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ORIGINAL PAPER

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The formation of *endo*-complexes between calixarenes and amines—a reinvestigation

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Abstract The formation of an *endo*-complex between *p*-allylcalix[4]arene and *t*-butylamine was described by Gutsche in 1985. However, for a comparable system, it has been shown using NOE methods that the amine does *not* reside inside the calix. Instead, an *exo*-calix complex is formed. A reevaluation suggests that the previous conclusion is an artifact due to improper NMR-data processing. DFT (RB3LYP/6–31G(d)) calculations confirm the higher stability of the *exo*-complex over its *endo*-counterpart.

Keywords DPFGSE-NOE · Nuclear Overhauser effect · Field gradient · Calixarene · Amine · *Endo*-complex · *Exo*-complex

Introduction

In 1872, Adolf von Baeyer first synthesized calixarenes by condensation of phenol derivatives and formaldehyde, [1] but it took another 70 years until the nature and structure of the *p-tert*-butylcalix[4]arene was suggested [2] and the great potential of this class of compounds was realized. The outstanding synthetic work by, among others, Gutsche, [3] Hayes and Hunter, [4] Kämmerer, [5] Böhmer, [6] and Shinkai [7] led to an enormous number of experimental [8] and theoretical [9] studies on calixarenes. Since the beginning, the main interest has been focused on the possibility of endohedral complexation of molecules in the calixarene cavity in order to mimic, e.g., protein receptors by a simple model [10]. The hydrophobic substrate pocket of calixarenes is formed by the aromatic phenol derivatives, which constitute the "walls". Thus, calixarenes may complex neutral [11] and charged [12] guests through CH–π-, [13] π–π- [14] and ion–π interactions [15]. These types of interaction contrast with those of classical cryptands, [16, 17] coronands, [18] and their metalla-analogues, [19] which almost exclusively complex metal ions or NH_4^+ [20]. Today, there is a wide range of possible tasks for calixarenes and their derivatives: ligand systems for potential catalytically interesting transition metal complexes, [21] chemosensors, [22] separation of lanthanoids and actinoids in radioactive waste, [23] selective complexation of ions, [24] the encapsulation of small compounds, [25] as platforms for dendrimers, [26] MRI-contrast agents [27] and chromatography [28]. Moreover, aesthetically pleasing molecules like the molecular equivalent of the Soccer World Cup by Soi and Hirsch [29] have been realized.

Dedicated to Professor Dr. Paul von Ragué Schleyer on the occasion of his 75th birthday.

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Materials and methods

Experimental

NMR spectra were recorded on a JEOL Alpha 500 spectrometer (11.7 T; 500 MHz). For the spectra of Figs. 3, 4 and 5, ca. 15 mg of *tert*-butylcalix[4]arene **1b** (Aldrich) was suspended in an NMR tube in CD_3CN and *tert*-butylamine was slowly added under stirring until the calixarene had completely dissolved. The clear solution was degassed and the tube was sealed. Integration of the ^1H NMR spectrum revealed a stoichiometric ratio of **1b** and *tert*-butylamine of 1:23. The NOESY spectrum (Fig. 4) was recorded in magnitude mode on an inverse probe-head with actively shielded gradient coils; 512 complex points in t_2, zero-filled to 1,024, four dummy scans, 16 scans per t_1-increment, acquisition time in t_2=0.1105 s, spectral width in f_1 and f_2=4,634 Hz, 64 t_1-increments, zero-filled to 256, relaxation delay 4.0 s, mixing time 200 ms, 90° ^1H-pulse

width 6.6 μs, sine bell window in t_1 and t_2. For the symmetrized spectrum (Fig. 5), the built-in JEOL routine was used. The individual 1D-NOE spectra (Fig. 3b–f) were recorded under the following conditions: pulse sequence DPFGSE-NOE, [30] inverse probe-head with actively shielded gradient coils, spectral width 4,554 Hz, 16,384 data points, acquisition time 3.6 s, relaxation delay 4 s, 512 scans with four dummy scans, hard 90° pulse width 6.2 μs, mixing time 600 ms, gradient duration 1 ms, gradient strength ratio 19.6:8.4:5.6:−5.6 G/cm. For the selective irradiations, an attenuated 40-ms 180° Gaussian pulse was applied.

Quantum chemical methods

All structures were fully optimized at the B3LYP/6–31G(d) density-functional theory (DFT) level [31] using the Gaussian 03 program [32]. Frequencies were computed at the same level to characterize stationary points and obtain zero-point vibrational energies (ZPEs). All frequencies are unscaled. DFT, in particular B3LYP, has been shown to provide accurate geometries and good harmonic vibrational frequencies for a broad range of molecules and ions [33]. As shown recently, the level of theory selected is well suited for NMR [34, 35] and NICS calculations [36].

Results and discussion

A recently established course on supramolecular chemistry at the Institut für Organische Chemie of the University of Erlangen–Nürnberg prompted us to set up an easy NMR experiment for students. In this experiment, the *endo*-complexation of an amine within a calixarene was to be demonstrated using homonuclear (^{1}H) Overhauser effect (NOE) methods. We chose to focus on an experiment described earlier by Gutsche, [8d] in which the reaction of various calix[4]arenes with *tert*-butylamine was thought to proceed via a proton transfer from one phenol-OH to the amine as a first step to form an ion pair. In a second step, the formation of an *endo*-complex between the ammonium ion and the calixarene-phenolate was postulated. These findings were corroborated in a follow-up paper [8e] by a 2D-NOESY experiment. The relevant reaction scheme and the relevant NOESY spectrum are reproduced from the original paper [8e] in Figs. 1 and 2.

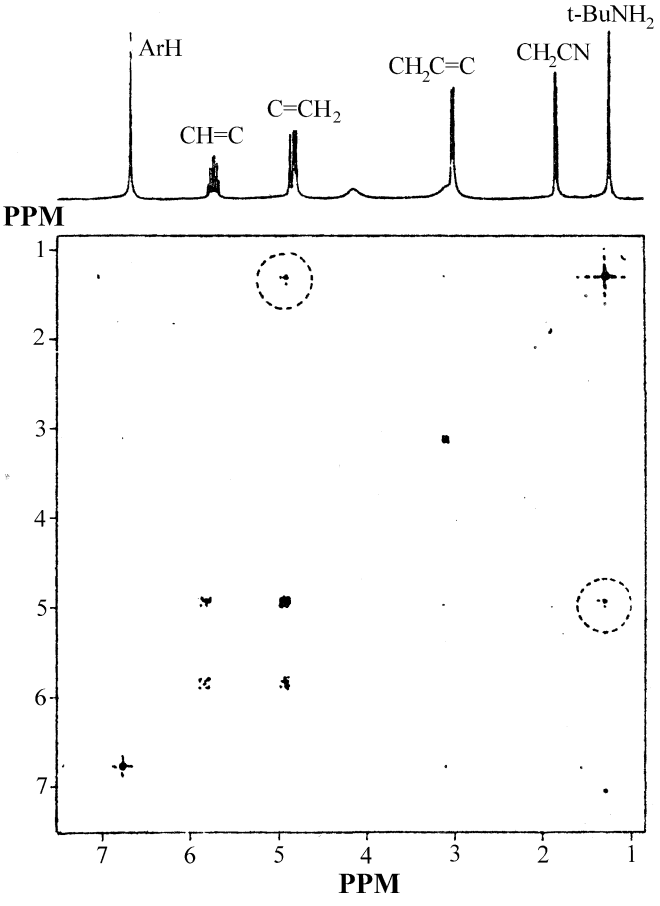
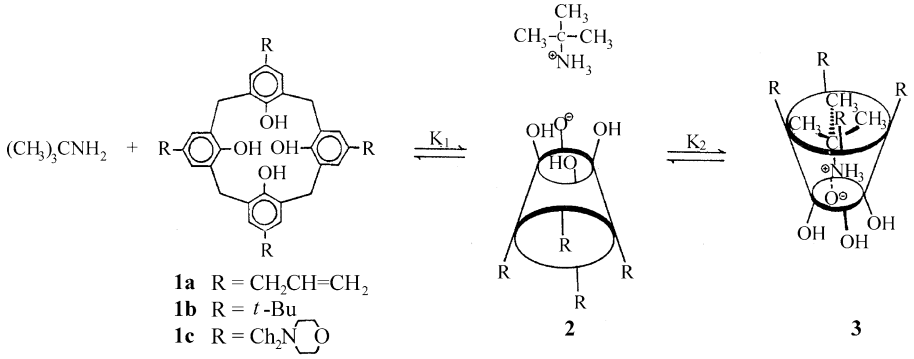


Fig. 2 Facsimile of the NOESY spectrum (300 MHz) of a 1:1 mixture of *tert*-butylamine and *p*-allylcalix[4]arene in CD_3CN at 17.8 °C. The *circled cross peaks* are claimed to be indicative of an *endo*-calix complex. Reproduced with permission from [8e]

In [8e], a pair of cross peaks in the original NOESY spectrum (Fig. 2) (circled) was claimed to indicate an *endo*-calix complex between *p*-allylcalix[4]arene and *tert*-butylamine. These cross peaks involve the protons of the amine *tert*-butyl group and the terminal CH_2-protons of the allyl group. Surprisingly, a cross peak

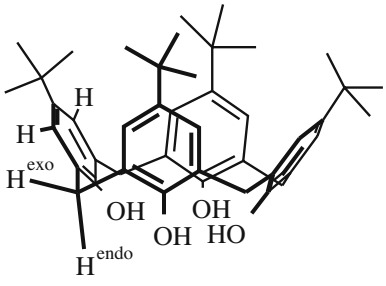
Fig. 1 Facsimile of the postulated reaction scheme of calix[4]arenes with *tert*-butylamine to form a postulated *endo*-calix complex. Reproduced with permission from [8e]



Formation of *exo*-calix and *endo*-calix complexes from amines and calix[4]arenes.

between the *tert*-butyl group and the protons at the aromatic rings of the calix is missing. In the text of [8e], the authors state (p. 4317): *Although the ^{1}H NMR data in Tables I–V are commensurate with either the exo-calix or endo-calix postulate, the NOE data provide strong evidence for the latter*. On the other hand, the authors themselves doubt this result a few lines above: *As an additional check, however, one-dimensional NOE difference spectral determinations were also made as well as a simple 2D HOMCOR NMR determination which showed no cross resonances arising from the tert-butylamine protons and the calixarene protons.*

In order to prove the presence or the absence of an *endo*-calix complex we repeated the NOE measurements of [8e] under comparable conditions. Instead of *p*-allylcalix[4] arene we used *tert*-butylcalix[4]arene **1b**.



1b

In contrast to the conditions employed by Gutsche, [8e] we chose to add *tert*-butylamine in large excess in order to shift the equilibria shown in Fig. 1 to the right hand side. A degassed sample of **1b** admixed with *tert*-butylamine in a 1:23 molar ratio (solvent: CD_3CN) was prepared and a series of one-dimensional NOE was recorded. The pulse sequence used was the DPFGSE (double pulsed field-gradient spin echo) method, [30] which has become a routine measurement in many NMR labs. In contrast to the conventional difference NOE method, DPFGSE yields NOE spectra that are essentially free from subtraction artifacts, thus enabling the detection of even very weak NOEs (down to 0.01%). Hence, spatial relationships of protons up to ca. 5.5 Å can be detected.

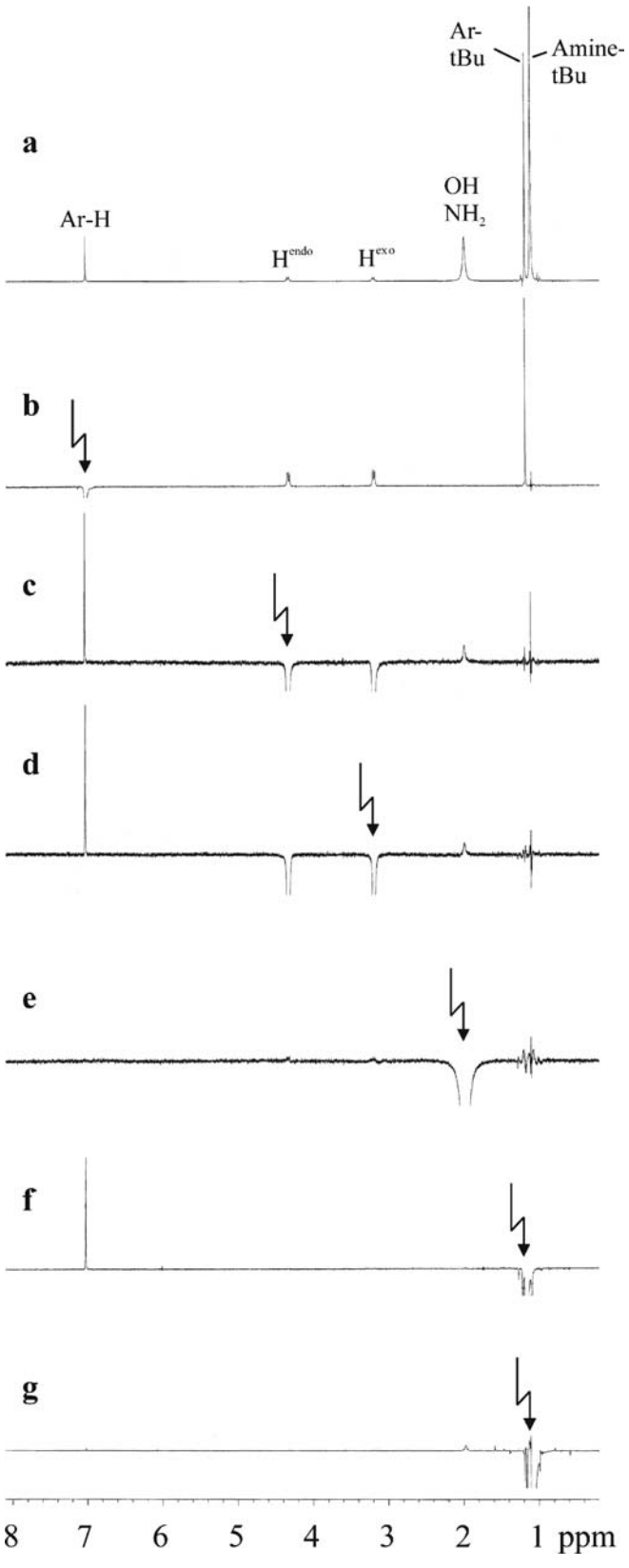
Figure 3 shows a series of DPFGSE-NOE spectra in which all individual resonances in the ^{1}H-spectrum were irradiated sequentially. Selective excitation of the calix-aryl protons (Fig. 3b) yields strong NOEs for the *endo*- and *exo*-protons of the calix CH_2-groups. While the NOE at the *exo*-proton is expected, the *endo*-proton NOE seems surprising at first. However, this NOE comes from rapid exchange of the *exo*- and *endo*-protons on the NMR time scale. This exchange has long been known for calixarenes and involves the well-established cone-partial cone-1,2-alternate-1,3-alternate exchange. A detailed study of these dynamics can be found in [37]. Thus, the observed NOE at the *endo*-CH_2-proton arises from a genuine *exo*-CH_2-proton NOE, which is subsequently transferred to the *endo*-position due to chemical exchange. In addition, Fig. 3b shows an expected strong NOE that involves the protons of the calix *tert*-butyl group. However, no or a vanishingly weak NOE is observed for the protons of the amine *tert*-butyl group. This is strong evidence against an *endo*-calix complex. Were the amine inside the calix in the way described by Gutsche, [8e] a strong NOE must be expected for the amine *tert*-butyl protons as well. It may be concluded from Fig. 3b that a proton transfer between the calixarene and the amine has taken place. However, the calixarene aryl-protons and the protons of the amine *tert*-butyl group are very remote.

Irradiating the resonance line of the *endo*-CH_2 proton (Fig. 3c) leads to the expected complimentary NOE at the calix aryl protons. In addition, an NOE to the OH protons is found; the signal at δ=2.0 ppm is the averaged resonance of the calix-OH protons, of the amine NH_2 protons, and of the residual water protons (from the solvent). Figure 3c shows an additional downward signal at the position of the *exo*-CH_2 proton. This comes from the chemical *exo–endo* exchange described above. No or vanishingly small NOEs are found in Fig. 3c for the calix- and the amine *tert*-butyl groups. The observed weak signals originate from residual subtraction artifacts.

Irradiation of the *exo*-CH_2 proton resonance (Fig. 3d) leads to a spectrum that is identical to Fig. 3c. Again, the reason is rapid *exo–endo* exchange. Irradiating the OH/NH_2-line (Fig. 3e) gives weak NOEs at the *exo*- and *endo*-CH_2 position, complimentary to Fig. 3c and e. When the calix *tert*-butyl resonance is irradiated (Fig. 3f), a strong NOE is found for the calix aryl-H resonance, in agreement with the results from Fig. 3b. Finally, irradiation of the amine *tert*-butyl resonance (Fig. 3g) leads to an NOE at the OH/NH_2-proton resonance line, an expected NOE. A very weak NOE in Fig. 3g is also observed for the calix aryl-proton line. However, this NOE does not indicate close proximity of the amine and the calix. Rather, the bandwidth of the selective 180° Gaussian pulse means that partial irradiation of the close calix *tert*-butyl resonance cannot be avoided, thus giving the expected NOE.

In summary, all individual spectra of Fig. 3 are consistent with *remote* calixarene and amine units. From the chemical behavior during the sample preparation, it is evident that a proton transfer between the calixarene-OH protons and the amine NH_2 group must have taken place: calixarene **1b** is virtually insoluble in CD_3CN. However, it dissolves upon addition of the amine. This proton transfer is well documented in the literature, and we will discuss it in more detail in the Calculational section with respect to ^{13}C-chemical shifts. On the other hand, no formation of an *endo*-calix complex is observed, in contrast to Gutsche's postulate. These findings are summarized in Scheme 1. The nature of the complex between the calixarene-phenolate and the ammonium can be an ion pair or an *exo*-calix complex. However, *the amine has no close contacts with the upper rim of the calixarene*.

A recent paper [38] strongly supports the above conclusions that an *endo*-calix complex is not formed. In this work, conductometric and spectrophotometric mea-



◀ **Fig. 3** Series of DPFGSE-NOE spectra on a 1:23 molar-ratio mixture of *tert*-butylcalix[4]arene **1b** and *tert*-butylamine in CD_3CN at +25 °C. The residual solvent signal resides *beneath* the OH/NH_2-signal under these conditions. **a** Normal ^1H NMR spectrum with assignments. **b**–**g** NOE spectra with irradiation at the positions indicated by *arrows*. For conditions, see the Methods section

surements at various concentrations led to similar conclusions of the formation of an *exo*-calix complex with Coulombic attraction between the calixarene-phenolate and the ammonium ion.

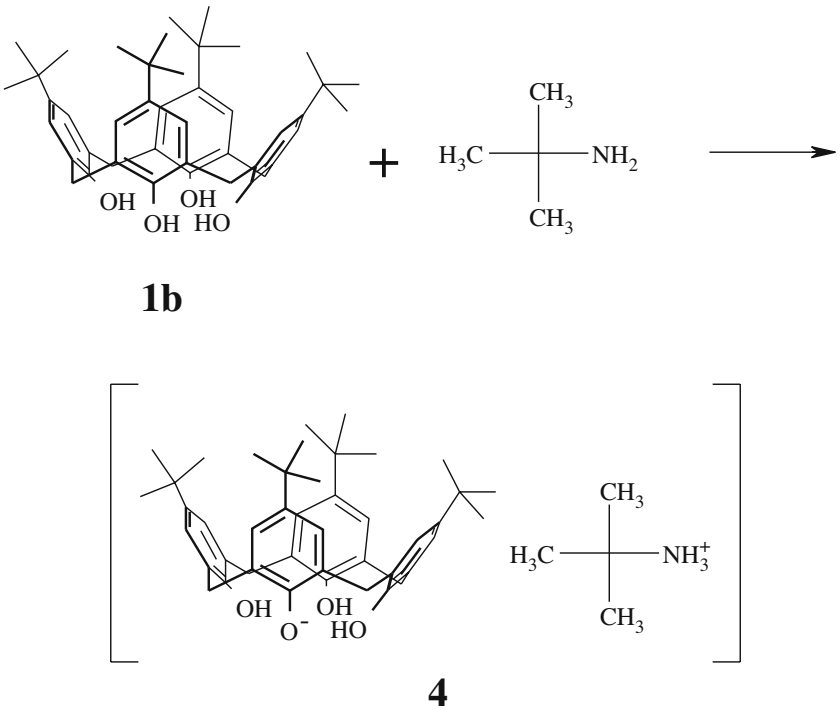
What is the origin of the postulate of an *endo*-calix complex by Gutsche which, in our view, must be wrong? This postulate is based, as outlined above, on the presence of cross peaks in the NOESY spectrum shown in Fig. 2. Virtually all NMR software-processing packages offer the possibility of symmetrizing COSY and NOESY spectra. The idea behind this procedure is to improve spectra cosmetically. COSY and NOESY spectra are principally symmetrical with respect to the diagonal; in principle data points appear with pair-wise equal intensities. In practice, however, 2D-spectra show more or less intense "t_1-ridges" that run vertically through the spectrum at the resonance-line positions. These artificial signals arise from spectrometer and temperature instabilities during a long-term (several hours) 2D-measurement. The symmetrization procedure consists of intensity comparison of the data point pairs above and below the diagonal. The lower of the two intensity numbers is then stored back at both positions in the 2D-matrix.

Gutsche et al. carried out the symmetrization procedure on their 2D-NMR data (see Experimental Section in [8e]). Authors of NMR textbooks usually warn strongly against this cosmetic "spectrum polishing" since artifacts may be introduced. A spectacular example can be found in the well-known book of Derome [39] on p. 225 (Fig. 8.32; *The symmetrisation trap; beware of falling into it*). There, a sample consisting of $CHCl_3$ and CH_2Cl_2 was used to record a COSY spectrum. Of course, no cross peaks between the two singlets observed in the proton NMR spectrum can be expected. Instead, in the non-symmetrized 2D-plot, strong t_1-ridges are observed; the spectrum looks quite awful to a non-expert. Symmetrization of these data leads to a spectrum which, from a "cosmetic" point of view, looks much better. However, spurious cross peaks are now present between the resonances of the two components that may lead to the erroneous conclusion of scalar coupling between chloroform and dichloromethane.

Analogous to [8e] we recorded a 2D-NOESY spectrum on the 1:23 molar ratio mixture of *tert*-butylcalix[4]arene **1b** and *tert*-butylamine in CD_3CN. The recording conditions and spectral parameters were comparable to those described by Gutsche. The processed but not symmetrized 2D-plot is shown in Fig. 4.

The spectrum (in magnitude mode) shows cross peaks between the calix aryl resonances and the resonances of the *exo*- and *endo*-CH_2-protons. In addition, intense exchange cross peaks are observed among the *exo*- and the *endo*-CH_2-protons. These findings are in complete agreement with the results from Fig. 3. However, the spectrum also exhibits strong t_1-noise artifacts reaching from top to

Scheme 1 Proton transfer between calixarene **1b** and tert-butylamine



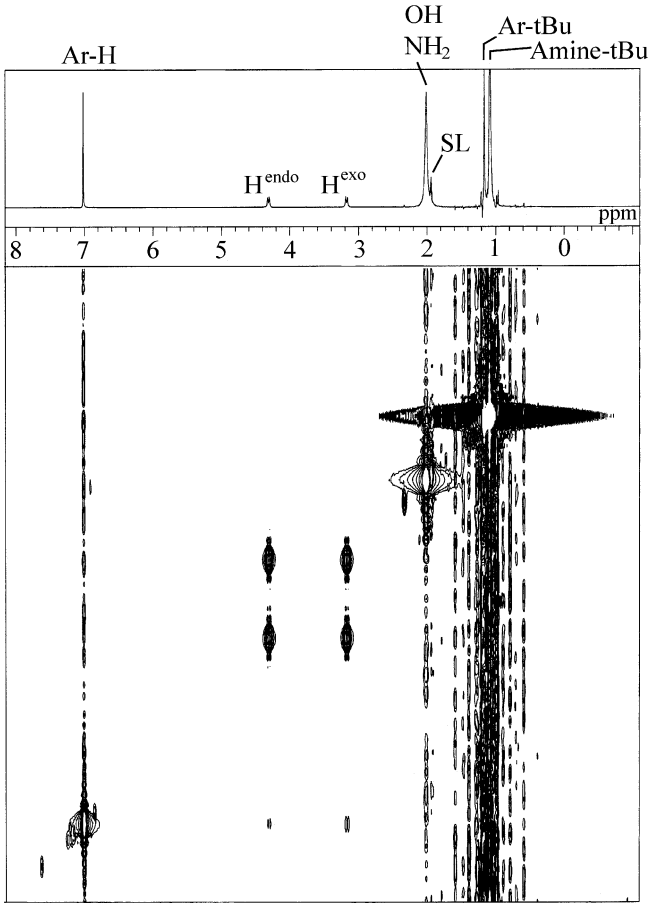


Fig. 4 2D-NOESY spectrum (magnitude mode) of a 1:23 molar-ratio mixture of *tert*-butylcalix[4]arene **1b** and *tert*-butylamine in CD_3CN at +25 °C; SL=solvent. No symmetrization processing has been applied. For spectral parameters, see the Methods section

bottom at all resonance lines. The origins of these artificial signals have been outlined above.

When the symmetrization procedure is applied to the data of Fig. 4, the spectrum shown in Fig. 5 is obtained. To the untrained observer, this spectrum looks much "better" and "cleaner". Note, however, that the genuine cross peaks between the calix aryl-proton resonances and the signals of the CH_2-group have now disappeared, thus forming a potential source of misinterpretation. The most crucial artifact comes from the circled cross peaks, of which one is magnified in Fig. 5b. Here, a genuine cross peak manifests itself between the calix aryl-proton resonance and the calix *tert*-butyl group. However, a second cross peak (highlighted with a dashed box) arises between the calix aryl-protons and the amine *tert*-butyl group. Based on this cross peak (which is analogous to the circled cross peaks in Fig. 2), one might conclude close proximity (and, hence, an *endo*-calix complex) between the groups involved. Clearly, this particular cross peak is an artifact, introduced by the weird symmetrization procedure.

From the findings of Figs. 4 and 5, we again conclude that Gutsche's postulate of an *endo*-calix complex between the calixarene and the amine must be based on erroneous and artificial cross peaks introduced by a cosmetic NMR-data processing routine.

Calculations

^{13}C NMR chemical shifts

The experimental ^{13}C NMR spectra of *tert*-butylcalix[4]arene **1b** and its deprotonated form **4** (in presence of excess *tert*-butylamine and with *tert*-butylammonium as counter-

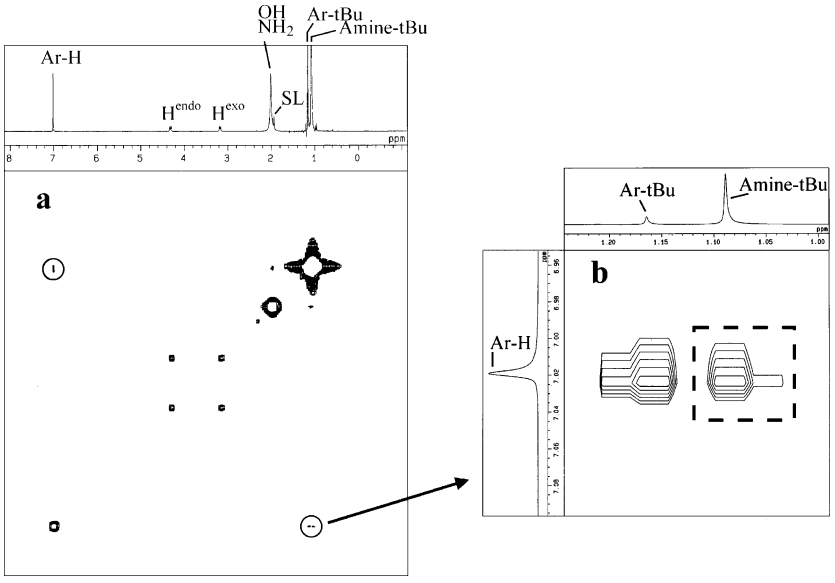
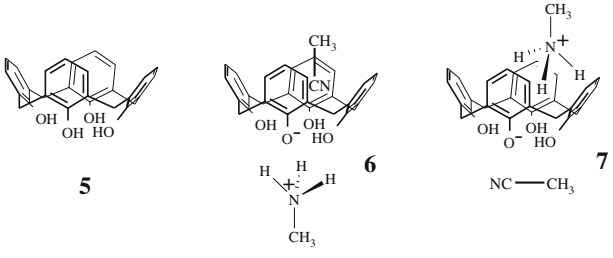


Fig. 5 2D-NOESY spectrum (magnitude mode) of a 1:23 mixture of *tert*-butylcalix[4]arene **1b** and *tert*-butylamine in CD_3CN at +25 °C; SL=solvent. The data shown in Fig. 4 were used with an additional symmetrization procedure. **a** Full data matrix. The *circled cross peaks* are the crucial ones that indicate the presence or the absence of an *endo*-calix complex. One of the *circled cross peaks* is magnified in (**b**); the *left cross peak* is genuine, whereas the *right cross peak circled with a dashed box* is artificial and has been introduced by the symmetrization step. Based on this *cross peak*, an erroneous conclusion might be drawn on the existence of an *endo*-calix complex. For spectral parameters, see the Methods section

ion) differ significantly. We take this as strong evidence for the established proton transfer from the phenol to the amine. The relevant experimental and calculated data are shown in Table 1.

The largest difference, as expected, is observed for the phenolic carbon. The experimental number is averaged between three intact phenols and one phenolate.

For the calculations, we omitted the *tert*-butyl groups on the calixarene. Instead, the unsubstituted calix[4]arene **5** and its conjugate phenolate systems **6** and **7**, were used. Figure 6 shows the calculated structures of **5**, **6** and **7**. Hence, substituent effects of the *tert*-butyl residue on the ^{13}C-chemical shifts are not included, and the shift data of the C-position para to the OH group have not been included in Table 1. Nonetheless, the calculated data of Table 1 show good agreement with the experimental chemical shifts and again confirm the proton transfer from the calixarene to the amine. Clearly, the experimental data for **4** show better agreement with those for the calculated *exo*-complex **6** than for the *endo*-complex **7**. We take this as further evidence for the existence of the *exo*-complex in CD_3CN solution.



Exo-complexation of the amine is further corroborated by DFT calculations. As a model we employed the unsubstituted calix[4]arene and methylamine. To reach the complex formed by the deprotonated calixarene anion and the methyl ammonium cation, the uncharged moieties must be united first, no matter if an inclusion complex or an

Table 1 Experimental and calculated ^{13}C-chemical shifts of calixarenes and their conjugate phenolates (with *tert*-butylammonium and methylammonium, as counterions)

C-position	**1b** (exp.)[a]	**5** (calc.)	**4** (exp.)[b]	**6** (calc.)[c]	**7** (calc.)[c]
CH_2	32.62	33.82	33.80	35.68	35.31
Ar-CH	125.93	128.77	125.20	128.33	128.45
Ar-C-CH_2	127.69	129.55	131.65	131.81	132.18
Ar-C-O	146.67	149.66	152.74	154.95	156.60

Structure **6** is the *exo*-calix complex with one CH_3CN inside the calix; structure **7** is the *endo*-calix complex with one CH_3CN outside the calix

[a]in $CDCl_3$ at +25°C

[b]in CD_3CN in presence of excess *tert*-butylamine

[c]averaged numbers of three C-OH and one C-O^- moieties

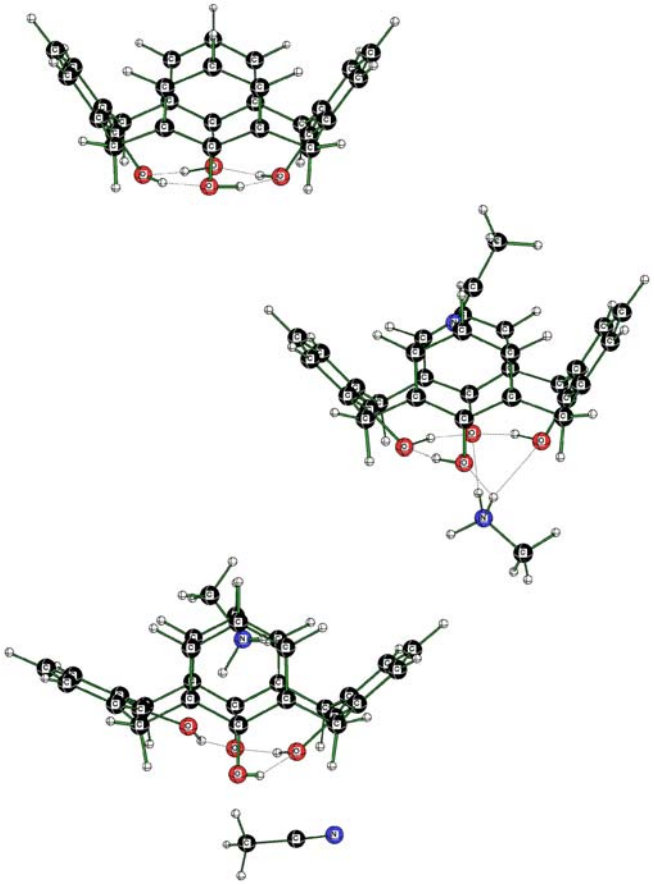


Fig. 6 Calculated (RB3LYP/6-31G(d)) structures of **5** (top), **6** (center) and **7** (bottom). H-bonds are indicated by *dashed lines*

exo-complex are formed. If an inclusion complex is formed in the first step, the NH_2–CH_3 is included in a reaction that is exothermic by only 0.3 kcal mol^{-1}. With −5.3 kcal mol^{-1} the formation of the *exo*-complex between calix[4]arene and methyl amine is clearly exothermic and favors the formation of the *exo*-complex, which is the precursor for the system observed by NMR. The next step is the proton transfer. Transferring the proton from the calix[4]arene to the included amine costs 0.4 kcal mol^{-1}. In the case of the *exo*-complexed amine, 10.1 kcal mol^{-1} are necessary. This energy is certainly overestimated. While in solution charge separation is stabilized by solvent effects, in gas-phase DFT-calculations, charge separation is unfavorable and the energy differences are therefore too high. Implicit solvent methods, such as the polarizable continuum model with an isodensity molecular surface (IPCM) offer a possibility to approximate such effects, but these methods often fail for technical reasons, as in this case, and could therefore not be used [40].

NICS-calculations

The main interaction for complexing guests inside the calixarene nest is based on the cyclically delocalized π-electrons in the benzene moieties. NICS has become one of the most used tools for investigating aromatic systems in recent years. Comparing the total NICS(1)—values inside (−11.0) and outside (−10.7) of the model calix[4]arene funnel shows that the total value inside is slightly more negative than outside. Comparing the NICS values inside and outside with the NICS(1)—total value of 2,6-dimethylphenol (−10.7) the calixarene appears to be a normal aromatic compound substituted by two methyl and one hydroxy groups. This finding is supported by the NICS values of the *endo*- and *exo*-complexes. A real perturbation of the aromatic system is the deprotonation of one hydroxyl group. While deprotonation of 2,6-dimethylphenol moves the NICS(1) value to −7.9, the NICS shift after removing a proton from a calixarene hydroxyl group is only shifted to −9.8 in mono-deprotonated calix[4]arene. We attribute the modest change in the NICS value after mono-deprotonation to the hydrogen-bond network established in the calixarenes investigated. The aromaticity of calix[4]arene is best described as four absolutely independent 2,6-dimethylphenol unities that do not communicate with each other.

Conclusions

A DPFGSE-NOE study of a 1:23 molar ratio mixture of *tert*-butylcalixarene **1b** and *tert*-butyl amine in CD_3CN has demonstrated that *no endo*-calix complex is formed. Rather, an *exo*-calix complex is present after the proton-transfer step. The contradicting results of Gutsche [8e] are almost certainly based on the misinterpretation of a 2D-NOESY spectrum where artificial cross peaks were introduced by the cosmetic symmetrization procedure. This strongly supports all warnings never to apply symmetrization to 2D-NMR data. Other erroneous conclusions that may have been drawn with respect to *endo*-calix complexes and related by other authors should be investigated.

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