The conformational behaviour of thiacalix[4]arenes: the pinched cone–pinched cone transition †

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This work is focused on the dynamics and thermodynamics of the pinched cone ↔ pinched cone interconversion of calix[4]arenes. The behaviour of methylene bridged non-substituted tetraalkoxycalix[4]arene and its tetraalkoxythiacalix[4]arene analogue is compared. Energetic and structural changes during this interconversion have been closely studied by HF and DFT quantum chemistry methods in combination with temperature-dependent ^{1}H NMR spectroscopy. The most important stationary points—minima and transition states—on the potential energy surface have been identified and their symmetry and other structural properties have been determined.

Introduction

Artificial molecules possessing an ability to selectively interact with defined ions or neutral molecules are of great importance in supramolecular chemistry, where they can find many applications in the construction of host-guest type receptors. Cyclic phenolic oligomers—calix[n]arenes[1,2]—represent very attractive building blocks for supramolecular systems due to their unique concave molecular architecture and the adjustable size of the inner cavity. The combination of suitable size, conformation, preorganisation of molecular shape, rigidity, and appropriate non-covalent interactions enables the design of very sensitive and specific sensors.

Especially, the chemistry of calix[4]arene **I** (Scheme 1) has

Fig. 1 Basic conformations of calix[4]arene derivatives.

behaviour and hence, with different potential applications as a molecular scaffold and/or useful building blocks in supramolecular chemistry.

Recently described thiacalix[4]arene[3] represents a new member of the calix[n]arene family characterized by the presence of sulfur atoms instead of methylene groups. This makes thiacalix[4]arenes **I** and **II** (Scheme 1) very interesting molecules with many novel features if compared with the chemistry of "normal" calixarenes. Many reactions, essentially unknown in the chemistry of calix[4]arenes, including the transformation of sulfur atoms (oxidation to appropriate tetrasulfoxide[4] or tetrasulfone[5,6] derivatives, regio- and stereoselective oxidation[7]) or the reactions of the aromatic skeleton (formation of lactone derivatives[8]) have been described. As we reported recently, simple tetraalkylated products[9] possess interesting conformational behaviour[10] that differs to a high degree from that of "normal" calix[4]arene derivatives. In this paper we report another example of the different conformational behaviour of thiacalix[4]arene derivatives. It is known[1b] that the C_{4v} symmetry observed usually in the ^{1}H NMR spectra of the *cone* conformation of calixarenes is in fact the time-averaged signal of the two conformations possessing lower C_{2v} symmetry. It was shown that the structure having C_{4v} symmetry represents rather the transition state of the pinched cone/pinched cone interconversion while both C_{2v} conformers can be found as minima on the potential energy hypersurface[11–14] (Fig. 2).

I	R = H	X = *t*-Bu	Y = S
II	R = H	X = H	Y = S
III	R = CH₃	X = H	Y = S
IV	R = C₂H₅	X = H	Y = S
V	R = *n*-C₃H₇	X = H	Y = S
VI	R = C₂H₅	X = H	Y = CH₂
VII	R = *n*-C₃H₇	X = H	Y = CH₂

Scheme 1 Thiacalixarenes.

achieved rapid development during the last decade. It is well documented that the introduction of bulky substituents to the lower rim (phenolic hydroxyls) of calix[4]arene derivatives can lead to the immobilization of conformational movement and hence to the formation of four basic conformations, which are denoted *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* (Fig. 1). Any of these conformations represents a special three-dimensional arrangement with different complexation
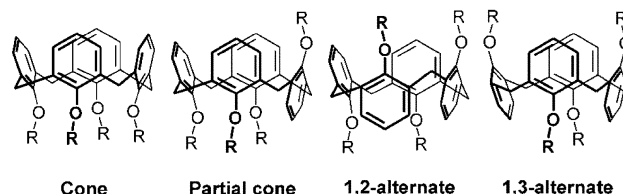
† Dedicated to Professor Jaroslav Jonas on the occasion of his 65th birthday.
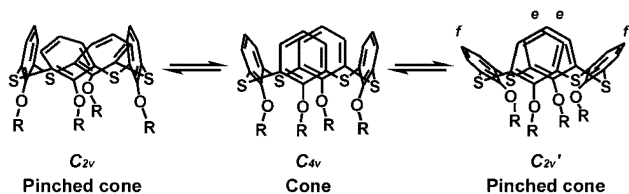
**Fig. 2** Graphic representation of pinched cone/pinched cone interconversion.

Several authors have studied the above-mentioned equilibrium in normal calix[4]arene series using dynamic ^{1}H NMR techniques or theoretical methods.[7,11–14] Unfortunately, the coalescence phenomenon of tetraalkylated calix[4]arene derivatives, bearing simple alkyl substituents, was not observed for up to the lowest accessible temperatures (170–180 K), thus indicating the very low energetic barrier of this transition. The introduction of four sulfur atoms into a calixarene skeleton leads surprisingly to a dramatic change in conformational behaviour. As we found out, simple cone conformers of thiacalix[4]arene **III**–**V** (R = Me, Et, Pr) surprisingly demonstrate line broadening of their ^{1}H NMR spectra at room temperature, which was ascribed to the pinched cone/pinched cone interconversion. Obviously, this reflects the surprisingly high difference between the energy barriers in the thiacalixarene series compared with these of "normal" ones **VI**, **VII**. To gain a better insight into this unexpected conformational behaviour of thiacalix[4]arene derivatives we have carried out this computational study and we have tried to compare our theoretical results with the data obtained by temperature dependent ^{1}H NMR investigations.

Methods

Theory

Conformational searches were performed on several levels of quantum mechanics to describe the changes on energy and geometry during the pinched cone/pinched cone interconversions. The results of detailed quantum mechanics and NMR studies of the tetraalkoxythiacalix[4]arene system have been compared with the properties of a normal calixarene skeleton. Tetraethoxythiacalix[4]arene **IV** and tetraethoxycalix[4]arene **VI** have been chosen as model systems for all presented calculations.

Automated algorithms for conformational driving on closed cyclic systems are generally inaccessible. Therefore "step by step" driving changes and constraints on selected coordinates were used for the description of molecular transition between the important areas on the potential energy surface (PES). We have used two different methodologies. (a) The increasing or decreasing of distance d between the carbon atoms on the upper rim (in *para* position to ethoxy group) of two opposite aromatic moieties (Scheme 2/A). This approach assumes the
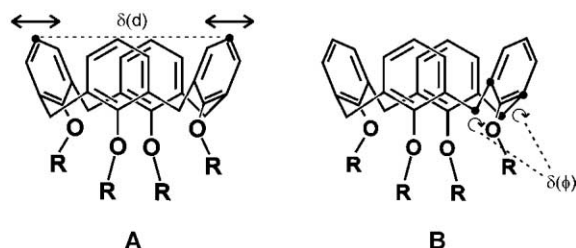
Scheme 2 The methodology for the description of pinched cone ↔ pinched cone interconversion. (A) constrained driving of the distance d between two opposite carbon atoms on the upper rim of the calixarene skeleton; (B) simultaneous driving of torsion angles ϕ connecting each aromatic unit to the rest of the tetramer.

symmetrical conformational transition pinched cone (C_{2v}) → cone (C_{4v}) → pinched cone (C_{2v}'), where the minima are represented by the pinched cone structures and the transition state is represented by the C_4 symmetrical cone structure. b) The constrained rotation of one aromatic moiety through the horizontal plane of a calixarene skeleton. The movement is enabled by the change of torsion angle ϕ between the rotated aromatic moiety and both the neighbouring aromatic moieties (Scheme 2/B). In this case, the symmetry is decreased or completely unrestrained. The remaining parts of the calixarene skeleton are fully optimised (apart from the requested symmetry) in both the approaches. All these assumptions are in agreement with previously published experimental and theoretical data.[13,14]

The input geometry for pinched cone structures (minimum) was prepared in correspondence with the results of crystallographic analysis.[9] Saddle points were generated by theoretical approaches. Several theoretical methods were tested in our studies. Molecular mechanics force fields, in general, do not include the right parameters for Ar–S– or –S–Ar–S– systems. To the best of our knowledge, there is only one paper published on the investigation of properties and conformational behaviour of Ar–S–C fragment.[15] Semiempirical quantum chemistry methods did not provide correct results in the description of transition states. Therefore, in the first approximation, a detailed conformational search was performed on the HF/STO-3G *ab initio* quantum mechanics level. The obtained data were refined on the HF/6-31G** *ab initio* level. The accuracy of selected stationary points (transition states and the global minimum) was tested on the B3LYP/6-31G** level. The availability of MP2 data is problematic due to the large computational requirements (studied systems included about 70 atoms). All stationary points on the PES were confirmed by a vibration analysis on all the used levels of theory. All theoretical data were obtained by the GAUSSIAN v94, Gaussian Inc., UK quantum chemical program.

NMR experiments

Conformational behaviour of the cone conformer was studied on tetraethoxythiacalix[4]arene **IV**, tetrapropoxythiacalix[4]-arene **V** and the "normal" analogue tetrapropoxycalix[4]arene **VII**. Tetrapropoxy derivatives **V** and **VII** were studied more extensively than the tetraethoxy analogues because the former species do not experience conformational transition towards the other basic calix[4]arene conformations (partial cone, 1,3-alternate, 1,2-alternate) at ambient temperature.[10] Therefore, the spectra of the tetrapropoxy systems are easier to quantify while the conformational behaviour is essentially the same (see Discussion). Five different solvents were used in order to assess the effect of solvent on the size of the interconversion barrier. The solvents used were tetrachloroethane-d$_2$ (99.8% d, Eurorad, Germany), chloroform-d (99.8% d, Fluka, Switzerland), dichloromethane-d$_2$ (99.8% d, VEB Berlin-Chemie, Germany), dimethyl formamide-d$_7$ (99.8% d, Central Institute for Isotope and Radiation Res. Leipzig, Germany) and chlorobenzene-d$_5$ (98.5% d, Aldrich, Germany).

The dynamics of pinched cone/pinched cone interconversion was studied by means of temperature dependent NMR spectroscopy. The detailed study was carried out on a samples of tetrapropoxy derivative of thiacalix[4]arene **V** dissolved in tetrachloroethane-d$_2$ in a concentration of about 30 mmol.dm^{-3}. The sample was degassed by the three times freeze–pump–thaw procedure and sealed in a 5 mm NMR tube. Experiments were carried out on a Bruker Avance 500 spectrometer (11.75 T).

The temperature dependent rates of chemical exchange were measured by two methods: by 2D EXSY (NOESY) in the region of the slow chemical exchange (temperature 226.5, 237.5, 247.4 K), and by a dynamic NMR (simple 1D spectra

followed by lineshape analysis) in the intermediate chemical exchange region (close to coalescence temperature).

The EXSY was run in a semiselective manner—the excited region covered 4 ppm including the aromatic and –O–CH$_2$– region. The semiselective excitation was accomplished by the DPFGSE segment with two soft gaussian cascade π pulses of 1 ms duration. Using this method, it is possible to achieve better digital resolution in the indirect domain in a shorter measurement time. Typical parameters of the EXSY spectra were π/2 pulse length 10 μs, 2k data points in the f_2 and 128 data points in the f_1 dimension zero-filled to 1k. Exchange rates were determined by fitting the initial cross-peak volume build up. Spectra were acquired for five values of mixing time (0.02–0.5, 0.01–0.2, 0.005–0.03 s, for temperature 226.5, 237.5, 247.4 K, respectively). Relaxation delay was always set longer than 5 × T_1. ^{1}H non-selective longitudinal relaxation times T_1 were established by means of the fast inversion recovery sequence.

Seventeen 1D ^{1}H NMR spectra were acquired in the temperature range of 216–377 K. Five of the spectra in the intermediate chemical exchange regime were employed to determine the exchange rate constant. They were carefully processed without exponential multiplication of the time domain data and subjected to a lineshape analysis using the gNMR v4.1 program (Cherwell Scientific, Oxford, UK). The determined exchange rate constants k (three constants from EXSY, five constants from the lineshape analysis) were used in the subsequent calculation of thermodynamic parameters using the Eyring eqn. (1) (activation free energy ΔG_0^*, activation enthalpy ΔH_0^*, activation entropy ΔS_0^*; k_B, h and R are the Boltzmann, Planck and gas constants, respectively, and T is absolute temperature).

$$k = (k_B T/h) \exp(-\Delta G_0^*/RT) \qquad (1)$$

$$\Delta G_0^* = \Delta H_0^* - T\Delta S_0^* \qquad (2)$$

In the fitting routine, the constants from the lineshape analysis were weighted according to the size of the chemical exchange contribution to the line width, i.e. the weight of the data point in temperature dependence decreases fast with distance from coalescence. In addition, weights constructed in this way were scaled down by a RMSD of the lineshape fit. The data from EXSY were weighted equally to the best weighted value from the lineshape analysis because their error is estimated to about 5%.

The rest of the measurements in the other solvents and/or with other calix[4]arene derivatives **IV**, **VI**, **VII** (see Table 5) consisted of the acquisition of about 13 ^{1}H spectra in the large temperature region in order to determine coalescence temperature T_c. The experiments were carried at 500 MHz (Bruker Avance 500), except for a sample of **VII** in dichloromethane-d$_2$, which was measured at 300 MHz (Varian Mercury 300). The coalescence temperature was used for calculation of the free activation energy ΔG_0^* (eqn. (3), Δv being the chemical shift difference of the exchanging types in the absence of chemical exchange).

$$\Delta G_0^* = RT_c[22.96 + \ln(T_c/\Delta v)] \qquad (3)$$

Results and discussion

In order to get a closer insight into pinched cone ↔ pinched cone interconversion, we decided to use non-substituted tetraalkoxythiacalix[4]arene and normal non-substituted tetraalkoxy[4]calixarene for a comprehensive investigation and comparison of their dynamic and thermodynamic behaviour.

The first important question is connected with the symmetry of the pinched cone minimum and the cone transition state. There are two possible symmetrical solutions for each stationary point: C_2 or C_{2v} symmetry for the stable conformer and C_4

or C_{4v} symmetry for the transition state. These symmetrical differences result from the rotating of alkoxy groups attached to the lower rim of the calixarene skeleton. The fast changes between these conformations are not observable in NMR spectra, but simple speculation about the structure of the transition state as well as the global minimum indicates the likelihood of their existence. Schematic representation of possible structural types is shown in Figs. 3 and 4. However, asymmetrical structures may also be considered.
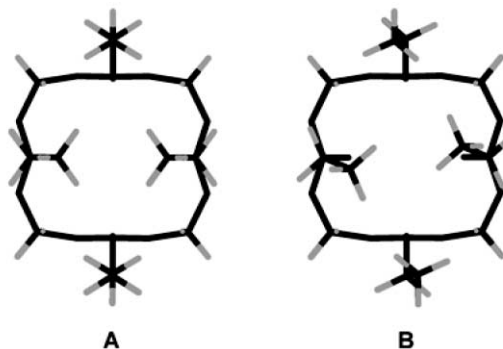
Fig. 3 *Pinched cone* conformation—mutual orientation of ethoxy groups attached to the lower rim of the calixarene skeleton: (A) geometry with C_{2v} symmetry; (B) geometry with C_2 symmetry.

A detailed conformational search using methodology A (see the "Methods" section) was performed for both systems. All stationary structures were optimised with relevant constrained symmetries. The most stable conformers (energy minima) were also fully optimised without symmetry constraints.
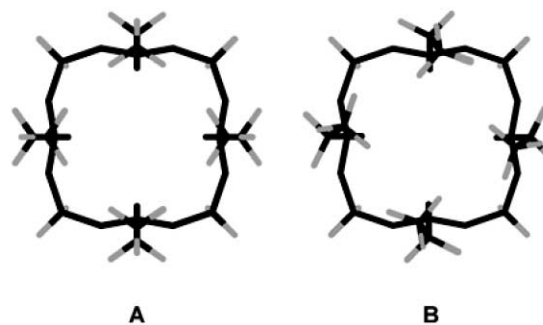
Fig. 4 *Cone* conformation—mutual orientation of ethoxy groups attached to the lower rim of the calixarene skeleton: (A) geometry with C_{4v} symmetry; B) geometry with C_4 symmetry.

Calculations on tetraethoxythiacalix[4]arene IV

The conformational search for tetraethoxythiacalix[4]arene was started with a pinched cone structure, which was obtained from X-ray analysis and then energy minimized on the HF/STO-3G level. Important geometrical properties of all calculated stationary points are summarized in Table 1, and energy data are summarized in Table 2.

The conformational search shows some structural dissimilarities between the global minimum of tetraethoxycalix[4]-arene and that of tetraethoxythiacalix[4]arene. Most notably, the most stable conformation has only C_s symmetry. Comparative calculations starting with constrained C_2 and C_{2v} geometries resulted in a system with slightly higher energy and C_{2v} symmetry. The difference between C_s and C_{2v} geometries is caused by the reorientation of one ethoxy group inwards the lower part of the calixarene cavity. The associated effect is the asymmetrical slope of "opened" opposite aromatic moieties (Fig. 5). The torsion angles ϕ_a are different, while the remaining couple of aromatic moieties is oriented symmetrically. All ethoxy groups are oriented exactly upright to the plane of corresponding aromatic moiety, equally as in the C_{2v} geometry.

Table 1 Tetraethoxythiacalix[4]arene **IV**—The selected geometrical parameters of calculated stationary points in the "cone" part of the PES

Method	Symmetry	d_a/Å	d_b/Å	d_c/Å	ϕ_a/°	ϕ_b/°
HF/STO-3G	C_s	10.0	4.72	—	139.9 / 121.4	82.8
	C_{2v}	9.88	4.78	—	128.3	83.0
	C_4	7.73	$d_a = d_b$	2.40	106.9	$\phi_a = \phi_b$
	C_{4v}	7.73	$d_a = d_b$	2.31	106.9	$\phi_a = \phi_b$
HF/6-31G**	C_s	9.85	5.31	—	131.8 / 125.5	87.0
	C_{2v}	9.84	5.31	—	128.4	87.0
	C_4	8.00	$d_a = d_b$	2.51	109.8	$\phi_a = \phi_b$
	C_{4v}	7.88	$d_a = d_b$	2.27	108.0	$\phi_a = \phi_b$
B3LYP/6-31G**	C_s	10.0	4.97	—	140.7 / 122.7	82.3
	C_{2v}	10.05	4.91	—	130.0	83.8
	C_4	7.97	$d_a = d_b$	2.37	108.8	$\phi_a = \phi_b$
	C_{4v}	7.87	$d_a = d_b$	2.17	107.3	$\phi_a = \phi_b$

Table 2 Tetraethoxythiacalix[4]arene **IV**—The energy differences between different geometries of cone-like structures

Method	ΔE/kcal mol^{-1}		
	$C_{2v} \leftrightarrow C_4$ (ΔE_1)	$C_4 \leftrightarrow C_{4v}$ (ΔE_2)	$C_s \leftrightarrow C_{2v}$ (ΔE_3)
HF/STO-3G	6.52	0.15	0.12
HF/6-31G**	6.34	1.21	0.001
B3LYP/6-31G**	7.13	0.65	~0
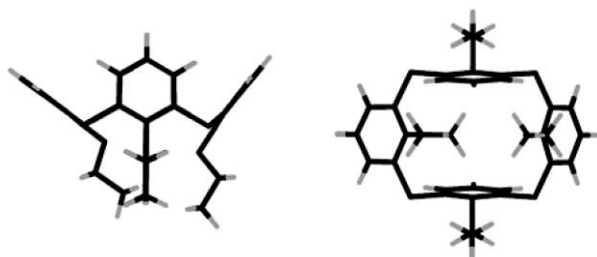
Fig. 5 Tetraethoxythiacalix[4]arene **IV**—structure of the global minimum with C_s symmetry.
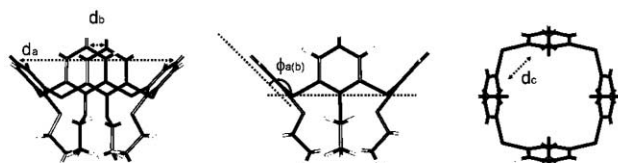
**Scheme 3** Denotation of selected structural parameters of calixarene cavity.

Distances d_a (rings f) and d_b (rings e, see Fig. 2 and Scheme 3) are similar for both the C_s and C_{2v} geometries.

The above facts lead to an idea that the system may interconvert by the simultaneous motion of opened opposite aromatic moieties between two C_s minima *via* the C_{2v} saddle point. This effect is characteristic only for studied thiacalix[4]arenes. Nevertheless, the height of the energy barrier of this transition is very low. The energy difference between the C_s and C_{2v} structures calculated on the HF/STO-3G level is approximately 0.12 kcal mol^{-1}, while the HF/6-31G** and the B3LYP/6-31G** give, in fact, no energy difference between the most stable C_s conformer and C_{2v} transition state (see Table 2). Vibration analysis confirmed the C_s conformer as one of the minima. The C_{2v} structure has been identified as the true transition state, probably between two C_s minima. The found imaginary frequency corresponds to the transition from C_{2v} to C_s geometry.

The situation is rather different for the transition state structures. The dissimilarity between the C_4 and C_{4v} structures is remarkable and comparison of these geometries produces some interesting results. The initial studies have again been performed on the HF/STO-3G level. The slope of the cavity, considered with respect to the horizontal plane of the calixarene skeleton, is similar for both the C_{4v} and C_4 geometries. The most important difference between these structures is connected with the orientation of the ethoxy groups. The mutual distance between neighbouring hydrogens d_c (see Scheme 3) increases from 2.31 Å (C_{4v}) to 2.40 Å (C_4). This change minimizes repulsions between hydrogen atoms of terminal methyl groups. The C_{4v} structure can also be a transition state localized between two possible C_4 structures. The energy barrier of the transition from C_4 to C_{4v} is about 0.15 kcal mol^{-1}. Calculation with the HF/6-31G** provides the highest value of this barrier (1.21 kcal mol^{-1}), while the B3LYP/6-31G** approach gives only a half value (0.65 kcal mol^{-1}). The distance d_c increases from 2.27 Å to 2.51 for HF/6-31G** level and from 2.17 Å to 2.37 Å for B3LYP/6-31G** level, respectively.

The C_4 structure is a true transition state with one imaginary frequency and the C_{4v} structure is the second-order saddle point localized between two possible C_4 transition states. The energy barrier of pinched cone C_s/pinched cone C_s transition is 7.13 kcal mol^{-1} (B3LYP/6-31G**). Both HF approaches provide lower values (Table 2). The schematic reaction coordinate of pinched cone/cone interconversion based on theoretical data is shown in Fig. 6.
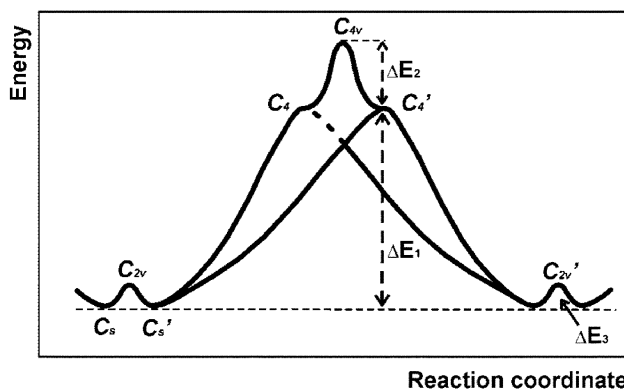
Fig. 6 Tetraethoxythiacalix[4]arene **IV**—energy changes during the pinched cone/pinched cone interconversion.

Table 3 Tetraethoxycalix[4]arene **VI**—selected geometrical parameters of calculated stationary points in the "cone" part of the PES

Method	Symmetry	d_a/Å	d_b/Å	d_c/Å	ϕ_a/°	ϕ_b/°
	C_{2v}	9.34	5.65	—	125.0	89.5
HF/STO-3G	C_4	7.80	$d_a = d_b$	2.37	109.3	$\phi_a = \phi_b$
	C_{4v}	7.80	$d_a = d_b$	2.22	109.3	$\phi_a = \phi_b$
	C_{2v}	9.35	5.61	—	125.9	89.6
HF/6-31G**	C_4	8.00	$d_a = d_b$	2.45	109.9	$\phi_a = \phi_b$
	C_{4v}	7.89	$d_a = d_b$	2.24	108.0	$\phi_a = \phi_b$
	C_{2v}	9.37	5.64	—	125.5	89.6
B3LYP/6-31G**	C_4	7.97	$d_a = d_b$	2.35	108.9	$\phi_a = \phi_b$
	C_{4v}	7.87	$d_a = d_b$	2.15	107.3	$\phi_a = \phi_b$

Calculations on tetraethoxycalix[4]arene VI

Important geometrical properties of all calculated stationary points of tetraethoxycalix[4]arene are summarized in Table 3, and energy data are summarized in Table 4.

The initial structural and thermodynamic data for tetraethoxycalix[4]arene were obtained on the HF/STO-3G quantum mechanics level. The detailed inspection shows that the molecular geometry of tetraethoxycalix[4]arene in its global minimum has the C_{2v} symmetry. Comparative studies starting from C_2 and asymmetrical structures also produced the C_{2v} minimum. In this case, all ethoxy groups are oriented exactly upright to the plane of corresponding aromatic moiety. The distances between opposite carbon atoms on the upper rim of the skeleton d_a and d_b (see Scheme 3) are 9.34 and 5.65 Å, respectively. The torsion angles ϕ_a and ϕ_b (see Scheme 3), formed by intersection of the horizontal plane of the calixarene ring and planes defined by aromatic moieties are 125.0 and 89.5°, respectively.

The optimization on the HF/6-31G** and B3LYP/6-31G** levels confirmed the C_{2v} symmetry of the global minimum. Geometric parameters obtained by these methods are comparable with results calculated with the HF/STO-3G (Table 3).

The initial studies on C_4/C_{4v} transition states were performed on the HF/STO-3G level. Results for C_4/C_{4v} transition states are identical with the results obtained for the sulfur calixarene system. Geometry with C_{4v} symmetry has been identified as a transition state localized between two possible C_4 structures. Corresponding stabilization energy (energy barrier of $C_4 \leftrightarrow C_{4v} \leftrightarrow C_4'$ transition), calculated on the HF/STO-3G level, is about 0.4 kcal mol^{-1}. The stabilization is again accompanied by the increasing of distances between hydrogens of terminal methyl groups on the lower rim of the calix[4]arene skeleton. The mutual distance between neighbouring hydrogens d_c (see Scheme 3) increases from 2.22 Å (C_{4v}) to 2.37 Å (C_4). Calculation with the 6-31G** basis set gives the energy difference of 0.96 kcal mol^{-1}. The distance d_c increases from 2.24 Å for C_{4v} to 2.45 for C_4 systems. The value of the stabilization energy provided by the B3LYP/6-31G** method is 0.59 kcal mol^{-1}. The mutual distance between neighbouring hydrogens increases from 2.15 to 2.35 Å. Remaining structural parameters are similar for all three methods.

The frequency calculations were performed for all obtained stationary point geometries. The absence of imaginary frequencies confirmed the C_{2v} structure as the global minimum on PES. The C_4 structure is a true transition state with one imaginary frequency, and the C_{4v} structure is the second-order saddle point localized between two possible C_4 transition states.

The values of activation energy of the pinched cone C_{2v}/pinched cone C_{2v}' transition calculated by different methods are collected in Table 4. The HF/6-31G** level provides the highest value of the energy barrier (6.48 kcal mol^{-1}), while the calculation with the B3LYP/6-31G** gives 5.76 kcal mol^{-1}. In general, calculated stabilization energies are lower than these of tetraethoxythiacalix[4]arenes (compare Tables 2 and 4). The schematic reaction coordinate of pinched cone/pinched cone interconversion obtained by quantum mechanics calculations is shown in Fig. 7.

Table 4 Tetraethoxycalix[4]arene **VI**—the energy differences between different geometries of cone-like structures

Method	ΔE/kcal mol^{-1}	
	$C_{2v} \leftrightarrow C_4$ (ΔE_1)	$C_4 \leftrightarrow C_{4v}$ (ΔE_2)
HF/STO-3G	3.88	0.40
HF/6-31G**	6.48	0.96
B3LYP/6-31G**	5.76	0.59
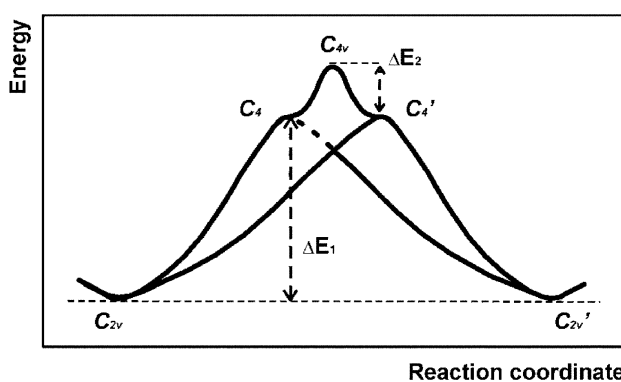
Fig. 7 Tetraethoxycalix[4]arene **VI**—energy changes during the pinched cone/pinched cone interconversion.

NMR investigation of tetrapropoxythiacalix[4]arene V

A detailed ^{1}H NMR temperature dependence study has been performed for tetrapropoxythiacalix[4]arene **V** dissolved in tetrachloroethane-d$_2$. Sample ^{1}H spectra are shown in Fig. 8. The coalescence temperature is about 313 K. Signal assignment of the rings *e*, *f* is based on the concept of shielding of the parallel rings *e* by the declined rings *f*. The situation is opposite for the alkoxy residues—the *f* ones approach the calixarene cavity causing their increased shielding.
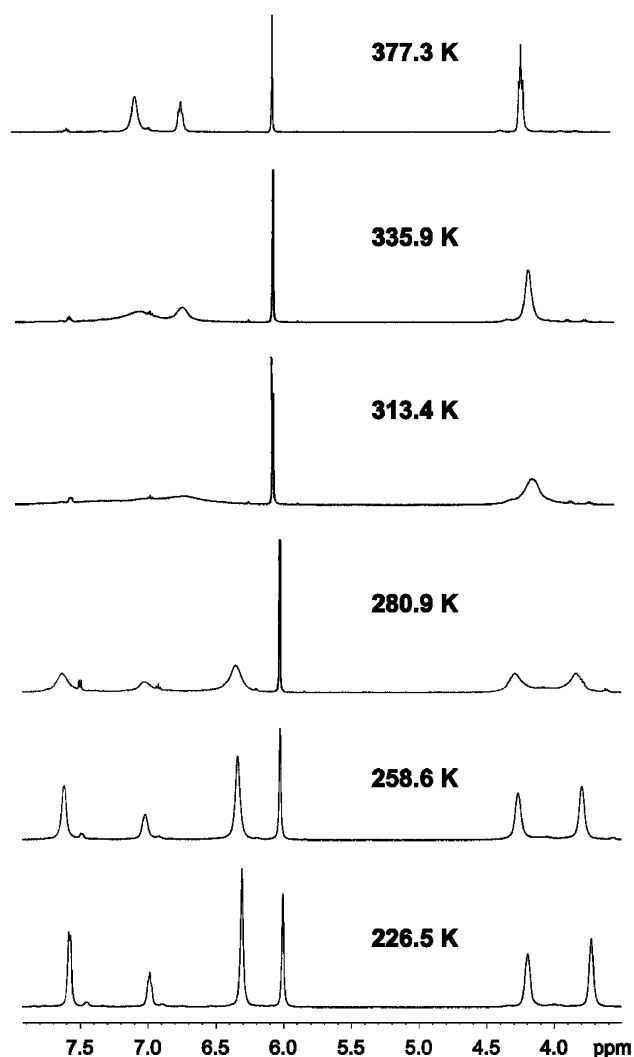
The temperature dependences of the determined chemical exchange rate constants of the pinched cone/pinched cone interconversion are listed in Table 5. The fit to the Eyring eqn. (1,2) is shown in Fig. 9. The resulting activation thermodynamic parameters are $\Delta H_0^* = 11.9$ kcal mol^{-1} (± 0.3 kcal mol^{-1}), and $\Delta S_0^* = -6.2$ cal mol^{-1} (± 1.3 cal mol^{-1}).

The rate constants determined from the EXSY measurements fit fairly well with the constants obtained by the lineshape analysis. The two methods are complementary—EXSY is very precise (we estimate error in k to 5%) in the regime of slow chemical exchange when exchange broadening is small. From the lineshape analysis, reliable rate constants are obtained in the intermediate regime with substantial broadening due to chemical exchange. The remaining parts of temperature dependence are less useful because at coalescence, signal intensity is very poor, and above coalescence, the information is limited to a single peak only. Therefore, only spectra at temperatures below 293 K were used for calculation of thermodynamic parameters.

Table 5 The experimentally determined chemical exchange rate constants k and the corresponding activation free energies ΔG_0^* for pinched cone ↔ pinched cone interconversion in tetrapropoxythiacalix[4]arene **V**

T/K	k/s^{-1}	$\Delta G_0^*/kcal\ mol^{-1}$
226.5	0.94[a]	13.3
237.5	2.5[a]	13.3
247.4	7.4[a]	13.4
258.6	32.7[b]	13.5
269.7	62.7[b]	13.5
280.9	142[b]	13.6
292.3	402[b]	13.7

[a] Values from EXSY experiments [b] Values from lineshape analysis.

Fig. 9 Temperature dependence of the chemical exchange rate constants of the pinched cone ↔ pinched cone interconversion in tetrapropoxy thiacalix[4]arene **V** with curve fitted using the Eyring eqn. (1,2).

Fig. 8 Tetrapropoxythiacalix[4]arene **V**—temperature dependent ^{1}H NMR partial spectra (aromatic and –O–CH$_2$– region). Coalescence temperature is about 313 K.

Solvent dependence of the activation free energy

The suspicion of there being significant interaction of thiacalix[4]arene with solvent molecules was qualitatively examined by means of a temperature dependent study with chloroform, dichloromethane, dimethyl formamide (DMF) and chlorobenzene. The activation free energies ΔG_0 at the coalescence temperatures (calculated using eqn. (3)) of all the studied species in the different solvents are collected in Table 6. The chemical shift difference $\Delta \nu$ between the exchanging aromatic doublets of all the studied thiacalix[4]arene derivatives (at 500 MHz resonance frequency) varies only negligibly (for the given

purpose) from 633 Hz (tetrapropoxythiacalix[4]arene in tetrachloroethane) to 732 Hz (tetrapropoxythiacalix[4]arene in dimethyl formamide). The former value was used for the compounds dissolved in tetrachloroethane, in chloroform, in dichloromethane and in chlorobenzene while the latter was used for DMF solutions.

In the case of tetrapropoxythiacalix[4]arene **V**, the coalescence temperature is very similar for the solvents tetrachloroethane, chloroform, dichloromethane and chlorobenzene, ranging from 298 to 313 K. There is a significant solvent effect in the case of DMF. Because especially chlorobenzene and tetrachloroethane are often considered as non-interacting solvents with calix[4]arenes,[16] it can be concluded that there is an observable interaction between thiacalix[4]arene **V** and DMF as a solvent that significantly decreases the activation free energy of the pinched cone ↔ pinched cone interconversion.

The behaviour of tetraethoxythiacalix[4]arene **IV** is similar to that of the compound **V**, but the coalescence temperatures are constantly from 20–40 K lower. This indicates the higher mobility of this compound. The decrease in the energy barrier can be explained by the geometry of the transition state when the alkoxy groups appear in closest proximity. Therefore, the ethoxy derivative may experience less steric hindrance than the tetrapropoxy compound **V**. Comparison of the different solvents again suggests the increased affinity towards DMF.

We succeeded to reach the coalescence temperature (188 K) for O–CH$_2$ groups of the "normal" compound **VII** in dichloromethane at 300 MHz, providing the free activation energy of 8.7 kcal mol^{-1}. We employed $\Delta \nu$ = 120 Hz determined at 168 K. Other solutions froze above the coalescence temperature, and only an upper bound for the activation energy can be given in the Table 6 (for measurements at 500 MHz, $\Delta \nu$ was multiplied by 5/3). Utilization of a spectrometer with larger magnetic field will in future, perhaps, allow for determination of the coalescence temperature in these solvents.

Previous calculation confirms observed trend in stability of studied systems. Contrary to the NMR results, the calculations provide relatively similar values of energy necessary for pinched cone ↔ pinched cone interconversion in both calix[4]arene and thiacalix[4]arene. The difference $\Delta\Delta E$ (eqn. 4) between them is about 1.4 kcal mol^{-1} (B3LYP/6-31G**). The minimal difference between experimentally observed barriers is about 4.2 kcal mol^{-1}.

$$\Delta\Delta E = \Delta E_{1,thia} - \Delta E_{1,normal} \qquad (4)$$

Since the difference is so small and we are not able to get more precise experimental and/or theoretical data, we can only speculate about the reasons for such behaviour. The first reason could be solvation.

Table 6 Coalescence temperature T_c, and the corresponding activation free energy ΔG_0^*. The coalescence temperatures were determined to ± 5 K that causes ΔG_0^* to be accurate to 0.3 kcal mol^{-1}

Solvent	Tetrapropoxythiacalix[4]arene **V**		Tetraethoxythiacalix[4]arene **IV**		Tetrapropoxycalix[4]arene **VII**	
	T_c/K	ΔG_0^*/kcal mol^{-1}	T_c/K	ΔG_0^*/kcal mol^{-1}	T_c/K	ΔG_0^*/kcal mol^{-1}
Tetrachloroethane-d$_2$	313	13.8^a	271	11.9	<216	<9.8
Chloroform-d	298	13.3	270	11.9	—	—
Dichloromethane-d$_2$	293	12.9	—	—	188^b	8.7
Dimethyl formamide-d$_6$	259	11.3	238	10.3	—	—
Chlorobenzene-d$_5$	308	13.6	—	—	<216	<9.8

^{a} Calculated from ΔH_0^* and ΔS_0^*. ^{b} Measured at 300 Hz.

Since the ground state is not solvated very well,[14] the difference between theoretical and experimental data could be related to the solvation of transition states inside the cavity. The stabilization of the C_4 (C_{4v}) transition state in comparison with the C_{2v} ground state is probably due to more effective intermolecular hydrogen bonding in the more symmetrical transition structure.[14] In accordance with this idea, we have performed additional theoretical studies on the solvation of C_4 transition states of both calix[4]arene types. The complex of calix[4]arene with one molecule of dichloromethane (located inside the cavity) has been used as an initial system. Calculations on the HF/STO-3G, HF/6-31G** and B3LYP/6-31G** levels lead to different results for both calix[4]arenes. The C_4 transition state of tetraethoxythiacalix[4]arene does not create a stable complex with the used solvent (CH$_2$Cl$_2$). Calculated interaction energies are 0.8 kcal mol^{-1} for the HF/STO-3G level, 1.6 kcal mol^{-1} for the HF/6-31G** level and 0.9 kcal mol^{-1} for the B3LYP/6-31G** level. In this case, the solvent molecule is rather rejected from the cavity and the calixarene system interconverts to the C_{2v} ground state. On the other hand, the transition state of normal tetraethoxycalix[4]arene is relatively stabilized by the interaction of solvent molecule with π-electron system inside the cavity. Corresponding calculated interaction energies are 1.2 kcal mol^{-1} for the HF/STO-3G level, 3.6 kcal mol^{-1} for the HF/6-31G** level and 2.3 kcal mol^{-1} for the B3LYP/6-31G** level. Finally, the relative stabilization of the transition state by solvation probably decreases the energy barrier of the interconversion process (tetraethoxycalix[4]arene). The different solvation of both types of calixarenes can lead to different values for the energy barrier and for the coalescence temperatures of studied interconversions.

The second reason can be different stabilization of ground states by stacking. We have found out (B3LYP/6-31G**) that the distances between the opposite aromatic rings is 5.7 and 4.9 Å for normal tetraethoxycalix[4]arene and tetraethoxythiacalix[4]arene, respectively. This will decrease the ground state energy for the sulfur derivative, which may imply increasing the activation energy.

The third thing that must be taken into account is different electronic structure of both above bridges. Larger volume and higher polarizability of sulfur bridges can lead to better stabilization of pinched cone conformer of thiacalix[4]arene. The interactions of sulfur lone pair with the aromatic π-electron system will also play a role. Unfortunately, the size of studied systems did not allow us for an application of more accurate theoretical methods, which better include electron correlation.

Conclusions

Studied conformational motion is very fast for the normal (methylene bridged) calix[4]arene skeleton. Therefore, in correspondence with the literature, the experimental characterization is impossible for the pure phenol type systems. We have found two most important stationary points on the potential energy surface: a minimum with C_{2v} symmetry and a transition state with C_4 symmetry. The C_{4v} structure has been confirmed as a second-order transition state located between two possible structural geometries with C_4 symmetry. The existence of these structurally important geometries results from the different orientation of alkoxy groups.

In contrast with normal calix[4]arenes, the stable pinched cone conformer of thiacalix[4]arenes has C_s symmetry with an asymmetrical slope of "opened" opposite aromatic moieties. The structure with C_{2v} symmetry has been identified as a transition state of interconversion between two possible C_s geometries. The true transition state of pinched cone/pinched cone transition has the C_4 symmetry. Similarly to tetraethoxycalix[4]arene **VI**, the structure with C_{4v} symmetry has been identified as the second-order transition state. The pinched cone/pinched cone interconversion of tetraalkoxythiacalix[4]arenes is relatively slow and easily observable by NMR spectroscopy at normal temperature. The thermodynamic activation parameters of the interconversion were determined for tetrapropoxythiacalix[4]arene **V** by means of temperature dependent measurements.

The effect of the interaction of both calix[4]arene types with solvent molecules has been qualitatively investigated by means of temperature dependent ^{1}H NMR measurements with 1,1,2,2-tetrachloroethane, chloroform, dichloromethane, dimethyl formamide and chlorobenzene. Unfortunately, the energy barrier for normal calix[4]arenes was possible to measure only for dichloromethane. The different coalescense temperatures observed for thiacalix[4]arenes may indicate the influence of the solvent on the energy of the transition state. At the same time, a role may be played by different stacking and also by differences in charge distribution on both derivatives caused by high polarizability of the sulfur atom.

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