

PROBLEMS WITH A CONFORMATION ASSIGNMENT OF ARYL-SUBSTITUTED RESORC[4]ARENES

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Acid-catalyzed condensation of resorcinol with 3,5-diisopropoxybenzaldehyde and 3,5-dihydroxybenzaldehyde afforded aryl substituted resorc[4]arenes **1a** and **1b**, respectively. All 16 hydroxyls in **1b** were acetylated providing resorc[4]arene **1c**. The conformational behaviour of **1a**, **1b** and **1c** was studied by NMR spectroscopy and quantum chemical calculations. It was found that the stabilization of their conformations is an effect of competing π - π and OH- π interactions, hydrogen bonding and steric features, respectively. As a result, C_2 symmetrical *boat* conformations **1a**, **1b** and **1c** with aryls in axial positions were identified in all cases. In case of **1c** also the formation of C_2 symmetrical conformation with aryls in equatorial positions (*boat-eq*) was identified. Moreover, compounds **1a** and **1b** being able to create hydrogen bonds, adopt also symmetrical C_4 *crown* conformations. For **1c**(*boat-ax*), the *boat-boat* conversion with energy barrier of 80 kJ/mol was observed, while the **1c**(*boat-eq*) was found to be rigid in the whole accessible temperature range. Both conformers of **1c** exhibit also second dynamic process – rotation of bridge aryl rings ($\Delta G^\ddagger = 66$ kJ/mol).

Keywords: Aryl-substituted resorc[4]arenes; Conformational analysis; Density functional theory; NOE.

Resorc[4]arenes are of wide interest as macrocyclic host for a variety of organic guest molecules or as building blocks for the construction of larger supramolecular systems^{1–3}. The bridging between proximal hydroxyl groups in resorc[4]arenes can lead to cavitands, capsules, carceplex, hemicarceplex, dendrimers and other supramolecular species^{4–11}. The binding properties of resorc[4]arenes can be influenced by their stereochemistry. Moreover, conformation of basic skeleton determines the direction and shape of spreading dendrimer as well as the form of desired cavity. The macrocyclic ring

may exist in five extreme conformations named *crown* (with the inner macrocyclic ring symmetry of C_{4v}), *boat* (C_{2v}), *chair* (C_{2h}), *saddle* (D_{2d}) and *diamond* (D_{2d}) as it is depicted on Fig. 1. The relative configuration of the substituents at the methylene bridges gives though the all-*cis* (ccc), *cis-cis-trans* (cct), *cis-trans-trans* (ctt) and *trans-cis-trans* (tct) stereoisomers and can be seen on Fig. 2. Finally, the orientation of the substituents in the conformers with C symmetry can be either axial or equatorial². Several studies suggest that hydrogen bond formation and the axial orientation of

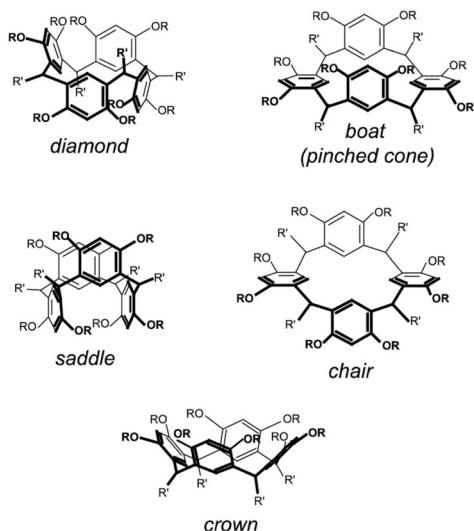


FIG. 1
The macrocyclic ring conformation definitions

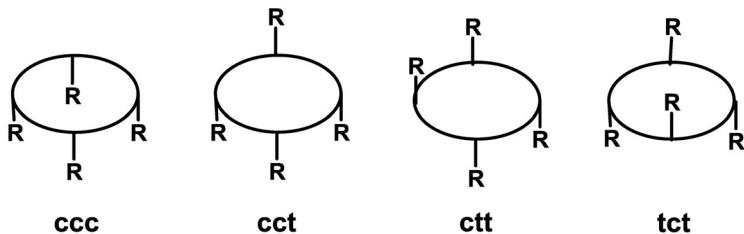
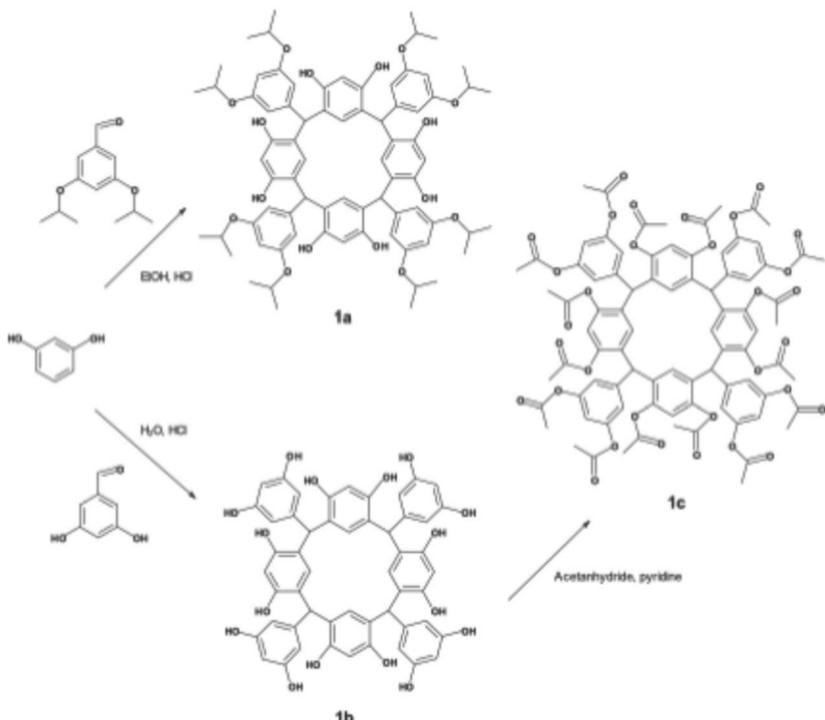


FIG. 2
The set of resorc[4]arene stereoisomers defined by the relative configuration of the substituents at the methylene bridges

bridge substituents could be the driving force of their formation and indicate that in the *boat* stereoisomer both effects contribute to stabilize this conformation^{1,12–15}. Other papers revealed that also the *chair*, *crown*, *diamond* or *saddle* conformers can be also stable under certain conditions^{2,16–19}. Selective formation of the rctt chair stereoisomer of octa-O-alkylresorc[4]arenes as the thermodynamic product under Brønsted-acid catalysis has been reported recently²⁰.

In this paper, we report problems which can occur within a detailed conformational analysis presented on a series of aryl functionalized resorc[4]arenes **1a**, **1b** and **1c** (Scheme 1). Studied systems were synthesized but obtained in a mixture of conformers with different macrocyclic symmetry. The conformational distribution was strongly influenced by a formation of noncovalent interactions (e.g. π - π , OH- π or hydrogen bonding interactions). Standard analysis based on NMR experiments was compli-



SCHEME 1
The synthesis of aryl substituted resorc[4]arenes

cated by similar NMR signal patterns given by conformers with different symmetry of macrocyclic ring. Thus the experimental technique had to be completed with molecular modelling studies to shed a light on this problem. Such knowledge could help to design a suitable model compound for studying binding properties of aryl substituted resorc[4]arenes.

RESULTS AND DISCUSSION

Synthesis of Model Compounds

The reaction of resorcinol with 3,5-diisopropoxybenzaldehyde gave tetrakis-(3,5-diisopropoxyphenyl)resorc[4]arene **1a** in 49% yield. According to TLC, three conformers of **1a** were present in the reaction mixture (R_F 0.50, 0.55, 0.60) but only two of them (R_F 0.50, 0.60) were isolated by flash chromatography in the yield of 26 and 14%, respectively (Scheme 1). Tetrakis-(3,5-dihydroxyphenyl)resorc[4]arene **1b** has been already synthesised by the reaction of resorcinol with 3,5-dihydroxybenzaldehyde in aqueous hydrochloric acid⁵. Repeating the described procedure we prepared resorc[4]arene **1b** in the yield of 34% as a non separable mixture of two conformers. Convenient acetylation of **1b** with acetic anhydride in pyridine gave tetrakis(3,5-diacetoxyphenyl)octa-O-acetylresorc[4]arene **1c** in the yield of 99%. We tested also the condensation of diisopropylresorcinol with either 3,5-dihydroxybenzaldehyde or 3,5-diisopropoxybenzaldehyde to prepare complementary structures to **1a** but the reactions completely failed. This observation suggests that the presence of suitable oriented free hydroxyl groups in resorcinol can contribute to the cyclization being able to hold the conformation of an acyclic intermediate through hydrogen bonds between adjacent resorcinol units.

NMR Conformational Study

The high spectral symmetry of the major conformer of compound **1a** (Fig. 3D) is consistent with the C_{4v} symmetrical *crown* conformation. The axial arrangement of bridge aryl rings was determined by strong NOE connectivities between bridge aromatic proton H-2' and cavity proton H-1 (Fig. 3A, 3B). No NOE enhancement was observed between bridge aromatic proton H-2' and cavity H-4 (Fig. 3C) that should be essential for equatorial arrangement of bridge aryl rings (Fig. 3).

The less abundant conformer of **1a** revealed the less symmetrical (C_2) spectral pattern (Fig. 4D). The doubled resonances of the cavity aromatic

protons H-1 and H-4 were consistent with the symmetry of either a *boat* or a *chair* conformation. NOE turned out to be the key method for determination of the orientation of bridge aromatic rings (axial or equatorial) and also for specification of two different orientations of cavity aromatic protons H-1 and H-4 (parallel vertical, H_{ver} or planar, H_{pla}): while H-1_{ver} (δ 6.68 ppm) exhibits strong NOE enhancement of bridge aromatic protons (Fig. 4A), the effect of H-1_{pla} (δ 6.33 ppm) is only negligible. The strong NOE enhancement of bridge aromatic protons H-2' with H-1_{ver} (Fig. 4A) determines axial arrangements of bridge aryl rings. This axial position was further supported by absence of NOE between cavity H-4_{ver} (Fig. 4C) and

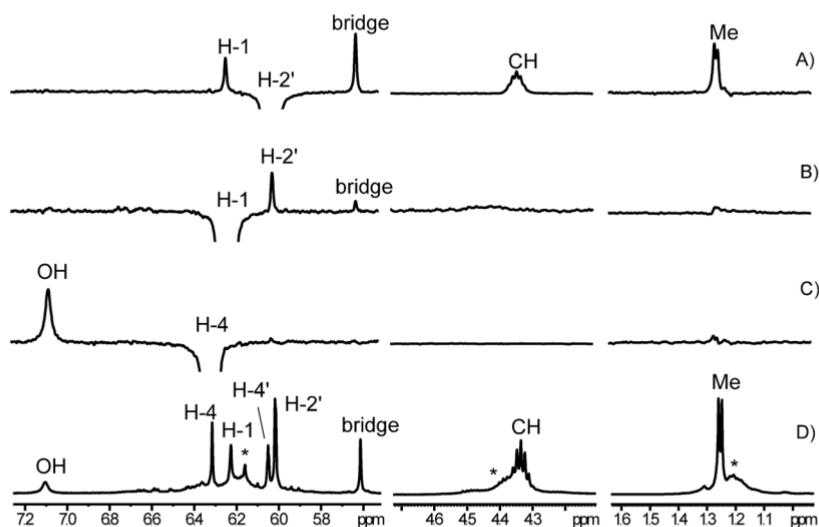


FIG. 3

Identification of resorcinarene **1a(crown)** with aryls in axial positions; partial DPGSE-NOE spectra with A H-2' irradiated, B H-1 irradiated, C H-4 irradiated, D part of ¹H NMR spectrum in *d*₆-acetone at 298 K; * impurities

bridge aromatic protons. On the other hand the H-4_{pla} protons show pronounced NOE to *iPr* protons of bridge aromatic rings (Fig. 4B). Unfortunately, as the spectral symmetry and the NOE connectivities of both possible *boat* and *chair* conformations with bridge aryls in axial positions are identical, it was not possible to determine the type of conformation unambiguously on the basis of NMR experiments. Taking into account that *chair-ax* and/or *boat-ax* conformations have been previously reported for similar aryl substituted resorc[4]arenes^{2,15,16,20-22}, we can assume that both *chair-ax* and *boat-ax* conformations of **1a** could be formed in the re-

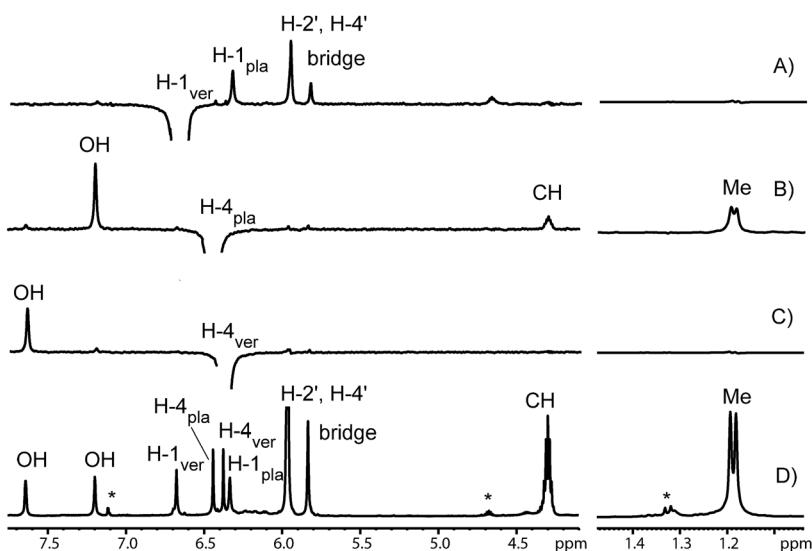


FIG. 4
Identification of resorcinarene **1a**(*boat*) with aryls in axial positions; partial DPFGSE-NOE spectra with A H-1_{ver} irradiated, B H-4_{pla} irradiated, C H-4_{ver} irradiated, D part of ¹H NMR spectrum in *d*₆-acetone at 298 K; * impurities

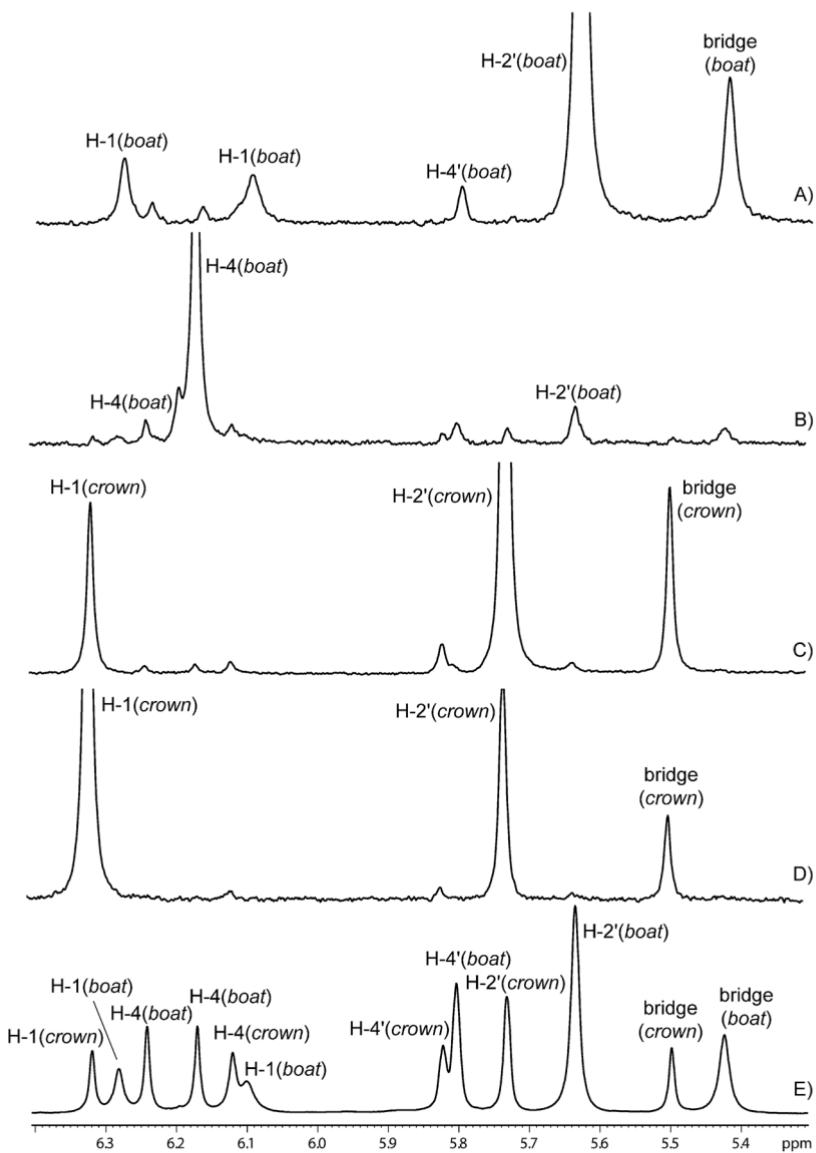


FIG. 5

Identification of resorcinarene **1b(crown)** and **1b(boat)** with aryls in axial positions; partial DPGSE-NOE spectra with A H-2'(boat) irradiated, B H-4(boat) irradiated, C H-2'(crown) irradiated, D H-1(crown) irradiated, E part of ^1H NMR spectrum in d_6 -dimethylsulfoxide at 298 K

action. Molecular modelling study (see bellow) indicated the presence of **1a**(*boat-ax*) conformation that is about 5.1 kJ/mol lower in energy than **1a**(*chair-ax*) (Fig. 9). Consequently, the less abundant isolated conformer of **1a** (14% isolated yield) might have a *boat-ax* conformation while a *chair-ax* conformation can be assigned to a non-isolated remaining **1a** stereoisomer (9%).

The spectral pattern of 3,5-dihydroxyphenyl substituted resorc[4]arene **1b**, previously prepared, but not thoroughly analysed⁵ indicated in contrast to **1a**, the presence of a mixture of two non separable conformational species within the whole accessible temperature range (193–353 K): the C_{4v} symmetrical crown and C_2 symmetrical either *boat* or *chair* conformer. The observed NOE contacts (Fig. 5A–5D) determine that the bridge aryl rings occupy axial positions in both conformations. However, contrary to **1a**, the less symmetrical conformer prevailed over the *crown* (2:1). No chemical exchange between the *crown* and second isomers was observed in **1b**, in contrast to several previously described alkyl¹⁷ and pyrazine-bridged resorc[4]arenes²³. On the other hand, a slow chemical exchange was found to take part within the prevailing conformer, which is demonstrated in NOE difference spectra in Fig. 5. (The interpretation of NOE difference spectra in this case was slightly complicated by the fact that the NOE enhancements peaks had the same polarity as the inverted resonances and the exchange peaks as a result of slow molecular motion of **1b** in highly viscouse dimethylsulfoxide.) The exchange peaks between the corresponding cavity protons H-4 (Fig. 5B) indicate a presence of a conformational equilibrium between two identical species. Consequently, the conformation with C_2 symmetry was attributed to the *boat* conformation as such a movement has been already described within similar systems^{21,23,24}. This result is, however, somewhat inconsistent with the original paper⁵, where the compound **1b** in *chair* (rctt) conformation was mentioned as the second condensation product, however, no experimental data have been presented.

The lack of the hydroxyl groups in resorc[4]arene **1c** caused significant increase of its flexibility, and, thus ^1H NMR spectrum displayed several broad resonances at room temperature (Fig. 6). Flexibility of the molecules depends on experimental conditions, mainly on temperature, so that more effective molecular symmetries can be observed in the NMR experiment for the same species. For our system molecular motions with speeds comparable to the NMR time scale include rotation of bridge aryl moiety and inverting of the *boat* conformation between two identical species. For monitoring of these dynamic processes in the solution the dynamic NMR spectroscopy was utilized. The ^1H temperature dependence (in the range of 263–383 K) il-

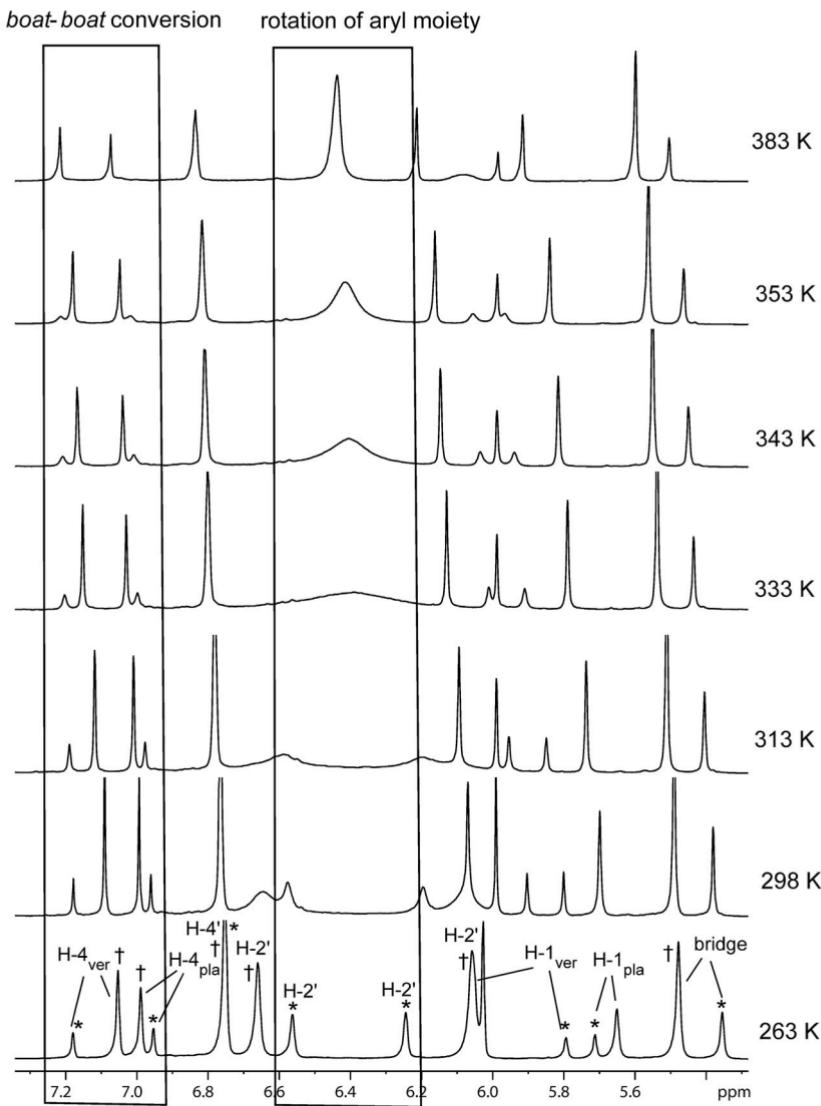


FIG. 6
Temperature dependent ^1H NMR spectra of of peracetylated resorcinarene **1c** in d_2 -1,1,2,2-tetrachloroethane; **1c**(boat-*ax*) is marked by asterisk (*), **1c**(boat-*eq*) is marked by dagger (†)

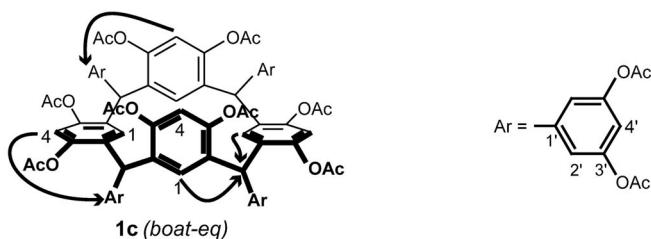
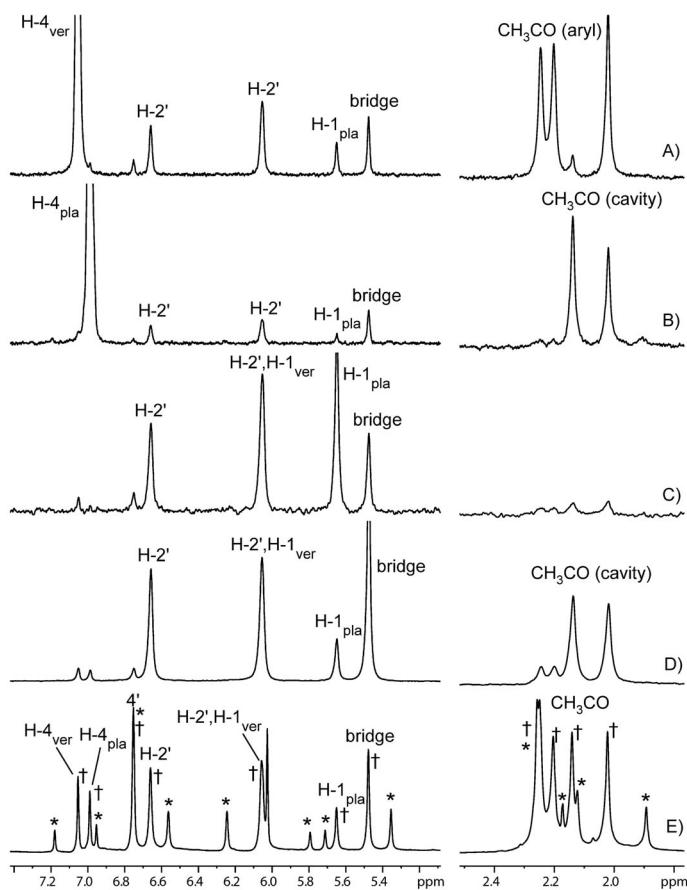


FIG. 7

Identification of resorcinarene **1c**(boat-eq); partial DPFGSE-NOE spectra with A H-4_{ver} irradiated, B H-4_{pla} irradiated, C H-1_{pla} irradiated, D bridge H irradiated, E part of ¹H NMR spectrum in *d*₂-1,1,2,2-tetrachloroethane at 263 K; **1c**(boat-ax) is marked by asterisk (*), **1c**(boat-eq) is marked by dagger (†)

lustrates the characteristic features typical for chemical exchange of cavity protons H-1 and H-4 and for bridge aromatic protons H-2' (Fig. 6). At 263 K two species, possessing C_2 symmetry in 3:1 ratio, were characterized (Figs 6, 7 and 8).

The major conformer of **1c**, being stable in the whole temperature range (Figs 6 and 7, marked with †), seems to have aryl groups in all the equatorial positions based on the following NOE connectivities: H-4_{ver}-H-2', H-4_{pla}-H-2', H-1_{pla}-H-2', H-bridge-both H-1_{ver} and H-1_{pla}, combined with the absence of H-1_{pla}-CH₃CO contact. However, it should be noted that the proximity between H-4_{ver}-H-2' and H-4_{pla}-H-2' in **1c** allows similar NOE interactions also for the *chair-ax* conformation and, thus, it is difficult to decide what is the prevalent conformation. But, on the basis of remaining, usually weak, NOE signals it can be assumed that *boat-eq* conformation is more likely preferred. The other possibility, the *chair* conformation with equatorial substituents (*chair-eq*), is too energetically demanding, which was clearly documented by molecular modelling studies, in which *boat-eq* is about 30 kJ/mol lower in energy than *chair-eq* (Fig. 9). Thus, the major conformer of **1c** adopts most likely the *boat-eq* conformation.

The minor conformer of **1c** (Figs 6 and 8, marked with *) is a subject of a conformational exchange: rather narrow resonances at low temperatures (263 K) indicate the presence of two conformers in the range of slow exchange (Fig. 6). Increasing the temperature the doubled resonances of H-1 and H-4 of the minor conformer **1c(boat-ax)** gradually broaden and finally split into one average signal, which characterizes the range of fast chemical exchange. Unfortunately, the solvent did not allowed us to increase the temperature above 363 K, consequently, the average signals of H-1 and H-4 are too broad to be clearly recognized in the spectra. The observed strong NOE contacts between H-1_{ver}-H-2' and only weak NOE contacts between H-4_{ver}-H-2' and H-4_{pla}-H-2' (Fig. 8A, 8B and 8C) allowed us to define the axial position of the bridge aryls in case of the minor conformer of **1c** at 263 K. The NOE difference spectra of the minor conformer of **1c** at this temperature contain exchange cross peaks between H-1_{ver}-H-1_{pla} (H-4_{ver}-H-4_{pla}, respectively) (Fig. 8B, 8C). This feature, analogous to that of the major conformer of **1b**, confirms the presence of an equilibrium between two identical *boat-ax* conformations of **1c**. Consequently, it was unambiguously determined that the minor conformer of **1c(boat-ax)** exhibits conformational equilibrium between two identical *boat* conformations (Fig. 8) while the major species of **1c(boat-eq)** do not allow such process.

The rotation of bridge aryl moiety, an additional dynamic process, was characterized by doubled resonances of the bridge aromatic protons H-2'

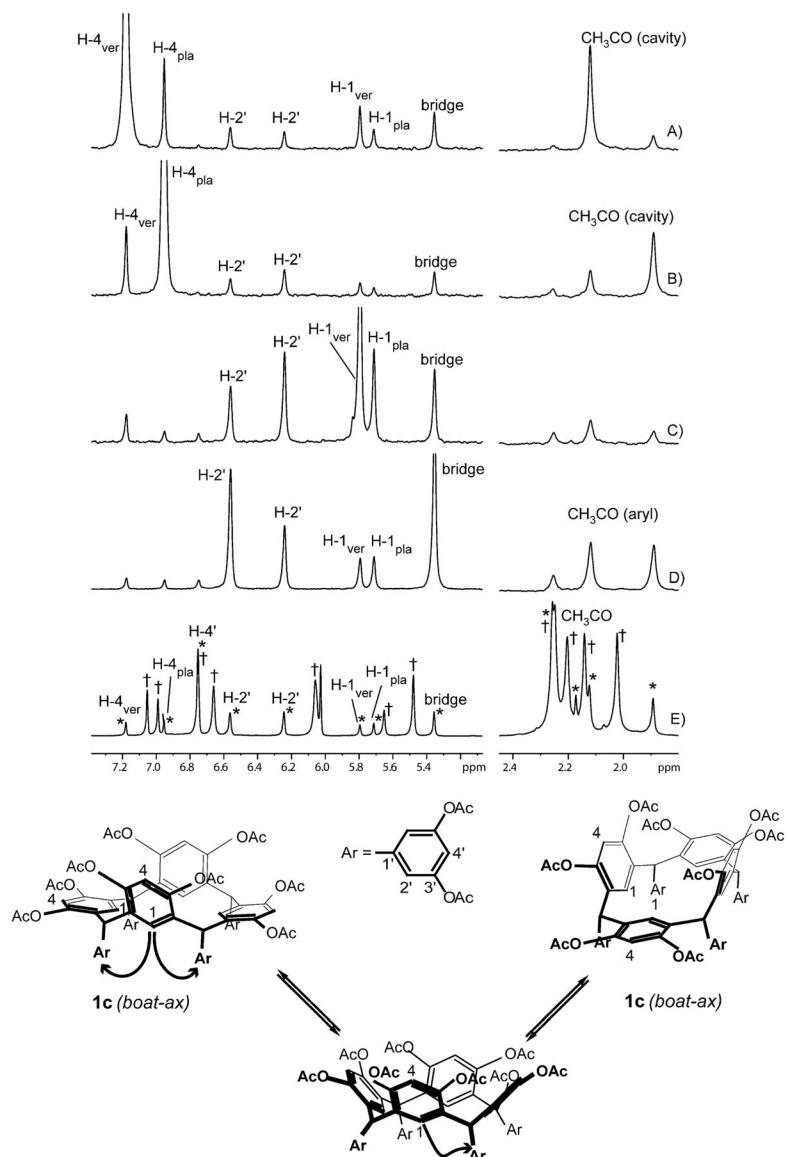


FIG. 8

Identification of resorcinarene **1c**(boat-ax); partial DPFGSE-NOE spectra with A H-4_{ver} irradiated, B H-4_{pla} irradiated, C H-1_{ver} irradiated, D bridge H irradiated, E part of ¹H NMR spectrum of **1c** in *d*₂-1,2,2-tetrachloroethane at 263 K; **1c**(boat-ax) is marked by asterisk (*), **1c**(boat-eq) is marked by dagger (†)

for both **1c**(*boat-eq*) and **1c**(*boat-ax*) isomers (Fig. 6). Thus, this dynamic process takes place regardless of the type of the conformation or the position of the bridge aryl ring.

The temperature dependence was used to calculate activation free energies ΔG^\ddagger at the coalescence temperature (T_C) of the both described dynamic processes. It is obvious that the activation free energies of both processes are significantly influenced by the steric demands of the bridge phenyl substituents. Thus, the activation free energy ($\Delta G^\ddagger = 80$ kJ/mol for $T_C = 383$ K) of the *boat-boat* conversion in **1c**(*boat-ax*) corresponds well with that of similar resorc[4]arene systems²¹ (79.5 kJ/mol); however, it is much higher than recently published for bridge alkyl substituted resorc[4]arenes^{23,24} (48.4 and 50 kJ/mol) and than of analogous *pinched cone*-*pinched cone* conversion in (thia)calix[4]arene series²⁵ (57 kJ/mol). Analogously, the activation free energy of aryl rotation ($\Delta G^\ddagger = 66$ kJ/mol for $T_C = 333$ K) corresponds well with those of calixphyrin²⁶ (68 kJ/mol) and some calix-pyrrole systems²⁷ (67–77 kJ/mol). On the other hand, the activation free energy found for phenyl bridge substituted resorc[4]arene systems²¹ (49 and 54 kJ/mol) was significantly lower.

Molecular Modelling Study

The conformational space of the studied aryl-substituted resorc[4]arene **1a**, **1b** and **1c** and transition structure connecting two *boat-ax* conformations of **1c** were investigated by multi-scale molecular modelling. A molecular mechanics (MM) force field in combination with the density functional theory (DFT) were chosen as a combination well-balancing the accuracy and the computational cost²⁸. Although the conformational search might not fully cover the conformational space, based on the experimental data we suppose that we recorded all significant trends in the conformational behaviour of the studied compounds. This is also confirmed by comparison of the computed structures to the NOE data. The most energetically favourable optimized geometries of compounds **1a**, **1b** and **1c** are depicted in Fig. 9; Table I summarizes the characteristic atomic distances.

The *boat* conformer of **1a** is predicted to be lower in energy by about 1.7 kJ/mol if compared to the *crown* conformer. Although the *crown* conformation is stabilized via the H-bonds connecting the neighbouring hydroxyl groups, such interaction could not be sufficient to overcome the steric hindrance and spatial requirements of the attached aryl rings. Hence the *boat* conformation is slightly preferred. The *boat* conformation can be stabilized by a π - π interaction as indicated by the orientation of the aromatic rings

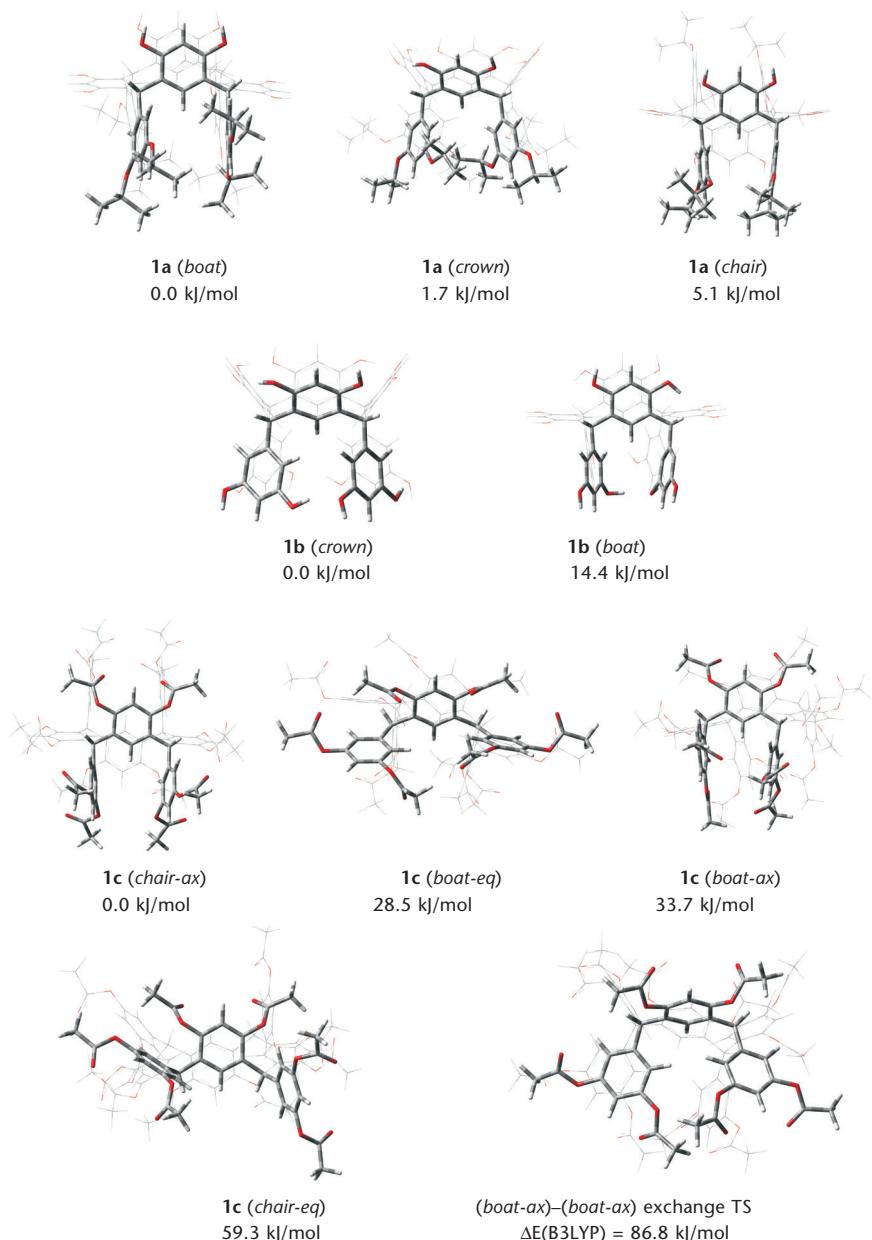


FIG. 9
The optimized geometries and relative energies of compounds **1a**, **1b** and **1c**

TABLE I
Selected atomic distances (in Å) of global minima of **1a**, **1b** and **1c**

1a			1b			
<i>crown</i>	H-1-H-2'	1.9–3.3	<i>crown</i>	H-1-H-2'	2.5–3.0	
	H-1-H-bridge	~3.8		H-1-H-bridge	~3.8	
	H-4-OH	~2.2		H-4-OH	~2.3	
	H-2'-H-bridge	2.2–3.4		H-2'-H-bridge	3.0–3.3	
	H-2'-H-CH	2.1–4.5		H-2'-OH	~2.4	
	H-2'-H-Me	2.4–4.5	<i>boat</i>	H-1 _{ver} -H-1 _{pla}	~3.3	
	H-1 _{ver} -H-1 _{pla}	~3.2		H-1 _{ver} -H-2'	2.8–3.1	
	H-1 _{ver} -H-2'	2.7–3.5		H-1 _{ver} -H-bridge	~3.6	
	H-1 _{ver} -H-bridge	~3.7		H-1 _{pla} -H-2'	2.8–3.1	
	H-4 _{ver} -OH	~2.2		H-1 _{pla} -H-bridge	~3.7	
<i>boat</i>	H-4 _{ver} -H-CH	>5.0		H-4 _{pla} -OH	~2.3	
	H-4 _{pla} -H-Me	>4.0	1c			
	H-1 _{ver} -H-1 _{pla}	~3.2	<i>boat-ax</i>	H-1 _{ver} -H-1 _{pla}	~3.0–3.4	
	H-1 _{ver} -H-2'	2.7–3.5		H-1 _{ver} -H-2'	2.8–3.3	
	H-1 _{ver} -H-bridge	~3.7	<i>boat-eq</i>	H-1 _{ver} -H-bridge	~3.6	
	H-4 _{ver} -OH	~2.3		H-1 _{ver} -H-1 _{pla}	3.6–3.9	
<i>chair</i>	H-4 _{pla} -OH	~2.3		H-1 _{ver} -H-2'	3.5–4.2	
	H-4 _{pla} -H-CH	>5.5		H-1 _{ver} -H-bridge	~2.3	
	H-4 _{pla} -H-Me	>4.5		H-1 _{pla} -H-bridge	~3.6	
	1c			H-1 _{pla} -H-4 _{ver}	~4.1	
	boat-ax			H-4 _{ver} -H-2'	>4.5	
	boat-eq			H-4 _{pla} -H-2'	~4.2	
<i>chair-ax</i>	H-1 _{ver} -H-1 _{pla}	~3.3	<i>chair-ax</i>	H-1 _{ver} -H-1 _{pla}	~3.3	
	H-1 _{ver} -H-2'	2.7–3.4		H-1 _{ver} -H-2'	2.7–3.4	
	H-1 _{ver} -H-bridge	~3.6		H-1 _{ver} -H-bridge	~3.6	
	H-1 _{pla} -H-bridge	~3.7		H-1 _{pla} -H-bridge	~3.7	
	H-1 _{pla} -H-4 _{ver}	~4.8		H-1 _{pla} -H-4 _{ver}	~4.8	
	H-4 _{ver} -H-2'	>4.5		H-4 _{ver} -H-2'	>4.5	
	H-4 _{pla} -H-2'	~3.0		H-4 _{pla} -H-2'	~3.0	

attached to resorc[4]arene backbone as well as the bridge aryls being separated by ~ 5 Å. This effect is noticed even though the standard DFT functionals describe the dispersion interactions poorly. Thus, the steric effects seem to be the driving force in the formation of *boat* conformation. Compound **1a** could in addition make weak interactions with the acetone solvent to prejudice intramolecular H-bond formation. However, the CPCM model used for the simulation of the solvent effect in connection with the theoretical level might not be capable to describe accurately all the non-bonding weak interactions. Unfortunately, the size of the studied system and the need to average many conformations make the usage of an explicit solvent unfeasible. Although the experimentally more populated conformer is crown, the calculated energy difference is very low and close to the error given by the level of DFT precision and limitations described above. Hence it can be assumed that our results approximately support the experimental observation described above. Moreover, most of distances well agree with the experiment because they can provide adequate NOE signals (Table I). The H-1_{ver}-H-1_{pla}, H-1_{ver}-H-2' and H-1_{ver}-H-bridge distances for the **1a**(*boat*) and H-1-H-2', H-1-H-bridge, H-2'-H-bridge, H-2'-H-CH, H-2'-H-Me distances in the **1a**(*crown*) correspond especially well to the observed NOE spectra.

As we were not able to distinguish unambiguously between *chair* and *boat* conformation of **1a** based on NMR measurements only, the compound **1a** in a *chair* conformation was submitted to computational procedure described above. The most favourable **1a**(*chair*) conformer is depicted in Fig. 9. Interestingly, all tracked distances in the *chair* conformer of **1a** are similar to those in the *boat* conformer (Table I) indicating why NOE spectra failed in determination of *boat* or *chair* conformation in **1a**. However, the **1a**(*boat*) is about 5.1 kJ/mol lower in energy than **1a**(*chair*) and even though this energy difference is small we suppose the *boat* conformation for the isolated less abundant stereoisomer of **1a**. Note that the crude compound **1a** was a mixture of three different conformers detected by TLC, but only two of them were separated and investigated. Based on computations we assume that the third conformer adopts the *chair* form.

In case of **1b**, the *boat* conformation is ~ 14.4 kJ/mol higher in energy than the *crown* conformation. The observed discrepancy with the experimentally preferred *boat* conformation over the *crown* can be addressed to limitations of the theoretical model. The optimal **1b**(*crown*) structure has all hydroxyl groups coupled via intramolecular H-bonds while the *boat* conformer is stabilized via π - π and OH- π interactions between the neighbouring aromatic rings and such interactions are described at the DFT level only

roughly. Moreover, the orientation of the attached aryl rings both in the *crown* and the *boat* conformer can be stabilized by intramolecular H-bonds (Fig. 9). The *crown* conformation can be destabilized by interactions of free hydroxyl groups with the solvent (d_6 -dimethylsulfoxide) which competes with intramolecular H-bonds. However, both experimentally observed conformations and calculated distances indicate the presence or the absence of particular NOE signals as was detected by NMR (Table I).

As the compound **1c** has no free hydroxyl groups, which could stabilize the cavity ring in a *crown* conformation, only the π - π and electrostatic interactions can take part. NMR detected two different conformations. The minor conformer was unambiguously identified as the *boat-ax* conformation. As for the second species NMR cannot give a definite answer, two likely conformations were investigated; the *boat-eq* conformation with aryl substituents at the bridge carbons in equatorial position as well as the *chair-ax* conformation with axially oriented substituents. The calculations for all conformers of **1c** confirmed distances allowing NOE interactions between the following atoms: H-1_{ver}-H-1_{div}, H-1_{ver}-H-2', H-1_{ver}-Hbridge (Table I). The distances between H-4_{ver}-H-2' and H-4_{pla}-H-2' in **1c(boat-ax)** are too large to provide any NOE signal, while their proximity in **1c(boat-eq)** and **1c(chair-ax)** allows a weak NOE interaction. The relatively large calculated H-4_{ver}-H-2' and H-4_{pla}-H-2' distances can be likely explained by a dynamic movement of the bridge aryl rings. Such movement can make the conformational description of the DFT static model quite unreliable because it is reflecting only minima on the potential.

The **1c(chair-ax)** conformer was found to be 33.7 kJ/mol lower in energy than the **1c(boat-ax)** conformer and 28.5 kJ/mol lower than the **1c(boat-eq)** conformer similarly to the previously described conformers of octa-O-alkyl resorc[4]arene²⁰. The relatively higher energy difference (compared to **1a**) between the *chair-ax* and *boat-eq* conformations suggests that the major conformer of **1c** could be the *chair-ax*, but it does not agree with experimental conclusions. On the other hand, the presumption of the *chair* conformation being the second experimentally observed **1c** structure is strengthened by the almost equal H1_{ver}-H-bridge and H-1_{pla}-H-bridge distances found in the calculated *chair-ax* which correspond to the equally small NOE signals (Fig. 7). However, almost all other distances in both *boat-eq* and *chair-ax* conformations were found to be very similar. Hence a more apparent and precise decision about the **1c** unknown conformation cannot be made at this point with the static model presented in the work. Despite this, many other similar substituted resorcinarenes have been determined to adopt the *chair-ax* conformation^{1,5,15,16,18,19,21} and in case of

methylresorc[4]arenes²² symmetrical *chair* conformers in the crystalline state were found. Hence it is more probable that the unknown species of **1c** also adopts the *chair-ax* conformation.

The modelling provided one transition-conformer related to the conversion between two identical **1c**(*boat-ax*) conformers. Analogous transition in **1c**(*boat-eq*) is blocked by the presence of the bulky aryl rings in equatorial position. The transition is predicted to be realized by one step synchronous rotation of all four cavity rings. The reaction pathway goes through a saddle point resembling a deformed *crown* conformation. The C-4–C-4 distance was changing from the initial value of 4.8 Å (C-4_{ver} position) to 9.0 Å corresponding to the transition state. Then the distance was increasing until the final value of about 10.6 Å, which corresponds with the C-4_{pla}–C-4_{pla} position. The computed energy difference (B3LYP/6311±G**//AM1) for this conversion is ~86.8 kJ/mol, which is in a good agreement with the experimentally observed value. Small error is similar to this reported for the *pinched cone–pinched cone* transition of thiocalix[4]arenes²⁵. The transition state determined by AM1 may also contribute to the overall error, as this semiempirical method is known to lack some weak interactions. But it is surprising that the energy difference based on simple AM1 energies is about 83.1 kJ/mol and well corresponds to the experiment too. The reduction of the theoretical level was necessary because the systems studied in the present work were bigger (188 atoms for **1c**) and conformationally more complex than those reported previously^{24,25}. The quantitative agreement between the calculated and the measured data might be slightly hampered by the approximate solvent model. Nevertheless, we can conclude that the main experimental data and the observed conformational behaviour are well-explained by the calculations, including the ΔG^\ddagger Gibbs energy of the *boat-boat* conversion.

CONCLUSION

In this work we have shown that the conformational distribution decoding in the reaction mixtures of aryl functionalized resorc[4]arenes is not a simple task. On the basis of NMR spectroscopy and molecular modelling it was shown that the conformational behaviour of aryl functionalized resorc[4]arenes **1a**, **1b** and **1c** is significantly influenced by weak interactions. The mixing of intramolecular hydrogen bonds of hydroxyl groups in close proximity, π – π interactions between bridge aryl rings and by OH– π interactions within the neighbouring aromatic cavity units, respectively, rule the stability and hence the distribution of conformers.

The symmetrical (C_{4v}) *crown* conformation was identified in compounds **1a** and **1b** possessing the hydroxyl groups at the upper rim. The second conformer of **1a** and **1b** was identified by NMR as *boat* with aryl rings in axial position and the conformational equilibrium between two identical C_2 symmetrical species was observed for **1b**(*boat-ax*). The formation of hydrogen bonding array was not the key driving force leading to the predominant *crown* conformation in compounds **1b** as the *boat* conformer prevailed. The calculated energy differences between the possible conformers of **1a** are very low, thus the remaining unisolated **1a** species might be a *chair* stereoisomer. The compound **1c** is flexible at room temperature and two C_2 symmetrical conformers were identified only at 263 K. Both conformers of **1c** exhibit aryl ring rotation ($\Delta G^\ddagger = 66$ kJ/mol for $T_C = 333$ K). The minor **1c**(*boat-ax*) product exhibits dynamic equilibrium between two identical *boat* conformations. The energy barrier of the conversion ($\Delta G^\ddagger = 80$ kJ/mol, $T_C = 383$ K) acquired by dynamic NMR spectroscopy is in a good agreement with that obtained by quantum chemical calculations (~87 kJ/mol). The determination of the major conformation of **1c** was not unambiguous. NOE data indicated the *boat* conformation with bridge aromatic rings in equatorial positions. However, based on the molecular modelling it was found that *chair-ax* conformer could exhibit atom distances resulting in similar NOE patterns as *boat-eq* conformation but with lower electronic energy. On the other hand, due to the lower level of computational approach imposed by the system size, an anticipated error in energy could be in order of few kJ/mol and hence change the conformational sorting. Moreover, the limitation to the static model increases a possibility of errors.

We have shown that the conformational predictions based on the standard NOE analysis must be interpreted with care, as many factors influence the conformation of such big and flexible resorc[4]arene core. Even if the NOE is coupled with a molecular modelling the predictions could not be unambiguous. The solid state structure could be undoubtedly proved by crystallography but even in this case the conformation depends on the crystallization²². Thus, any definite statements should be critically judged with regard to the limitation of used methods. In this work the number of conformations, a particular functionalized resorc[4]arene can potentially adopt, is for example vast and is influenced actually by kinetic or thermodynamic control of the cyclization²⁰.

In general, a knowledge about conformational distributions and forces influencing any structural preferences could help to design a proper models for studying the binding properties of aryl substituted resorc[4]arenes.

EXPERIMENTAL

Solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa. Reactions were monitored using thin-layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F₂₅₄ silica gel. The compounds on TLC plates were visualized using UV radiation at 254 nm or by spraying with 1% cerium(IV) sulfate in 10% sulfuric acid and subsequent mineralization. Column chromatography was carried out on silica gel (100–160 µm, Merck). All solvents were dried prior to distillation and stored over molecular sieves. Resorcinol and 3,5-dihydroxybenzaldehyde were purchased from Sigma–Aldrich, 3,5-diisopropoxybenzaldehyde was prepared and identified according to published synthesis²³. The NMR spectra (δ , ppm; J , Hz) were measured on a Bruker DRX 500 Avance spectrometer operating at 500.1 MHz for ¹H and 125.8 MHz for ¹³C. Chemical shifts were referenced to Me₄Si. Typically, a spectral width of 7500 Hz, a size of 32k data points, a recycle time of 3.2 s and 16 scans were used. ¹³C NMR spectra were measured with a spectral width of 25000 Hz, 32k data points, a recycle time of 2.7 s and 5000 scans. Assignment was accomplished by means of 2D ¹H COSY, 2D ¹H–¹³C HMQC, 2D ¹H–¹³C HMBC and 1D-DPF GSE NOE experiments. 2D COSY was used for resolving ¹H spin systems (64 t1-increments for 1024 (1k) data points, 16 scans, and spectral widths of 3000–4000 Hz). One and three bond ¹H–¹³C connectivities for the assignment of carbon resonances were determined using 2D HMQC (128 t1-increments for 1k data points, spectral widths of 4 kHz (¹H) and 22.6 kHz (¹³C), 64 scans, a polarization transfer delay of 3.5 ms) and HMBC (128 t1-increments for 1k data points, spectral widths of 4 kHz (¹H) and 22.6 kHz (¹³C), 64 scans, polarization transfer delay) techniques. FAB MS spectra were measured on a ZAB-EQ VG analytical spectrometer. Spectra in acetonitrile solutions were recorded with a Q-TOF Micro (Waters-Micromass) with electrospray ionization in negative mode.

Dynamic NMR Study

For dynamic NMR study, temperature dependent ¹H NMR measurements were carried out. All studied compounds were measured in the temperature range of 163–298 K in CD₂Cl₂ (99.8% D, Merck, Germany). Activation free energies (ΔG^\ddagger) were determined using Eyring equations 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 gas constant, h is the Planck constant and $\Delta \nu$ is the chemical shift difference of the exchanging resonances in the absence of chemical exchange.

Computational Details

All electronic structure calculations were performed using the Gaussian 03 program³¹. The Molecular Mechanic studies were carried out using the MacroModel program³². Conforma-

tional space investigation at the force field level of all weighed forms of compounds **1a**, **1b** and **1c** (*crown*, *boat* and *chair*; with axial or equatorial substituents) was determined by a Monte Carlo (MM/MC) random variation of the torsion angles followed by the optimization with the MMFFs force field³³. The number of trial steps was set sufficiently high to ensure that all possible conformers were located. Localized minima under the energy cut-off of 50 kJ/mol in static approach were subsequently optimized at the DFT level with the standard Becke's hybrid functional³⁴ with three parameters B3LYP and 6-31G** basis set. Local minima of each structure (*crown/boat/chair*; **1a**, **1b**, **1c**) were then submitted to the single-point calculation at the B3LYP/6-311±G** level. The CPCM model was included in order to estimate the solvent effect.

A step-by-step driving changes and constraints on selected coordinate at the semi-empirical AM1 level were used for the description of the molecular transition between two *boat-ax* conformations of **1c**. The distance between the carbon atoms 4 on the upper rim of two opposite aromatic rings of resorcinarenes was increased or decreased and constrained, while the remaining part of the molecule was fully optimized. Energies of all important stationary points were then recalculated at the B3LYP/6-311±G**/CPCM level. The input geometry for the *boat-ax* **1c** geometry was taken from the preceding calculations. Selected stationary points of all investigated systems were confirmed by a vibrational analysis within the harmonic approximation at the B3LYP/6-31G** level.

Tetrakis(3,5-diisopropoxyphenyl)resorc[4]arene **1a**

Resorcinol (178 mg, 1.62 mmol) and 3,5-diisopropoxybenzaldehyde (360 mg, 1.62 mmol) were dissolved in ethanol (10 ml) and heated to 60 °C. Hydrochloric acid (1.4 ml) was added dropwise and the dark green mixture was stirred for 3 h at 60 °C. The mixture was allowed to cool to room temperature and water (10 ml) was added. Reaction mixture was then cooled to 4 °C and the precipitate was isolated, washed with water and dried in vacuum to give product **1a** (249 mg, 49%) as amorphous powder. TLC (chloroform:methanol 8:1) revealed the presence of three conformers with R_F 0.50, 0.55 and 0.60. Flash chromatography on silica gel with chloroform and then methanol gradient afforded major *crown* conformer (130 mg, R_F 0.60) in overall yield of 26% followed by less abundant *boat* conformer (71 mg, R_F 0.50) in overall yield of 14%.

1a. MS (ESI): m/z 1255 [M - H]⁻; MS (ESI): m/z 1257 [M + H]⁺. HRMS calculated for $[C_{76}H_{88}O_{16} + Na]^+$ 1279.5970; found 1279.6031.

1a(crown). 1H NMR ((CD₃)₂CO): 7.01 br s, 1 H (OH); 6.31 s, 4 H (H-4); 6.24 s, 4 H (H-1); 6.06 s, 4 H (H-4'); 6.02 s, 8 H (H-2'); 5.62 s, 4 H (bridged H); 4.34 hept, 8 H, J = 6.0 (CH(CH₃)₂); 1.26 d, 48 H, J = 6.0 (CH(CH₃)₂). ^{13}C NMR ((CD₃)₂CO): 158.26 (C-3'); 153.53 (C-3); 145.97 (C-1'); 130.53 (C-1); 121.25 (C-2); 108.74 (C-2'); 102.37 (C-4); 100.36 (C-4'); 68.69 (CH(CH₃)₂); 43.87 (bridged C); 21.71 (CH(CH₃)₂).

1a(boat). 1H NMR ((CD₃)₂CO): 7.64 s, 1 H (OH); 7.20 s, 1 H (OH); 6.68 s, 2 H (H-1); 6.44 s, 2 H (H-4); 6.38 s, 2 H (H-4); 5.96 m, 12 H (H-2', H-4'); 5.83 s, 4 H (bridged H); 4.34 hept, 8 H, J = 6.0 (CH(CH₃)₂); 1.26 d, 48 H, J = 6.0 (CH(CH₃)₂). ^{13}C NMR ((CD₃)₂CO): 158.96 (C-3'); 154.47 and 153.81 (2 \times C-3); 146.87 (C-1'); 132.52 and 131.17 (2 \times C-1); 122.80 and 122.10 (2 \times C-2); 109.51 (C-2'); 103.51 and 102.97 (C-4); 101.87 (C-4'); 69.37 (CH(CH₃)₂); 43.76 (bridged C); 22.47 (CH(CH₃)₂).

Tetrakis(3,5-dihydroxyphenyl)resorc[4]arene **1b**

Starting from resorcinol (406 mg, 3.69 mmol) and 3,5-dihydroxybenzaldehyde (510 mg, 3.69 mmol) and using described procedure⁵ a mixture of resorc[4]arene **1b** conformers (2:1) was obtained (285 mg, 34%) as amorphous powder. ¹H NMR ((CD₃)₂SO): minor **1b**(crown): 6.32 s, 4 H (H-1); 6.12 s, 4 H (H-4); 5.82 s, 4 H (H-4'); 5.73 s, 8 H (H-2'); 5.50 s, 4 H (bridged H); major **1b**(boat): 6.28 s, 2 H (H-1); 6.24 s, 2 H (H-4); 6.17 s, 2 H (H-4); 6.10 s, 2 H (H-1); 5.80 s, 4 H (H-4'); 5.64 s, 8 H (H-2'); 5.42 s, 4 H (bridged H). ¹³C NMR ((CD₃)₂SO): 157.39, 153.51, 153.19, 153.02, 147.74, 147.55 (C-3, C-3', C-1'); 132.13 and 131.0 (C-1); 121.07 (C-2); 108.09 and 107.83 (C-2'); 102.61, 102.39, 102.14 and 99.85 (C-4 and C-4'); 42.04 (bridged C). MS (ESI): *m/z* 919 [M - H]⁻; MS (ESI): *m/z* 921 [M + H]⁺. HRMS calculated for [C₅₂H₄₀O₁₆+H]⁺ 921.2395; found 921.2411.

Tetrakis(3,5-diacetoxyphenyl)octa-O-acetylresorc[4]arene **1c**

Resorc[4]arene **1b** (100 mg, 0.11 mmol) was dissolved in pyridine (2 ml) and acetic anhydride (0.5 ml) was added. The mixture was stirred for 2 h at room temperature and concentrated in vacuum. Product **1c** (174 mg, 99%) as a mixture of two conformers in ratio 3:1 was obtained by flash chromatography on silica gel using mixture chloroform-methanol (10:1) as an eluent. ¹H NMR (C₂D₂Cl₄, -10 °C): boat I: 7.05 s, 2 H (H-4_{ver}); 6.95 s, 2 H (H-4_{pla}); 6.75 s, 4 H (arom.); 6.66 s, 4 H (arom.); 6.06 s, 4 H (arom.); 6.06 s, 2 H (H-1_{ver}); 5.65 s, 2 H (H-1_{pla}); 5.48 s, 4 H (bridged H); 2.25, 2.20, 2.14, 2.02 4 × s, 48 H (16 × CH₃CO); boat II: 7.18 s, 2 H (H-4_{ver}); 6.95 s, 2 H (H-4_{pla}); 6.75 s, 4 H (arom.); 6.56 s, 4 H (arom.); 6.24 s, 4 H (arom.); 5.80 s, 2 H (H-1); 5.71 s, 2 H (H-1); 5.36 s, 4 H (bridged H); 2.26, 2.17, 2.12, 1.89 4 × s, 48 H (16 × CH₃CO). ¹³C NMR (C₂D₂Cl₄, 25 °C): boat I: 168.29, 168.10 (2 × CH₃CO); 150.90 br (C-3'); 147.11, 146.93 (2 × C-3); 141.13 (C-1'); 131.00, 129.41 (2 × C-1); 131.11, 130.90 (2 × C-2); 119.04 (C-2'); 117.24, 116.88 (2 × C-4); 113.32 (C-4'); 44.20 (bridged C); 20.98, 20.98, 20.26, 20.58 (CH₃CO); boat II: 168.37, 168.16 (2 × CH₃CO); 150.90 br (C-3'); 147.73, 147.38 (2 × C-3); 142.58 (C-1'); 132.10, 129.31 (2 × C-1); 130.28, 130.11 (2 × C-2); 119.04 (C-2'); 117.59, 116.08 (2 × C-4); 113.38 (C-4'); 44.77 (bridged C); 20.64, 20.22 (CH₃CO); the other CH₃ are overlapped. MS (ESI): *m/z* 1616 [M + Na]⁺, 819 [M + 2 Na]²⁺. HRMS calculated for [C₈₄H₇₂O₃₂ + Na]⁺ 1516.3904; found 1516.3956.

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