h reflux under argon, the Raney Ni was filtered over Hyflo and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (50 ml) and washed with H_2O (25 ml) and brine (25 ml). After drying over $MgSO_4$ and evaporation of the solvent, **7** was obtained as a white solid which was kept under argon; yield 98%; m.p. 143–144°C (MeOH). Anal. calcd. for $C_{44}H_{58}N_2O_8 \cdot 2HCl \cdot 1.5$ MeOH (742.95)[39]: C 63.26, H 7.70, N 3.24; found: C 63.02, H 7.75, N 3.30%. ^{1}H NMR: δ 6.75–6.55 (m, 6H, ArH), 5.97 (s, 4H, ArH), 3.92 and 3.03 (ABq, 8H, *J* 13.3 Hz, $ArCH_2Ar$), 4.09, 4.01 (t, 4H, $ArOCH_2$), 3.85–3.75 (m, 8H, $ArOCH_2CH_2$), 3.60–3.50 (m, 8H, OCH_2CH_3), 1.25–1.15 (m, 12H, CH_3). Ms (EI), *m/z* 742.420 (M^+, 742.419).

N,N'-*[25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene-5,17-diyl]bis[4-chloro-6-methoxy-1,3,5-triazin-2-amine] (cone)* (**8**)

A solution of **7** (140 mg, 0.19 mmol) in dioxane (10 ml) was added slowly to a solution of 2,4-dichloro-6-methoxy-1,3,5-triazine[40] (140 mg, 0.78 mmol) in dioxane (10 ml). After addition of 1N NaOH (0.8 ml), the solvent was evaporated and the mixture was taken up in CH_2Cl_2 (50 ml) and washed with 1N HCl (25 ml) and brine (25 ml). The organic layer was dried over $MgSO_4$ and evaporated to give **8** as a brown oil, which was sufficiently pure for synthetic purposes; yield 80%. ^{1}H NMR: δ 7.10–6.85 (br m, 6H, ArH), 6.92 (br s, 4H, ArH), 4.52 and 3.13 (ABq, 8H, *J* 15.0 Hz, $ArCH_2Ar$), 4.30–4.25 (m, 4H, $ArOCH_2$), 4.00–3.80 (m, 18H, OCH_2CH_2O and OCH_3), 3.60–3.45 (m, 8H, OCH_2Me), 1.25–1.15 (m, 12H, $OCCH_3$). Ms (FAB), *m/z* 1028.4 (M^+, calcd. 1028.8).

N,N'-*[25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene-5,17-diyl]bis[*N*-butyl-6-methoxy-1,3,5-triazin-2-amine] (cone)* (**9**)

A mixture of **8** (100 mg, 0.097 mmol) and *n*-butylamine (0.15 ml) in dioxane (10 ml) was refluxed for 4 h. After the solvent was evaporated, the mixture was taken up in CH_2Cl_2 (50 ml) and washed with 1N HCl (25 ml) and brine (25 ml). The organic layer was dried over $MgSO_4$ and evaporated to give an oil, that was crystallized from THF/heptane to give pure **9**; yield 50%; m.p. 92–94°C (THF/heptane). A satisfactory elemental analysis could not be obtained. ^{1}H NMR: δ 7.69–6.26 (m, 10H, ArH), 5.06 (br s, 2H, NH), 4.50 and 3.12 (ABq, 8H, *J* 13.5 Hz, $ArCH_2Ar$), 4.23–3.82 (m, 16H, OCH_2CH_2O), 3.85 (s, 6H, OCH_3), 3.61–3.47 (m, 8H, OCH_2Me), 3.38–3.15 (m, 4H, NCH_2), 1.57–1.14 (m, 28H, CH_2CH_2Me and $OCCH_3$), 1.14–0.90 (m, 12H, NHC_3CH_3). Ms (FAB), *m/z* 1104.1 [$(M + H)^+$, calcd. for $C_{56}H_{60}O_{10}$ 1103.6].

N-*Butyl*-N'-*(4-methoxyphenyl)-6-methoxy-1,3,5-triazine-2,4-diamine* (**10**)

A mixture of 4,6-dichloro-*N*-(4-methoxyphenyl)-1,3,5-triazin-2-amine[41] (500 mg, 1.84 mmol) and *n*-butylamine (270 mg, 3.70 mmol) in dioxane (20 ml) was stirred for 1 h at 40°C. The solvent was evaporated and the mixture was dissolved in CH_2Cl_2 (50 ml) and washed with 1N HCl (25 ml). After drying over $MgSO_4$, the solvent was evaporated to give 530 mg of crude product that was refluxed in MeOH (20 ml) containing NaOMe (330 mg, 6.1 mmol) for 2 h. After evaporation of the solvent, the mixture was taken up in CH_2Cl_2 (50 ml) and washed with H_2O. After drying with $MgSO_4$, the solvent was evaporated to give **10** as a pure oil; yield 93%. ^{1}H NMR: δ 7.50 and 6.86 (ABq, 2H, *J* 7.0 Hz, ArH), 7.42 and 6.86 (ABq, 2H, *J* 7.0 Hz, ArH), 6.80 and 6.75 (s, 0.5H, ArNH), 5.48 and 5.31 (br s, 0.5H, ArNH), 3.90 and 3.85 (s, 1.5H, 6-OCH_3), 3.80 (s, 3H, 4-OCH_3), 3.41 (q, 2H, Bu-1-H), 1.65–1.50 (m, 2H, Bu-2-H), 1.45–1.25 (m, 2H, Bu-3-H), 0.92 (t, 3H, Bu-4-H). ^{13}C NMR: δ 171.3, 170.8, 167.2, 165.3 (s, triaz-C), 155.9, 153.6 (s, Ph-4-C), 132.1, 131.7 (s, Ph-1-C), 122.9, 122.1 (d, Ph-2-C), 113.9 (d, Ph-3-C), 55.4 (q, 4-OCH_3), 54.0, 53.8 (q, 6-OCH_3), 40.7, 40.5 (t, Bu-1-C), 31.6 (t, Bu-2-C), 20.1 (t, Bu-3-C), 13.8 (q, Bu-4-C). Ms (EI), *m/z* 303.171 (M^+, calcd. 303.169).

Titrations

NMR titrations were performed by taking ten samples of different host/guest ratios (prepared from stock solutions), in which the host concentration was kept constant at 5 mM.

Molecular mechanics calculations

The calculations were performed with the program QUANTA 3.2 (CHARMm)[42]. All reported conformations were minimized until the root mean square (rms) of the first derivative of the energy was less than 0.0001 kcal · mol^{-1} · Å^{-1}. A dielectric constant with ε 1.0 was used.

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[32] In the case of reference compound **10**, the selective complexation of tautomer **10a** is not effected by the tautomeric equilibrium, since the ΔG of this equilibrium is $0\ kcal \cdot mol^{-1}$. Similarly, the selective complexation of one tautomer in the case of **9** is not expected to be influenced very much by the tautomeric equilibria, although no definite conclusions can be drawn in this case.

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