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Complexes of p-t-Butylcalix[4]arene Derivatives with Neutral Molecules: Structures and Stabilities

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Complexation of p-tert-butylcalix[4]arene derivatives with a series of neutral guests in CCl_4 solution was studied. The formation of inclusion-type complexes was determined. The solution structural data obtained were compared with solid state (X-ray) data and with the results of AMBER force field calculations for several compounds. Stability constants were measured by the conventional NMR titration technique. The relationship of the nature of the guest and substitution pattern in the calix[4]arene lower rim with the complex stabilities is discussed.

INTRODUCTION

Since the pioneering works of Gutsche[1], calixarenes in general and calix[4]arenes in particular[2,3], still receive much interest. This fact can be attributed to the unique combination of their features—the relative ease of syntheses and further modifications which lead to various structures with interesting physical and chemical properties. Calixarenes also have a wide range of applications: as ion carriers[4], as analytical sensors[5], as model structures for biomimetics research[6], as catalysts[7] and as tools for studying the role of H-bonding in molecular association [8–10].

These applications are mainly based on the ability of calixarenes to form complexes with ions or neutral molecules. Complexation of nonionic guests has been observed in the solid phase, solution and gas phase. The formation of stable solid complexes was observed even before the structure of the calixarenes has been established, and this feature continues to be a topic for study by X-ray crystallographers. However, it is a challenge for experimentalists to prepare pure, solvent-free calixarenes for elementary analysis. It is reported that calix[4]arenes tightly bind chloroform, benzene, toluene, xylene, anisole, acetonitrile[11–15].

The MS-study of gas-phase complexation of neutral molecules by upper rim bridged calix[4]arenes has recently been published[16].

The complexation of neutral guests by water-soluble calixarenes is well documented and has been recently reviewed[17]. Complexation of several calix[4]arene derivatives with some neutral guests in a solution was studied by Gutsche and co-workers[18]. Many papers have been published which deal with complexation of (poly)hydroxy

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compounds and carboxylic acids by calixarenes, forming multiple hydrogen-bonded complexes[19]. However, to the best of our knowledge there is no systematic study of factors influencing the stability of the calixarenes complexes. Especially scarce is data on the calixarenes complexes with neutral molecules in apolar and semipolar media. Only a few papers deal (at least partly) with the structure-complexing ability relationship of calix[4]arenes[20–21]. During preparation of this manuscript for publication, a paper appeared that discusses the relationship of the guest C-H acidity and complexation with monomethyl ether of monodeoxycalix[4]arene[22].

In this paper, we report our first results of the study of factors influencing the stability of inclusion complexes of calix[4]arene derivatives with neutral molecules.

RESULTS AND DISCUSSION

When starting this work, we wanted to consider complex formation which is controlled by the inclusion of a neutral molecule into the calix[4]arene cavity. The chemical nature of the cavity and its geometry seem essential for calix[4]arene inclusion complex formation. In this work, we tried not to vary the chemical nature of the cavity regarding only p-tert-butylcalix[4]arenes and varying the number and nature of the lower-rim substituents.

In the preliminary search, we tested several p-tert-butylcalix[4]arene derivatives with the following types of neutral molecules: aliphatic and aromatic hydrocarbons, iodoalkanes, alcohols, ethers, ketones, nitriles and nitroalkanes. We observed the strongest complexes for the first members of the homologous series and among them for the nitro- and cyano-compounds.Finally, various compounds containing cyano or nitro groups were chosen for the study of the influence of the guest size and nature (See Figure 1).

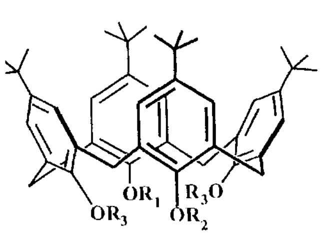
Measurements were performed in CCl_4 and in some cases in $CDCl_3$. The inspection of CPK models shows that the CCl_4 and $CDCl_3$ molecules are bulky enough so as not to occupy the p-tert-butylcalix[4]arene cavity. The preference was given to carbon tetrachloride. It has several advantages over the traditional deuterochloroform. First, stability constants of the p-tert-butylcalix[4]arenes in carbon tetrachloride are higher than in deuterochloroform (e.g. for the compound **1** with CH_3CN $K = 39\ M^{-1}$ in CCl_4 and $K = 5.6\ M^{-1}$ in $CDCl_3$) and therefore it is easier to follow the differences for the weak complexes when varying the host and guest structures in CCl_4. Second, it is more cost-efficient.

The values of measured stability constants and corresponding "Complexation Induced Shifts" (CIS) of unsubstituted, mono-, di- and tetrasubstituted p-tert-butylcalix[4]arene derivatives are summarized in Table I.

The Structure of Complexes

Despite the difference in the stability constants, the titration series of different systems reveal common features. Thus, in all disubstituted p-tert-butylcalix[4]arenes we observed downfield shift of the OH-groups, and downfield shift of the aromatic and tert-butyl protons of the moieties bearing the substituent. CIS's of the methylene bridge and lower-rim substituent protons are not significant. In the unsubstituted and monosubstituted p-tert-butylcalix[4]arenes, the upfield CIS's of the OH protons and downfield CIS's of the aromatic protons were observed. CIS's of other protons are not significant. In all cases, great upfield CIS's of the guest protons were observed.

The similarity of the systems behaviour during complexation allows one to expect the for-



	R$_1$	R$_2$	R$_3$
1	H	H	H
2	$C_2H_4OC_2H_5$	H	H
3	H	H	$C_2H_4OC_2H_5$
4	$CH_2COOC_2H_5$	$CH_2COOC_2H_5$	$CH_2COOC_2H_5$
5	C_4H_9	C_4H_9	C_4H_9
6	$CH_2CON(C_2H_5)_2$	$CH_2CON(C_2H_5)_2$	$CH_2CON(C_2H_5)_2$
7	H	H	CH_2CN
8	H	H	$CH_2C_6H_5$
9	H	H	CH_3
10	H	H	C_3H_7
11	H	H	$CH_2COOC_2H_5$
12	H	H	$C_2H_4NH_2$

FIGURE 1

mation of the similar types of complexes. Large upfield CIS of the guest, complexed by a cyclophane, is usually taken as proof of inclusion complex formation[23].

The acetonitrile complex of the compound **3** was taken for the more detailed study of the complex geometry. The CH_3 protons of acetonitrile are shifted from 2.0 ppm to −3.9 ppm (5.9 ppm upfield CIS). Compound **3** exhibits the 0.29 ppm downfield CIS of tert-butyl proton 1 (see Figure 2), 0.38 ppm downfield CIS of aromatic protons (3) and 1.1 ppm downfield CIS of OH proton (11).

1,3-lower-rim-disubstituted calix[4]arenes exist frequently in the flattened cone conformation in solution[3]. The degree of the calix[4]arene cone distortion can be estimated from the chemical shifts of the aromatic protons[24]. The approach of the peaks corresponding to aromatic protons 3 to protons 4 during complexation testifies that

TABLE I Stability constants[a] (M^{-1}) of the complexes of compounds **1–12**[b] with neutral guests in CCl_4 at 298°K

	1	**2**	**3**	**7**	**8**	**9**	**10**	**11**	**12**
$\Delta\delta^c$			0.34	0.38	0.32	0.37	0.34	0.23	0.23
CH_3CN	39	232	157	9.7	62	80	152	145	328
$ClCH_2CN$	27	109	—	8.3	49	65	94	—	—
ClC_2H_4CN	43	122	50	—	25	38	56	—	—
C_2H_3CN	14	98	42	3.1	19	27	43	31	—
C_2H_5CN	18	61	19	1.8	8.1	14	20	16	41
n-C_3H_7CN	3.5	2.9	1.4	—	0.71	1.4	2.1	1.4	3.6
i-C_3H_7CN	—	1.3	0.74	<0.5	—	—	1.1	1.0	1.7
C_6H_5CN	3.1	7.5	6.5	0.86	4.6	6.1	—	4.2	15
CH_3NO_2	52	284	129	7.7	47	76	132	110	263
$C_2H_5NO_2$	21	68	19	—	6.9	—	20	17.5	42
n-$C_3H_7NO_2$	4.7	3.9	1.5	0.44	—	1.9	—	—	2.8
$C_6H_5NO_2$	2.4	7.2	6.9	—	4.1	4.6	7.0	3.4	12
c-$C_6H_{11}NO_2$	NC[d]	—	NC	NC	—	NC	NC	—	NC

[a] Stability constants were determined as a weighted average of results obtained for several protons that were monitored for every molecule (see experimental part). Confidence intervals in all cases are less than ±10% of the stability constant.

[b] Compounds 4,5,6 do not form complexes with given guests except for compound **6** that forms complex with acetonitrile with K = 1.8 M^{-1}.

[c] The difference in chemical shifts of aromatic protons (in ppm) from the units bearing a substituent and hydroxy group for 1,3-disubstituted p-tert-butylcalix[4]arenes in uncomplexed state.

[d] NC—No complex formation observed

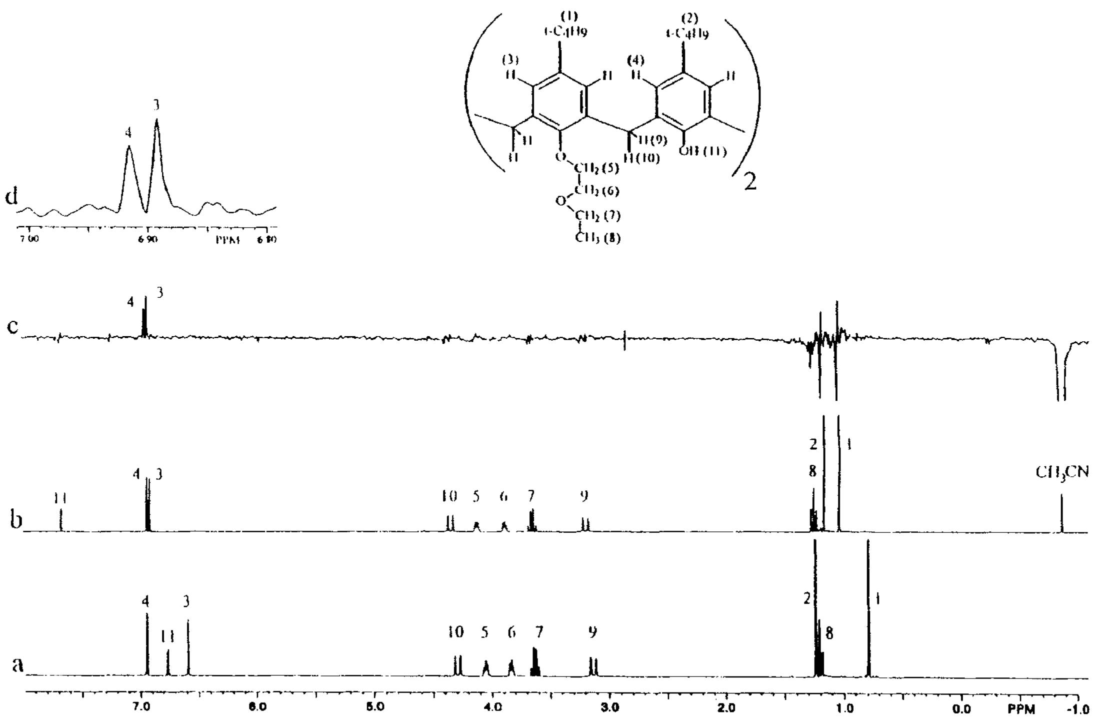


FIGURE 2 The ^{1}H NMR study of the complex formation of compound **3** with acetonitrile in CCl_4. a) The spectrum of the free compound **3**. b) The spectrum of 1:1 mixture of compound **3** and acetonitrile (80% of ligand is complexed). c) The NOEDif spectrum of the same mixture, acetonitrile protons irradiated. d) NOEDif peaks of the aromatic protons (expanded).

the flattened cone transformed into a circular one.

In order to determine the position of the acetonitrile methyl group in the complex, we performed the NOE experiment (equimolar amounts of ligand and substrate were used; complex concentration was 80%; methyl protons of acetonitrile were irradiated). The spectra **c** and **d** (Figure 2) show NOE signals corresponding to the interaction of the acetonitrile CH_3 group protons with both types of aromatic protons (3 and 4) of the calixarene. That can only be achieved when the acetonitrile methyl group is placed inside the cavity, in close proximity to the aromatic protons. NOE peak intensity (I) is proportional to the negative sixth power of the distance between interacting nuclei (r)[25]: $I \sim r^{-6}$. Similarity in NOE peaks corresponds to a negligible difference in the distances between acetonitrile and both pairs of the calixarene aromatic rings i.e. actual circular cone shape of the complex.

This also corresponds with the results of our MM3 simulations of the complex structure. The study has shown that the structure of the acetonitrile—**3** complex, with the CN-group pointing outside the cavity, is energetically preferred. If the opposite orientation of acetonitrile is taken as the starting point, the geometry minimization changes the orientation, placing the acetonitrile molecule with CN-group pointing outside. This is also in accordance with the X-ray data for the solid-state structure of the acetonitrile complex of calixarene **4**[26].

The structure of the compound **3**—acetonitrile complex is presented in Figure 3.

We have also performed NOESY experiment for the compound **2**—propionitrile complex. We

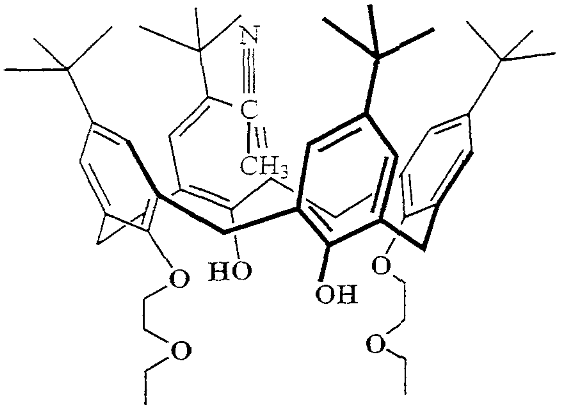


FIGURE 3 Compound 3—acetonitrile complex structure.

observed cross-peaks of the propionitrile methyl group with all aromatic protons of **2** and a cross-peak of the propionitrile methylene group with second (counting from the lower rim) methylene group of the substituent. For both methylene and methyl groups of propionitrile upfield CIS's (2.6 and 2.8 ppm, respectively) were detected. These observations mean that the propionitrile molecule is accomodated inside the cavity, with methylene group located deeper than the methyl group.

Host Structure

Data presented in Table I show the substitution in the lower rim affects the binding properties of the p-tert-butylcalix[4]arene cavity. Unsubstituted compound **1** reveals moderate binding properties toward studied guests. Mono- and 1,3-disubstituted p-tert-butylcalix[4]arenes generally form stronger complexes with corresponding guests. Tetrasubstituted compounds do not bind or form very weak complexes with the chosen guests. This is illustrated in Figure 4.

We suppose lower rim substituents of the p-tert-butylcalix[4]arenes, due to equality of the fragments directly attached to the lower rim, have similar effect on the electronic nature of the cavities. Furthermore, there is no correlation between the electron effect of the substituents (compounds **3**, **7–12**) and the complex stabilities.

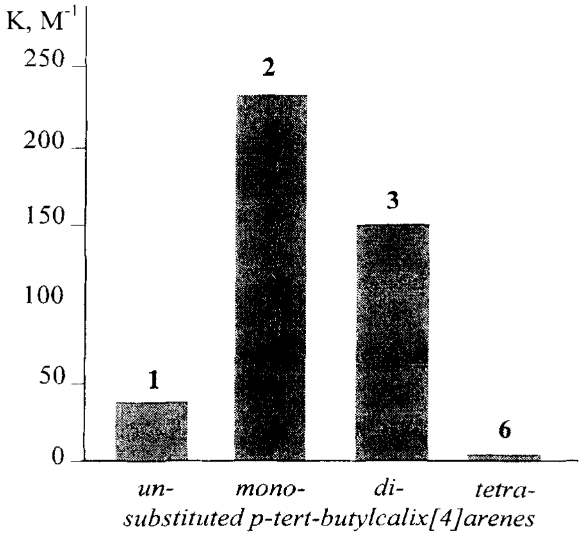


FIGURE 4 The stability constants of the acetonitrile complexes with differently substituted p-tert-butylcalix[4]arenes (compounds **1**, **2**, **3** and **6**).

Hence, the binding properties of the ligands studied seem to be controlled mainly by their geometry.

The cavity of tetrasubstituted calixarenes is flexible because of the absence of a rigidifying hydrogen bond network, which is well known and documented for the other three types of substitution pattern[3]. It has been reported[27] that tetrasubstituted compounds undergo fast interconversion between two conformations with C_{2v} symmetry, where the two distal aromatic rings are flattened and other two are in upright position. This flexibility results in the disability of tetrasubstituted p-tert-butylcalix[4]arenes to bind the studied guests. Compound **4** has been used to prove the role of cavity rigidity in the complexation of neutral guests. This compound does not form any complex with acetonitrile. It was suggested when studying the alkaline-cation complexation in different solvents that the possible binding of one molecule of acetonitrile inside the cone of **4** could preorganize the calixarene for cation complexation[28]. We have attempted to prove this "synergistic effect" in solution. We have reasoned that the cavity of **4** can be reinforced by the lower rim complexation of sodium (*in situ* addition of solid NaSCN to the deuterochloroform solution—$CDCl_3$ was chosen due to its higher solubility of inorganic salts). The gradual addition of acetonitrile to the 70% Na^+ saturated solution of compound **4** was monitored by NMR-titration experiment (figure 5).

Signals of both complexed (signals 1*,2*) and uncomplexed (signals 1,2) compound **4** appear separately in the NMR spectrum. Only the signals of the complex Na^+—**4** are shifted by the addition of acetonitrile. The stability constant for that complex has been calculated from the titration data as 31 M^{-1}.[1] A similar effect has been observed when the calixarene shape has been reinforced by covalent attachment of polyether bridges.[30]

Unsubstituted p-tert-butylcalix[4]arene in CCl_4 solution exists mainly in the cone conformation. Its aromatic moieties flip through the annulus. As a result, some time-averaged part of the molecules adopt transition shapes unfavourable for the guest inclusion. Lower rim modification suppresses such flipping and increases the time-averaged part of the molecules suitable for the inclusion complex formation. This appears to be the reason the studied guests are generally bound more strongly by partially substituted p-tert-butylcalix[4]arenes.

Introduction of substituents of a different nature to the 1,3-positions of the lower rim, leads to the formation of ligands with different binding properties. As was discussed above, the shape of 1,3-disubstituted p-tert-butylcalix[4]Farene changesfrom flattened to cir-

FIGURE 5 The ^1H NMR titration of the compound **4**—Na^+ complex by acetonitrile in $CDCl_3$. 70% of **4** is complexed by Na^+. Peaks of **4**—Na^+ complex are marked with asterisk, acetonitrile peak is marked with "A". Concentrations of agents are following: a) **4**—Na^+ complex 0.3 mM, no acetonitrile added; b) **4**—Na^+ complex 0.1 mM, acetonitrile 51 mM; c) **4**—Na^+ complex 0.1 M, acetonitrile 144 mM; d) **4**—Na^+ complex 0.3 mM, acetonitrile 298 mM.

cular cone during complexation. The total energy of complex formation is determined by the energy of interaction of the guest molecule with the cavity minus the energy necessary for the reorganization of the host shape. As the chemical nature of the cavities and the geometry of complexes is similar, we suppose the difference in energy of complex formation is determined by the difference in the shapes of the uncomplexed hosts. The distortion of calix[4]arenes reflects on their NMR spectra[25], i.e. a more flattened cone shape results in bigger separation of the aromatic protons signals. 1,3-disubstituted p-tert-butylcalix[4]arenes with less separated proton peaks generally tend to form stronger complexes (Table I).

The weakest complexes among the 1,3-disubstituted p-tert-butylcalix[4]arenes are formed by compound **7**. The positions of the aromatic protons in the NMR spectrum and the X-ray data[31] show the high distortion of the cone. Apparently, this distortion is due to the effect of the cyano group of the substituent which leads to the formation of a weaker intramolecular hydrogen bond than in the other 1,3-disubstituted p-tert-butylcalix[4]arenes. That is supported by the appearance of the OH-proton signal in the stronger field compared to other ligands.

The strongest complexes were observed for compound **12**. The NMR spectra and AMBER force field simulations show that this compound has the most circular cone shape among the 1,3-disubstituted ligands studied. This is likely the result of the substituent NH_2-group involvement in the formation of the circular array of intramolecular hydrogen bonds network. It is supported by NMR (signals of OH-protons are not visible what is contrary to all the other studied disubstituted ligands. The same is observed for NH_2-protons) and IR spectroscopy. We have compared IR spectra of the compounds **10** and **12** which differ in the terminal groups of the substituent (methyl and amino groups, respectively). The OH-group band of compound **12** (center of gravity is 3350 cm^{-1}) is shifted to lower frequencies and its intensity is higher than in the case of compound **10** (center of gravity of OH-band is 3395 cm^{-1}). This observation suggests higher stability of the intramolecular hydrogen bonds of compound **12**.

It is interesting to compare the stabilities of acetonitrile complexes formed by the 1,3-disubstituted ligands and the lower rim sodium complex of compound **4**, where the cavity is circular[28,31] and no reorganization is needed for the guest inclusion. As we were not able to perform measurements for the latter case in CCl_4, we did the titration experiments for compounds **7** and **12** with acetonitrile in $CDCl_3$. As in the CCl_4 solution, in $CDCl_3$ compound **7** is more flattened than compound **12** which is evident from NMR spectra ($\Delta\delta_{arom}$ 0.39 ppm for **7** and 0.05 ppm for **12**). Stability constants for compounds **7** (1.8 M^{-1}), **12** (21 M^{-1}) and the sodium complex of **4** (31 M^{-1}) prove that the stability of the complex is controlled by the initial geometry of the uncomplexed ligand.

It is worth mentioning that inclusion of toluene into the cavity of the p-tert-butyltetrahydroxycalix[4]arene, proven by X-ray diffraction in the solid state[13], was not observed in CCl_4 solution, characterizing the difference in solid-state and solution inclusion events.

Guest Structure

In this study nitriles and nitro compounds with the substituents of different size and nature were chosen as guests. The most stable complexes are formed with the first members of the homologous series. Stability constants gradually decrease for higher members, suggesting that a methyl group fits best in the calix[4]arene cavity. This observation corresponds very well with the supposed structure of the complexes formed with a dipolar substituent pointing out of the cavity. If these guests were complexed with the CN (or NO_2) pointing inside the cavity and the aliphatic tail pointing out of it, then there could be some difference between CH_3 and C_2H_5 substituents influence on CN or NO_2 group properties. But further elongation of the aliphatic tail would not influence the stability constant of complexes substantially. If the aliphatic tail is located in the calixarene cavity, however, then the increase of its length should prevent any complexation as the long aliphatic radical will not fit inside the cavity. The molecular dynamics study of the compound **6**—acetonitrile complex formation, in the gas phase, showed the preferential orientation for the acetonitrile with the methyl group positioned inside the cone[29].

CONCLUSIONS

The geometry of the complexes formed by p-tert-butylcalix[4]arenes with neutral molecules in CCl_4 corresponds to the inclusion type. Complexation was observed for unsubstituted, mono-, 1,3-disubstituted p-tert-butylcalix[4]arenes and for the sodium complex of compound **4**, i.e. ligands with stabilized shape. Flexible tetrasubstituted p-tert-butylcalix[4]arenes are not able to include neutral molecules or they form very weak complexes.

The complex stability is controlled by the initial ligand cone shape. The strongest complexes are formed by the ligands with the circular cone geometry. The complexation abilities of p-tert-butylcalix[4]arenes in the crystalline state and in solution are different.

EXPERIMENTAL

NMR spectra were recorded on a Varian Gemini 300 HC spectrometer. The resonance frequency for the ^1H measurements was 300.08 MHz. Spectra were obtained at 298 K in CCl_4 solutions with a capillary filled with D_2O and placed along the axis of the NMR tube, which was used for system lock and shimming. Additional shimming was done when necessary while monitoring the FID signal. Most measurements were done with scan number varying from 16 through 128 depending on the solutions concentrations. Sensitivity enhancing weighting was applied with LB = 0.2 Hz. The NOE difference experiment was performed with 6400 transients accumulated. Sensitivity enhancing weighting with LB = 0.5 was applied. The sample was used without degassing.

Concentrations of the components in the titration series were adjusted by sequential planning, in order to cover the range from 20 to 90% of substrate saturation and to have equidistant positions of experimental points on the Scatchard plot that was used along with the Fisher test for model consistence testing[33]. Additional study showed that this experimental plan is also one of the best for dispersion optimization. Binding constants and CIS values were computed with the original nonlinear regression curve-fitting program. Typically binding constants were estimated from data obtained for different protons and compared for self-consistency of the result. As a rule, calixarene protons were monitored in the presence of an excess of the guest. When possible, substrate and ligand concentrations were reversed, guest protons were monitored and the results were compared[2].

IR spectra were recorded with a Nicolet 750 FTIR spectrometer. All solutions were prepared by weighing and for concentrations of compounds less then 0.1% wt. by stepwise dilution of stock solutions. All measurements were done within 2 hours of the sample preparation.

Compounds **1**[34], **3**, **7**, **11**[31], **4**, **5**[36], **6**[37] were synthesized as described previously. Compounds **2**, **8**–**10** were synthesized analogously to the procedure described in the reference[35].

5,11,17,23-tetra-tert-butyl-26,28-bis(2-aminoethoxy)-25,27-dihydroxycalix[4]arene

A solution of 2 g (2.7 mmol) of compound **7** in 100 ml of dry THF was cooled using an ice-bath and then 60 ml (60 mmol) of BH_3 (1 M in THF) was added dropwise under nitrogen. The reaction mixture was then heated at 80° C for 8 h. After cooling, it was quenched with 50 ml of 1N HCl and stirred for 1 h. The solvent was removed under reduced pressure and the residue was mixed with 50 ml of 6 N HCl and heated to reflux for 3 h. After being cooled the acidic solution was washed with ether and then evaporated to dryness. The residue was suspended in dichloromethane and 2N NaOH was added until basic pH was reached. The organic layer was separated, dried and evaporated. The yield was 98%.

^{1}H NMR (CDCl$_3$) 1.12 and 1.25 (2s, 36H, t-Bu), 3.36 (br t, 4H, O-CH$_2$-*CH*$_2$-NH$_2$), 3.39 and 4.30 (2d, 8H, Ar-CH$_2$-Ar), 4.11 (br t, 4H, O-*CH*$_2$-CH$_2$-NH$_2$), 7.00 and 7.04 (2s, 8H, Ar-H). MS (CI) 735.2
Guest compounds of analytical grade were purchased from Aldrich and used without additional purification.
Solvents were purified by conventional methods described elsewhere[38].

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Endnotes

1. The molecular dynamics study of analogous system in gas-phase was recently reported[28].
2. The detailed description of the titration method and supplementary software is available at our address upon request.