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Synthesis and Conformational Properties of Partially Alkylated Methylene-Bridged Resorc[4]arenes – Study of the "*Flip-Flop*" Inversion

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The deprotection of resorc[4]arene octaisopropyl ether **5** by boron trichloride in dichloromethane has been found to give a parent resorc[4]arene, **1**, as well as a mixture of partially alkylated derivatives, **6**, **7**, **8** and **9**, the ratio of which depended on the conditions used. The conformational behaviour of the prepared alkyl ethers was studied with temperature-dependent ^{1}H NMR spectroscopy and quantum chemical calculations. It was found that the compounds **6**, **7** and **8** interconvert between two possible identical *crown* conformations (*flip-flop* inversion). The activation free energy $\Delta G^{\ddagger}$ values for this process, obtained by NMR, strongly depends on the number of hydroxy groups in the molecule; an increase in their number generally increases the values of $\Delta G^{\ddagger}$. The *flip-flop* inversion was not observed in the cases of fully deprotected **1** and monoisopropyl resorc[4]arenes **9**, which are soluble only in polar solvents, inconvenient for the formation of a hydrogen bonding system. Molecular modelling studies revealed that the *flip-flop* inversion proceeds via the consecutive rotation of two adjacent rings, leading to a transition state with deformed *chair* geometry. Subsequent rotation of the remaining two units leads to the formation of the second *crown* conformer. The calculated heights of the energy barriers correspond well with those obtained by NMR spectroscopy.

Introduction

Resorcinarenes are macrocyclic compounds in which resorcinol units are linked in their 2- and 6-positions by methylene bridges. Analogously to their relatives, calixarenes,[1–3] they have a rigid molecular skeleton, which gives them the capability to act as host molecules.[4–6] The bridging between proximal hydroxy groups in resorcinarenes leads to cavitands,[7] bowl-shaped species that can serve as synthetic receptors and are able to assemble into capsules.[8] The presence of a molecular cavity, which varies in size and properties depending on the nature and arrangement of introduced functional groups, indicates their potentially wide usage as receptor systems, efficient extractants, and building blocks for even larger supramolecular assemblies. Thus, we can find resorcinarenes as parts of carceplexes, hemicarceplexes,[9–11] dendrimers,[12–14] and other supramolecular entities.[15–16]

The binding properties of resorcinarenes can be significantly influenced by their stereochemistry. In theory, resorcinarenes can exist in several isomeric forms named *crown* (*cone*), *boat* (*pinched cone*), *chair* (*flattened partial cone*), *diamond* (*1,2-alternate*) and *saddle* (*1,3-alternate*) (Figure 1).[4,6] These basic conformations can be further modified by the substituents (R′) at the methylene bridges, forming *all-cis* (*rccc*), *cis-cis-trans* (*rcct*), *cis-trans-trans* (*rctt*), and *trans-cis-trans* (*rtct*) resorcinarene stereoisomers.[4,6] Any of the above-mentioned stable conformations represent a special three-dimensional arrangement with different complexation behaviour, and hence, with different potential applications as molecular scaffolds and advantageously useful building blocks in supramolecular chemistry.

On the other hand, experimental observations have indicated that these stabilized conformations are not absolutely rigid. Thus, the *boat* conformation (with C_{2v} symmetry) is often reported as being a *crown* (with C_{4v} symmetry). This is because *boat* conformers mutually interconvert very rapidly, which gives a time-averaged *crown* (*cone*) structure.[6,17–18] Non-alkylated resorcinarenes (R = H) with R′ in an all-*cis* arrangement or with unsubstituted methylene bridges give another example of a fast conformational motion. Similarly to unsubstituted calix[4]arenes, molecules of these compounds easily interconvert between two possible

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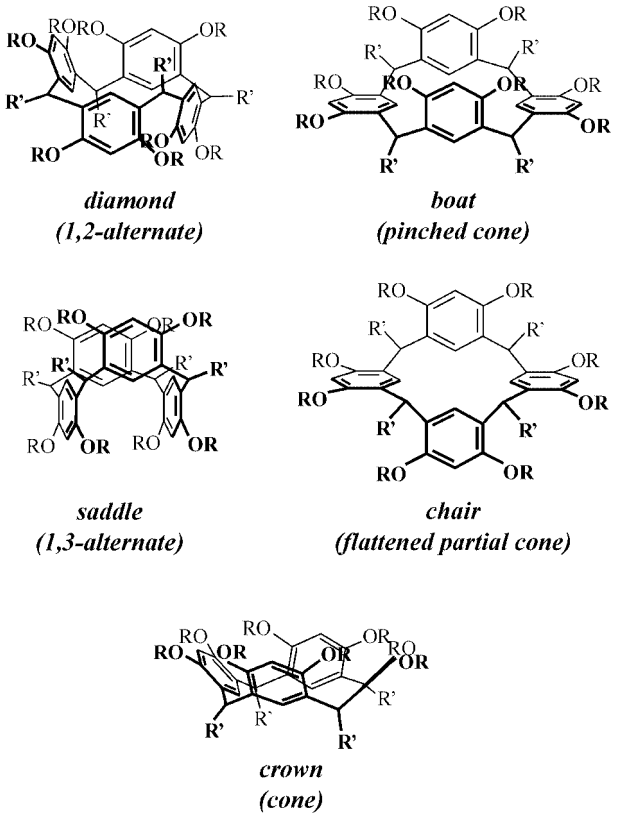


Figure 1. Main conformations of resorc[4]arenes.

crown (*cone*) conformations with C_{4v} symmetry. This motion has been described as the *flip-flop* inversion (Figure 2).[19] In both cases, the *crown* conformation is favoured due to its stabilization by four intramolecular hydrogen bonds, either between pairs of *exo* hydroxy groups in resorc[4]arenes or by the circular array of the *endo* hydroxy groups in calix[4]arenes.[19–21] This specific flexibility of the resorcinarene and calixarene rings is closely related to their ability to interact with other molecules, and hence, to their complexation properties and chemical reactivity.

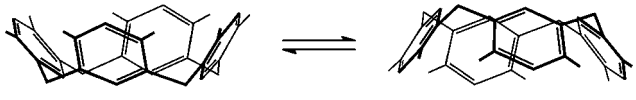


Figure 2. *Flip-flop* interconversion between two identical *crown* conformations.

Since the first synthesis and structure elucidation of resorc[4]arene **1**[22–23] a great number of various *C*-alkylated resorcinarenes have been readily prepared and their chemistry has been well established.[4,6] However, the synthesis of a parent methylene-bridged compound failed, and many alternative routes leading to resorc[4]arene octamethyl (**2**), octaacetyl (**3**) and octaallyl (**4**) ethers (Figure 3) were developed.[24–27]

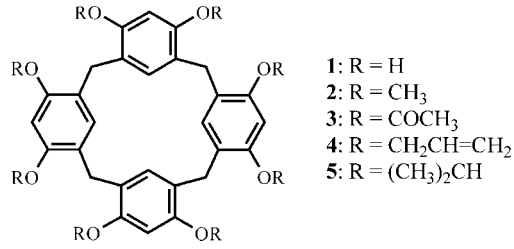


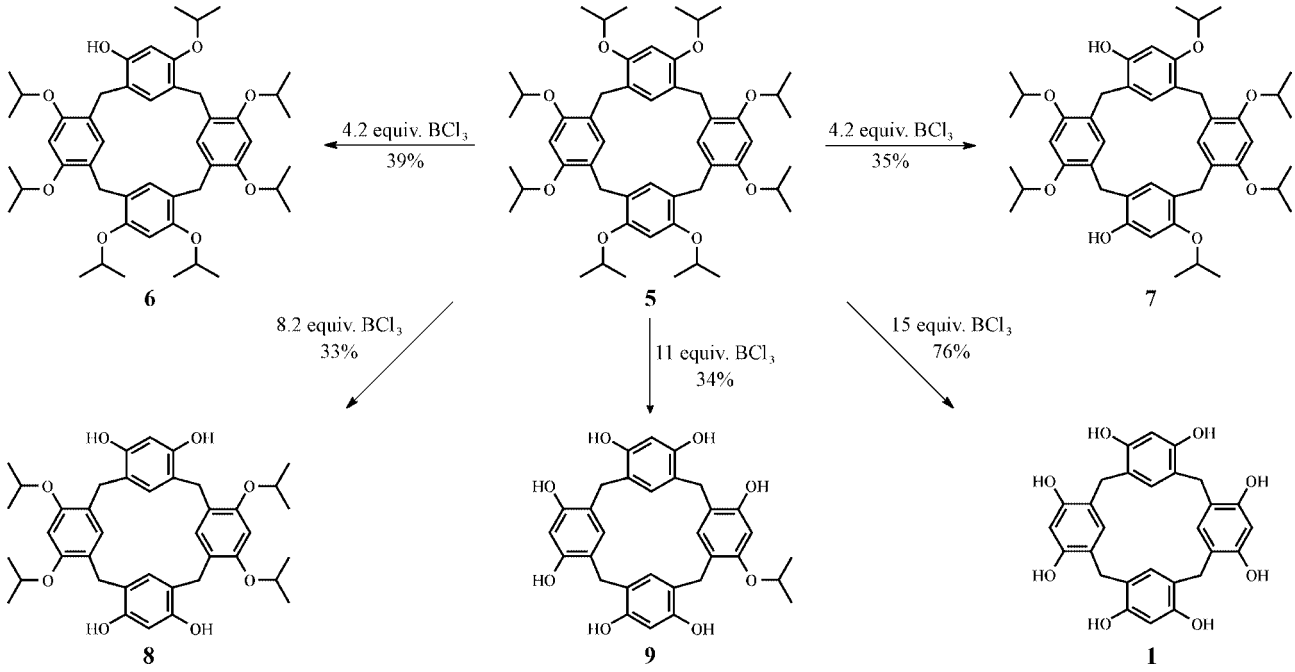
Figure 3. Structures of parent resorc[4]arenes.

We have recently described an efficient synthetic route leading to the formation of parent resorc[4]arene **1** from 2,4-diisopropoxybenzyl alcohol.[28] Its treatment with chlorotrimethylsilane in acetonitrile at room temperature produced a novel crystalline resorc[4]arene octaisopropyl ether **5** in 96% yield. Protecting groups were cleaved by boron trichloride in dichloromethane, and the parent resorc[4]arene **1** was isolated in 76% yield. During the deprotection procedure, we found that the isopropyl groups could be partially removed, and the ratio of the partially alkylated derivatives obtained depended on the conditions used. In this paper, we wish to report more thoroughly on the synthesis, isolation and identification of a number of partially alkylated products. Furthermore, the effects of weak interactions on the conformational behaviour of the prepared compounds are examined with NMR spectroscopy and quantum chemical calculations.

Results and Discussion

Synthesis and Characterization

Selective deprotection of octaisopropyl ether **5** (Scheme 1) was carried out in CH_2Cl_2 employing a 1 M solution of boron trichloride in CH_2Cl_2. The number of cleaved isopropyl groups was dependent on the amount of boron trichloride used in the reaction. Thus, 4.2 equiv. of boron trichloride were sufficient to cleave one or two isopropyl groups, and compounds **6** and **7** were obtained as major products in 39% and 35% yield, respectively. By using 8.2 equiv. of boron trichloride, tetraisopropyl resorcinarene **8** was isolated in 33% yield, besides a mixture of other partially alkylated resorcinarenes. Monoisopropyl derivative **9** was prepared in 34% yield, if 11 equiv. of boron trichloride were applied. This remarkable selectivity might be explained by prior complexation of the boron with suitably oriented hydroxy and isopropyloxy groups in the conformationally flexible resorcinarenes **6** and **7**. The regioselectivity of boron trichloride-promoted deprotection was only reported[29] for debenzylation of per-*O*-benzylated *C*-glycosyl compounds, where 1,2- or 1,3-*cis*-oriented secondary benzyl ethers were cleaved exclusively. However, a deeper insight into these reactions will require kinetics to be performed. The characterization of products **6**–**9** was based on a combination of standard NMR experiments (^{1}H, ^{13}C APT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC). The number of the isopropyl resonances and their



Scheme 1. Selective deprotection of octaisopropyl ether **5**.

integral intensities helped us to assign the degree of deprotection as well as the symmetry of the prepared compounds. The complete assignment of all proton and carbon resonances was accomplished with one-bond ^{1}H-^{13}C correlations in HMQC and three-bond correlations in HMBC experiments, respectively.

The spatial arrangement establishing the type of conformation of the prepared resorc[4]arenes was determined on the basis of the *Nuclear Overhauser Effect* (DPF GSE-NOE experiment). In all cases, NOE experiments revealed the proximity of isopropyl and corresponding hydroxy groups, and also the proximity between the H1 protons of adjacent resorcinol moieties (ring **A**–ring **B**, ring **A**–ring **C**) indicating the presence of the *crown* conformation. As an example, we present an NOE experiment proving the *crown* conformation of hexaisopropyl-substituted compound **7** (Figure 4). By selective excitation of the CH_2 (**C**) methylene protons, NOE enhancement of protons H1 (**C**), H1 (**A**) and OH (**A**)

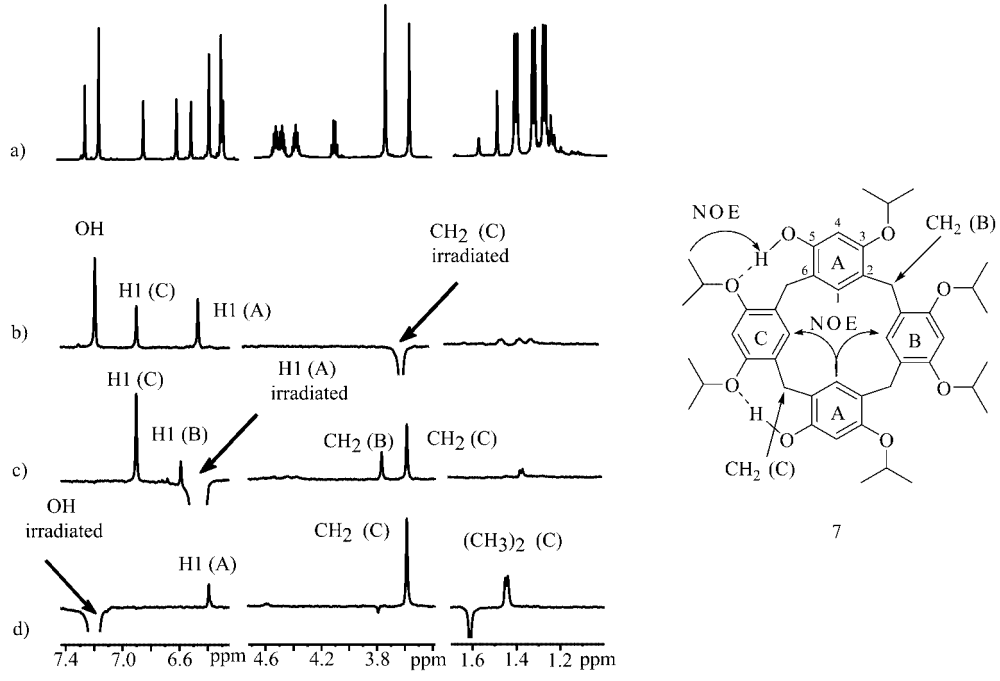


Figure 4. Identification of the *crown* conformer of **7**. a) ^{1}H NMR spectrum ($CDCl_3$, 298 K), b) DPF GSE-NOE spectrum with CH_2 (**C**) irradiated, c) DPF GSE-NOE spectrum with H1 (**A**) irradiated, d) DPF GSE-NOE spectrum with OH (**C**) irradiated.

was observed. The *conic* arrangement was further confirmed by NOE contacts between H1 (**A**) and H1 (**B**), between H1 (**A**) and H1 (**C**), and between the OH (**A**) and CH_3 groups of the **C** ring.

Conformational Study (Dynamic NMR)

The *conic* arrangement of all the studied isopropyl ethers, **6**, **7**, and **8**, unambiguously determined by NOE experiments, does not correspond with the spectral pattern of the methylene resonances in the corresponding ^{1}H NMR spectra. The methylene groups of the *crown* conformer are diastereotopic and should appear as a pair of doublets (with geminal coupling) instead of singlets. To explain this discrepancy, a dynamic NMR study was carried out. ^{1}H temperature-dependent NMR measurement appeared to be a suitable tool for the description of the dynamics of such systems. This approach allowed us to analyze the line shape of methylene protons at different temperatures.

^{1}H NMR temperature dependence was measured in CD_2Cl_2 in the temperature range of 298–163 K. The example of the temperature-dependent ^{1}H NMR spectra for the case of hexaisopropyl derivative **7** is outlined in Figure 5. Due to the fast chemical exchange, two average methylene singlets were observed at room temperature. Lowering of the temperature led to gradual broadening of the methylene singlets with coalescence at 183–193 K. Subsequent lowering of the temperature induced the appearance of new signals at 163 K, corresponding to the presence of a conformer

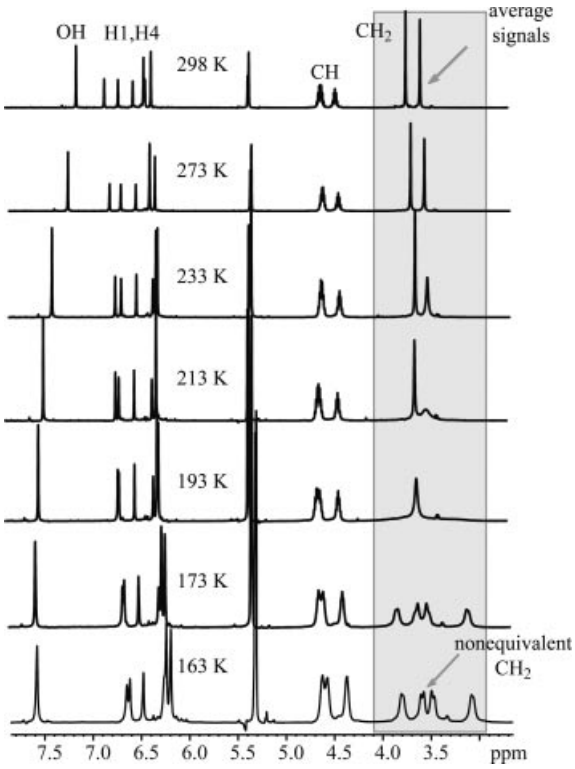


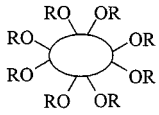
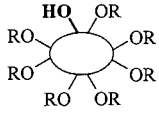
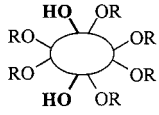
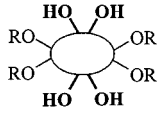
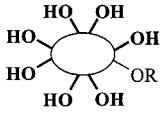
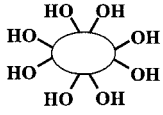
Figure 5. Temperature-dependent ^{1}H NMR spectra of **7** in CD_2Cl_2.

having lower symmetry. The formation of two pairs of nonequivalent methylene protons in the slow-exchange regime is consistent with the dynamics of *flip-flop* inversion between two *crown* conformers (Figure 2).

Thus, the described dynamic behaviour, as well as NOE experiments, proved that only *crown* geometry exists as a stable conformation of all partly alkylated resorcinarenes **6**–**8**. In this case, it is interesting that only one or two hydrogen bonds (compounds **6** and **7**) are sufficient for the stabilization of the *crown* conformation.

The temperature dependences for the studied compounds **6**–**9** enabled us to calculate activation free energies $\Delta G^{\ddagger}$ at the coalescence temperature (T_C) for this interconversion (Table 1). The corresponding values for already described fully alkylated product **5** as well as parent resorc[4]arene **1** are also given in Table 1 for completeness.[28]

Table 1. Values of T_C and the corresponding $\Delta G^{\ddagger}$. T_C was determined to ±5 K, which causes ΔG to be accurate to within 1.3 kJ mol^{-1}.

Compound	Formula	Solvent	T_c (K)	$\Delta G^{\#}$ (kJ mol^{-1})
5		CD_2Cl_2	–[a]	–[a]
6		CD_2Cl_2	<173	<32
7		CD_2Cl_2	193	36
8		CD_2Cl_2	223	42
9		$(CD_3)_2CO$	–[b]	–[b]
1		CD_3OD	–[b]	–[b]

[a] Compound **5** adopts either the *1,3-alternate* conformation or is in a fast equilibrium among conformationally flexible species.[22] [b] Compounds **1** and **9** are conformationally flexible.

The values in Table 1 clearly illustrate that the conformational properties of the studied compounds are very sensitive to even minor structural changes. Apparently, the crucial criteria affecting their conformational behaviour is the

number of hydroxy groups−the potential sites for the formation of hydrogen bonds. If there are more hydroxy groups in the molecule, they induce higher values of T_C, and hence, increase the $\Delta G^{\ddagger}$ of the *flip-flop* inversion. Heptaisopropyl derivative **6**, with only one hydroxy group, is the most flexible species among the isolated partially alkylated compounds. It was not possible to reach its T_C because the solvent freezes above it. However, the distinct line broadening of methylene singlets unequivocally indicated the coming coalescence. In the case of compounds **7** (Figure 5) and **8**, the T_C was reached, the splitting of each methylene signal into two doublets was observed, and $\Delta G^{\ddagger}$ could be calculated (36 kJ mol^{-1} and 42 kJ mol^{-1}, respectively). Due to the presence of seven or eight hydroxy groups, monoisopropyl **9** and parent octahydroxy **1** derivatives should be even less flexible, and values of $\Delta G^{\ddagger}$ of the *flip-flop* inversion are expected to be higher. Unfortunately, the dynamics of this process could not be observed, since the solubility of **1** and **9** in chlorinated (and other suitable non polar) solvents is extremely low. Polar solvents like acetone or methanol disrupt the system of intramolecular hydrogen bonds due to their polar and/or protic characters. Thus, the systems became flexible and no changes in temperature-dependent spectra were observed.

Comparison of the $\Delta G^{\ddagger}$ values obtained for the studied compounds (36 kJ mol^{-1} and 42 kJ mol^{-1}) with that of normal calix[4]arene (62 kJ mol^{-1}) is consistent with published results.[20] Stabilization of the *cone* conformation of calix[4]arenes by the hydrogen-bonding array of *endo* hydroxy groups is more effective than that by *exo* hydroxy groups in the *crown* conformation of resorc[4]arenes, which corresponds with the observed differences in the $\Delta G^{\ddagger}$ values.

Molecular Modelling Studies

The stabilities of potential resorcinarene conformers and the mechanism of the *flip-flop* inversion have also been investigated by molecular modelling. Tetramethyl calix[4]resorcinarene, an analog of compound **8**, was chosen as the model system. The study was performed on the *density functional theory* (DFT) level, which provides a good qualitative insight into the conformational behaviour of such systems.[30] Optimized geometries (B3LYP/6-31+G*) of the relevant stationary points found, as well as their calculated relative electronic energies ΔE, are summarized in Figure 6 and Figure 7. Energy data are related to the most stable *crown* conformer with a relative energy value assigned to zero. Hydrogen bond lengths were measured as the distance between interacting oxygen atoms. OH/π (CH/π) interaction distances were measured between the hydrogen and the closest carbon atom of the aromatic system.

The conformational flexibility of the studied compounds is strongly influenced by weak attractive intramolecular interactions – hydrogen bonds, and OH/π or CH/π interactions. Thus, the *crown* (*cone*), *partial cone*, *chair*, *diamond* (*1,2-alternate*) and *saddle* (*1,3-alternate*) conformers show significant differences in their stabilities. Besides these basic conformers, intramolecular interactions in studied resorcinarenes enable the formation of other structures exhibiting higher or lower stability.

The *crown* conformer represents a global minimum on the *potential energy surface* (PES) of compound **8**, probably due to its stabilization by four strong hydrogen bonds formed between the neighbouring *exo*-OH and *exo*-OCH_3 groups {*d*[O(H)···O] = 2.83 Å, Figure 6, a}. Because of the presence of two different types of aromatic rings in the studied tetramer, we have found two different geometries of the *partial cone* conformer (Figure 6, b and c). The rotation of the aromatic moiety with two unsubstituted hydroxy groups leads to a conformer with slightly lower energy (ΔE = 24.18 kJ mol^{-1}) than that with the second type of rotated unit (38.28 kJ mol^{-1}). Both obtained conformers are stabilized by two hydrogen bonds (2.89 Å and 2.84 Å, respectively). Moreover, the energy of the first one is also decreased by weak interactions between hydrogen atoms of the second pair of hydroxy groups and π-electron systems of adjacent aromatic moieties (OH/π interaction). The calculated distance between the hydrogen of the hydroxy group and the closest carbon of the aromatic moiety is 2.88 Å. A similar effect also plays a key role in the stabilization of the *boat* conformation with opened methoxylated rings (42.38 kJ mol^{-1}, Figure 6, d). All unsubstituted hydroxy groups as well as hydrogen atoms at the lower rim of the opened rings interact with π-electron systems of adjacent aromatic moieties. Interaction distances between the hydrogen atoms and their closest aromatic carbons are 2.51 Å (OH/π) and 2.62 Å (CH/π), respectively. The second possible *boat* conformation is not stable, due to the absence of any attractive interaction. In this case, the system forms the *saddle* conformer (Figure 6, f) instead, with energy increased by 68.32 kJ mol^{-1}, in comparison with the *crown* conformer. The geometry of the *diamond* (*1,2-alternate*) conformer is also stabilized by the formation of only two hydrogen bonds (2.80 Å), and its energy (46.90 kJ mol^{-1}) is similar to that of the stable form of the *boat* conformer (Figure 6, e).

Concerning *flip-flop* inversion, there are two basic theories regarding the simple reaction pathways: i) one-step inversion by synchronous or consecutive rotation of all four rings, and ii) step-by-step inversion accompanied by the formation of some stable conformations (e.g. *partial cone*, *chair*, *diamond* or *saddle* conformers) as intermediates. For the first pathway, we have primarily suggested two possible transition states geometries. The **TS1** structure, with wholly planar geometry of the resorcinarene ring, requires considerable deformation of the methylene bridges (the valence angle on the sp^3-hybridized carbon is about 130°) (Figure 7, a). Its calculated energy is more then 275.0 kJ mol^{-1} higher than that of the most stable *crown* conformer. The energy of the *half-chair* structure **TS2** (Figure 7, b) is also increased by similar strain, as well as by steric interactions between hydrogen atoms in the centre of the resorcinarene ring. The calculated energy of this barrier is approximately 160.0 kJ mol^{-1}. Moreover, vibrational frequency analyses indicate that both these molecular structures represent

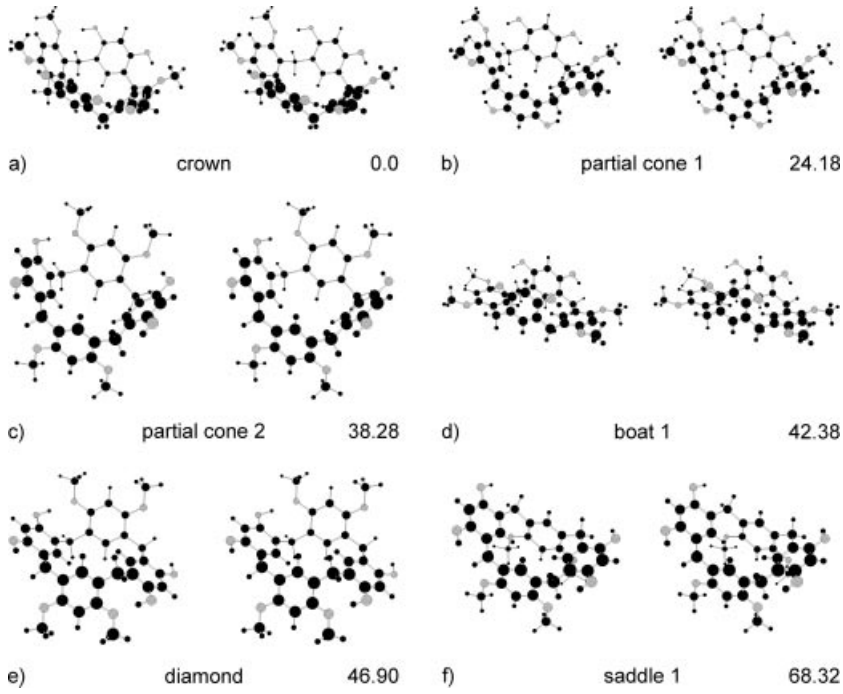


Figure 6. Geometries and relative electronic energies of stable conformers of tetramethyl calix[4]resorcinarene (stereoviews, calculated at the B3LYP/6-31+G* level).

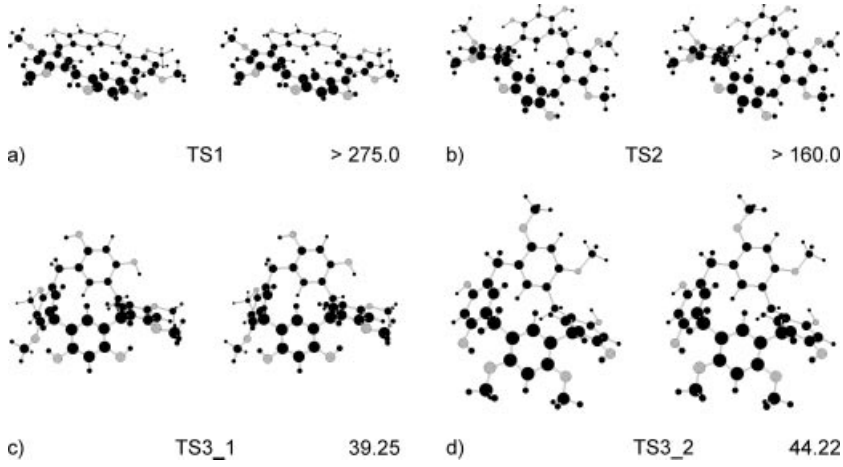


Figure 7. Geometries and relative energies of transition states proposed for the *flip-flop* inversion of tetramethylcalix[4]resorcinarene (calculated at the B3LYP/6-31+G* level).

higher order stationary points rather than the true transition states.

Experimental observations correspond well with the other (probably) single-step mechanism. In this case, the reaction starts with the consecutive rotation of all rings via transition states **TS3_1** or **TS3_2**, both with deformed *chair* conformer geometry (Figure 7, c and d). The existence of two reaction pathways also follows from the presence of the two different types of aromatic rings in the studied tetramer. Both structures are stabilized by three hydrogen bonds (2.85 Å, 3.35 Å, 3.47 Å for **TS3_1**, and 2.84 Å, 3.39 Å and 3.63 Å for **TS3_2**), which decrease the negative contributions of the appreciable resorcinarene ring deformation. Inversion then follows with the rotation of the remaining two units and formation of the second *crown* conformer. The energies of the stationary points found are 39.25 kJ mol^{-1} and 44.22 kJ mol^{-1} respectively, and both values are well in accordance with experimentally obtained values. Harmonic analysis confirms the stationary points found as true transition states. It may be possible that there are some flat minima at this reaction coordinate, which are not easily localizable by the standard PES investigation. However, more complicated step-by-step reaction pathways (e.g. pathway ii described above) leading through some stable conformers as intermediates (discussed in the text above) are unrealistic, mainly due to their low stability. This

idea corresponds well with experimental observations. We have not identified any other stable conformer during the NMR measurements.

Concerning the quantitative agreement between calculated and measured data, we must be careful and take into consideration the absence of solvent effects in the calculations. In some cases, solvent molecules could play a significant role in the stabilization of both minima and transition states.[31] Besides, DFT does not exactly describe electron correlation, and hence, weak interactions.

Conclusions

NMR spectroscopy and molecular modelling studies have given an interesting insight into the structural and electronic aspects of the conformational flexibility of the studied compounds. The stability or flexibility of resorc[4]-arene conformers are strongly influenced by weak intramolecular interactions. Two types of them have been observed in the molecules studied here – hydrogen bonds, and OH/π or CH/π interactions. Hydrogen bonds have a dominant effect and can be formed between oxygen atoms of alkoxy and hydroxy groups of the resorcinarene ring. OH/π and CH/π interactions are not so intense but also play a significant role in the stabilization of some structures.

The theoretical analysis, based on the DFT, of a model system derived from compound **8**, established the *crown* conformer as the most stable one. Its structure is stabilized by four intramolecular hydrogen bonds. Two possible *partial cone* conformers are stabilized by only two hydrogen bonds. The structure of the more stable form is favoured by the presence of attractive OH/π interactions. The *boat* conformer is formed only by the rotation of opposite aromatic units with a methoxy substituent. Its structure is stabilized purely by four OH/π and two CH/π interactions. The same rotation of the second pair of aromatic units leads to the *saddle* (*1,3-alternate*) conformation, which lacks the afore-mentioned intramolecular interaction, and hence, has the lowest stability.

The highest stability of the *crown* conformer was unambiguously documented by NMR spectroscopy. The dynamic NMR measurements, together with NOE experiments, established that partially isopropylated compounds **6**, **7** and **8** were present exclusively in the *crown* conformations, stabilized by intramolecular hydrogen bonds of *exo*-OH groups, and they interconvert between two identical *crown* conformations (*flip-flop* inversion). The dynamic NMR study was also utilized for the calculation of $\Delta G^{\ddagger}$ at the T_C; the more hydroxy groups that occur in the molecule, the higher is the $\Delta G^{\ddagger}$ of this process.

On the basis of DFT, two different mechanisms of *flip-flop* inversion have been suggested. The first one, the synchronous, symmetrical, single-step inversion of all four aromatic rings, requires considerable deformation of the methylene bridges. Inversion is also sterically hindered by the presence of all four hydrogen atoms in the centre of the resorcinarene ring. Another proposed mechanism represents a complicated process, with several relatively unstable conformers as intermediates. Additionally, the energy of the rate-controlling step is significantly higher than that obtained from experiments. The best model is based on the consecutive rotation of two adjacent rings, which leads to a transition state with a geometry of a deformed *chair* conformer with energies ΔE = 39.25 kJ mol^{-1} and ΔE = 44.22kJ mol^{-1}, respectively (with respect to the two different types of unit rotated first). Calculated electronic energies correspond well with those obtained by NMR spectroscopy. The inversion is completed by the rotation of the remaining two units and formation of the second *crown* conformer.

Experimental Section

Unless otherwise stated, solvents were evaporated at 40 °C and 2 kPa, and compounds were dried at 60 °C and 2 kPa. Reactions were monitored by thin-layer chromatography (TLC) on aluminium-backed plates coated with Merck Kieselgel 60 F_{254} silica gel. The TLC plates were analyzed with UV radiation at a wavelength of 254 nm or stained by exposure to an aqueous solution of $Ce(SO_4)_2$ (acidified with concentrated sulfuric acid), followed by charring. Commercially available reaction solvents were used. Accurate mass spectra were measured with a Q-Tof Micro instrument (Waters, USA) equipped with LockSpray in ES- mode.

NMR spectra were recorded with a Bruker DRX 500 Avance spectrometer operating at 500.1 MHz for ^{1}H and 125.8 MHz for ^{13}C. Chemical shifts were referenced to Me_4Si. Typically, a spectral width of 7500 Hz, a size of 32 K data points, a recycle time of 3.2 s and 16 scans were used. ^{13}C NMR spectra were measured with a spectral width of 25000 Hz, 32 k data points, a recycle time of 2.7 s and 5000 scans. Assignment was accomplished by means of 2D ^{1}H COSY, 2D ^{1}H-^{13}C HMQC, 2D ^{1}H-^{13}C HMBC and 1D-DPF GSE-NOE experiments. 2D COSY was used for resolving ^{1}H spin systems [64 t_1 increments for 1024 (1 K) data points, 16 scans, spectral widths of 3000–4000 Hz]. One and three bond ^{1}H-^{13}C connectivities for the assignment of carbon resonances were determined with 2D HMQC [128 t_1 increments for 1 K data points, spectral widths of 4 kHz (^{1}H) and 22.6 kHz (^{13}C), 64 scans, a polarization transfer delay of 3.5 ms] and HMBC [128 t_1 increments for 1 K data points, spectral widths of 4 kHz (^{1}H) and 22.6 kHz (^{13}C), 64 scans, a polarization transfer delay of 60 ms] techniques. The assignment of protons and carbons of rings **A**, **B** and **C** in compounds **7** and **8** is illustrated in Figure 4.

Dynamic NMR Study: For dynamic NMR study, temperature-dependent ^{1}H NMR spectra were recorded. All studied compounds were analyzed in the temperature range of 163–298 K in CD_2Cl_2 (99.8% D, Merck, Germany). $\Delta G^{\ddagger}$ values were determined according to the Eyring equations (1) and (2) for the rate constant k.

$$k = \frac{k_B T_C}{h} e^{-\frac{\Delta G^{\ddagger}}{RT_C}} \quad (1)$$

$$k = \frac{\pi \Delta \nu}{\sqrt{2}} \quad (2)$$

where k_B is the Boltzmann constant, T_C the coalescence temperature, R the gas constant, h the Planck constant and $\Delta\nu$ the chemical

shift difference of the exchanging resonances in the absence of chemical exchange.

Molecular Modelling Study: Input geometries of stable conformers and saddle points were based on our conceptions about the resorcinarene system and its properties. The Berny algorithm was used for both minimizations – optimizations to local minima and optimizations to transition states. In the first step, a detailed investigation of the PES was performed on the HF/STO-3G ab initio quantum mechanics level. The stationary points found were refined on the HF/6-31G* level. The geometries and energies of relevant stationary points were finally calculated on the B3LYP/6-31+G* level. Vibrational frequency analysis was used to confirm whether the stationary points found were minima or transition state structures. All calculations were performed with the GAUSSIAN03 quantum chemical program.[32] The geometries obtained, together with calculated B3LYP/6-31+G* electronic energies of important stable conformers, as well as transition states are discussed in the text and shown in Figure 6 and Figure 7.

General Procedure for the Preparation of Compounds 6 and 7: Octaisopropyl ether **5** (1 g, 1.2 mmol) was stirred in CH_2Cl_2 (100 mL) for 30 min at room temperature, during which time the solid dissolved. The solution was cooled to 4 °C in an ice bath, and a mixture of CH_2Cl_2 (10 mL) and boron trichloride (1 M solution in CH_2Cl_2, 5 mL) was added dropwise over 1 h. During this time, the colour of the pale violet solution turned to dark red. The reaction was quenched by the addition of MeOH (20 mL), and the mixture was stirred and warmed to room temperature. The solvent was evaporated under vacuum, and the crude syrup was purified by flash chromatography (5:1, v/v, petroleum ether/EtOAc as the eluent). Product **6** was obtained as a pale yellow solid (252 mg, 0.3 mmol, 39%).

Heptaisopropyl Ether 6: R_f = 0.54 (petroleum ether/EtOAc, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.99 (br., 1 H, OH), 6.70 (s, 1 H, arom.), 6.68 (s, 2 H, arom.), 6.51 (s, 1 H, arom.), 6.49 (s, 2 H, arom.), 6.46 (s, 1 H, arom.), 6.39 (s, 1 H, arom.), 4.62 [sept, J = 6.0 Hz, 1 H, $CH(CH_3)_2$], 4.50–4.30 [m, J = 6.0 Hz, 6 H, $CH(CH_3)_2$], 3.76 (s, 2 H, CH_2), 3.75 (s, 4 H, 2×CH_2), 3.62 (s, 2 H, CH_2), 1.45 [d, J = 6.0 Hz, 6 H, $CH(CH_3)_2$], 1.36–1.30 [3×d, J = 6.0 Hz, 18 H, 3×$CH(CH_3)_2$], 1.29–1.20 [3×d, J = 6.0 Hz, 18 H, 3×$CH(CH_3)_2$] ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ = 155.15, 154.56, 154.54, 154.46, 154.01, 153.90, 152.51, 151.53 (**C**-3 and **C**-5), 132.74, 131.59, 131.21, 131.11 (**C**-1), 125.39, 124.37, 123.81, 123.73, 122.87, 122.50, 122.00, 118.90 (**C**-2 and **C**-6), 103.14, 102.76, 102.35, 101.38 (**C**-4), 71.64, 71.53, 71.28, 71.12, 70.89, 70.48 [$CH(CH_3)_2$], 29.39, 28.58, 27.20, 27.01 (CH_2), 22.25, 22.22, 22.20, 22.13, 22.05, 21.87 [$CH(CH_3)_2$] ppm. HRMS: calcd. for $C_{49}H_{65}O_8$ [M–H]$^-$ 781.4644; found 781.4680.

Hexaisopropyl Ether 7: Product was obtained as a pale yellow solid (212 mg, 0.3 mmol, 35%). R_f = 0.41 (petroleum ether/EtOAc, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.17 (br. s, 2 H, OH), 6.87 (s, 1 H, arom. **C**-1), 6.65 (s, 1 H, arom. **C**-4), 6.65 (s, 1 H, arom. **B**-1), 6.44 (s, 2 H, arom. **A**-1), 6.36 (s, 2 H, arom. **A**-4), 6.40 (s, 1 H, arom. **B**-4), 4.49–4.59 [m, 4 H, 4×C*H*$(CH_3)_2$-**A**,**B**], 4.41 [sept, J = 6.0 Hz, 2 H, 2×C*H*$(CH_3)_2$-**C**], 3.74 (s, 4 H, 2×CH_2-**B**), 3.56 (s, 4 H, 2×CH_2-**C**), 1.41 [d, J = 6.0 Hz, 6 H, 2×$CH(CH_3)_2$], 1.36 [d, J = 6.0 Hz, 6 H, 2×$CH(CH_3)_2$], 1.31 [d, J = 6.0 Hz, 6 H, 2×$CH(CH_3)_2$] ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ = 155.10, 155.08 (**A**-3, **C**-3), 151.94, 151.84 (**B**-3, **A**-5), 134.11, 132.23, 130.16 (**C**-1), 124.13, 123.88, 123.70, 118.690 (**C**-2 and **C**-6), 102.59, 101.91, 100.30 (**C**-4), 71.93, 71.22, 70.38 [*C*$H(CH_3)_2$], 29.52, 27.14 (CH_2), 22.33, 22.30, 21.80 [$CH(CH_3)_2$] ppm. HRMS: calcd. for $C_{46}H_{60}O_8$ [M–H]$^-$ 739.4194; found 739.4210.

Tetraisopropyl Ether 8: Octaisopropyl ether **5** (300 mg, 0.4 mmol) was stirred in CH_2Cl_2 (25 mL) for 30 min at room temperature, during which time the solid dissolved. The solution was cooled to 4 °C in an ice bath, and a mixture of CH_2Cl_2 (5 mL) and boron trichloride (1 M solution in CH_2Cl_2, 3.3 mL) was added dropwise over 1 h. During this time, the pale violet solution turned a dark red colour. The reaction was quenched by the addition of MeOH (5 mL), and the mixture was stirred and warmed to room temperature. The solvent was evaporated under vacuum, and the crude syrup was purified by flash chromatography (3:1, v/v, petroleum ether/acetone as the eluent). Product **8** was obtained as a pale yellow solid (78 mg, 0.1 mmol, 33%). R_f = 0.39 (petroleum ether/acetone, 3:1). ^{1}H NMR (500 MHz, CH_3OD, 25 °C): δ = 6.59 (s, 2 H, arom. **B**-1), 6.53 (s, 2 H, arom. **B**-4), 6.40 (s, 2 H, arom. **A**-1), 6.28 (s, 2 H, arom. **A**-1), 4.50 [sept, J = 6.0 Hz, 8 H, 8×C*H*$(CH_3)_2$], 3.61 (s, 8 H, 4×CH_2), 1.28 [(d, J = 6.0 Hz, 24 H, 8×$CH(CH_3)_2$] ppm. ^{13}C NMR (125.8 MHz, CD_3OD, 25 °C): δ = 153.42, 153.17 (**A**-3, **B**-3), 131.40, 130.86 (**A**-1, **B**-1), 123.66 (**B**-2), 118.79 (**A**-2), 102.22, 101.96 (**A**-4, **B**-4), 71.22 [*C*$H(CH_3)_2$], 27.89 (CH_2), 21.01 [$CH(CH_3)_2$] ppm. HRMS: calcd. for $C_{40}H_{48}O_8$ [M–H]$^-$ 655.3276; found 655.3271.

Monoisopropyl Ether 9: Octaisopropyl ether **5** (100 mg, 0.1 mmol) was stirred in CH_2Cl_2 (8 mL) for 30 min at room temperature, during which time the solid dissolved. The solution was cooled to 4 °C in an ice bath, and boron trichloride (1 M solution in CH_2Cl_2, 1.1 mL) was added dropwise over 1 h. During this time, the pale violet solution turned a dark red colour. The reaction was quenched by the addition of MeOH (3 mL), and the mixture was stirred and warmed to room temperature. The solvent was evaporated under vacuum, and the crude syrup was purified by flash chromatography (10:1, v/v, $CHCl_3$/CH_3OH as the eluent). Product **9** was obtained as a pale yellow solid (22 mg, 0.04 mmol, 34%). R_f = 0.25 ($CHCl_3$/MeOH, 10:1). ^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C): δ = 8.54 (br., 7 H, OH), 7.19 (s, 4 H, arom. H1), 7.15 (s, 4 H, arom. H1), 7.13 (s, 4 H, arom. H1), 7.10 (s, 4 H, arom. H1), 6.48 (s, 4 H, arom. H4), 6.34 (s, 4 H, arom. H4), 6.32 (s, 4 H, arom. H4), 6.28 (s, 4 H, arom. H4), 4.60 [sept, J = 6.0 Hz, 1 H, C*H*-$(CH_3)_2$], 3.75 (s, 8 H, 4×CH_2), 3.71 (s, 8 H, 4×CH_2), 3,70 (s, 8 H, 4×CH_2), 3.69 (s, 8 H, 4×CH_2), 1.35 [d, J = 6.0 Hz, 6 H, CH-$(CH_3)_2$] ppm. ^{13}C NMR (125.8 MHz, $(CD_3)_2CO$, 25 °C): δ = 154.36, 153.54, 153.46, 153.31, 153.16, 153.09 (**C**-3 and **C**-5), 132.66, 132.40 (**C**-1), 123.44, 121.94, 121.31, 121.14, 120.95, 120.73, 120.68, 120.62 (**C**-2 and **C**-6), 103.76, 103.64, 103.49, 102.59 (**C**-4), 71.93 [*C*$H(CH_3)_2$], 4×*C*H_2, overlapped by the residual signal of acetone, 21.96 [$CH(CH_3)_2$] ppm. HRMS: calcd. for $C_{31}H_{30}O_8$ [M–H]$^-$ 529.1871; found 529.1863.

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