

CHEMISTRY A European Journal



Accepted Article Title: Correlating solution and solid state structures of conformationally flexible resorcinarenes - the significance of a sulfonyl group in intramolecular self-inclusion Authors: Małgorzata Pamuła, Maija Nissinen, and Kaisa Helttunen This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article. To be cited as: Chem. Eur. J. 10.1002/chem.201905211 Link to VoR: http://dx.doi.org/10.1002/chem.201905211 **Supported by**

Supported by ACES



Correlating solution and solid state structures of conformationally flexible resorcinarenes – the significance of a sulfonyl group in intramolecular self-inclusion

Małgorzata Pamuła,^[a] Maija Nissinen^[a] and Kaisa Helttunen*^[a]

Abstract: In this study, the synthesis of tetramethoxy resorcinarene podands bearing p-toluene arms connected by -SO₃- (1) and -CH₂O-(2) linkers is presented. In the solid state, the resorcinarene podand 1 forms an intramolecular self-inclusion complex of the p-toluene group, whereas the resorcinarene podand 2 did not show selfinclusion. The conformation of the flexible resorcinarene podands in solution was investigated by 1D and 2D NMR spectroscopic techniques using variable temperature experiments, as well as, with computational methods including conformational search and subsequent density functional theory (DFT) optimization for representative structures. The ¹H NMR spectra of 1 and 2 at room temperature show a single set of proton signals that are in agreement with C_{4v} -symmetry. At low temperatures the molecules exist as a mixture of boat conformations featuring slow exchange on the chemical shift time scale. An energy barrier ($\Delta G^{\ddagger_{298}}$) of 55.5 kJ/mol and 52.0 kJ/mol was calculated for the boat-to-boat exchange of 1 and 2, respectively. The results of the ROESY experiments performed at 193 K and computational modelling suggest that in solution the resorcinarene podand 1 adopts similar conformation to that present in its crystal structure, whereas podand 2 populates more versatile range of conformations in solution.

Introduction

Inclusion complexes, along with control of self-inclusion behaviour, play an essential role in the preparation and function of self-assembled nanomaterials.^[1-3] In supramolecular chemistry, macrocyclic hosts are important building blocks providing cavities for inclusion complexation thereby enabling the self-assembly of multiple supramolecular architectures. These supramolecular assemblies range from simple 1:1 inclusion complexes and pseudorotaxanes,^[4,5] to polymers^[6–9] and particles^[10,11] featuring in some cases gelation properties.^[12] In particular, supramolecular polymers attract increasing interest

 Małgorzata Pamuła, Prof. Maija Nissinen, Dr. Kaisa Helttunen Department of Chemistry, Nanoscience Center University of Jyvaskyla
 P.O. Box 35, FI-40014 University of Jyvaskyla, Finland
 E-mail: kaisa.j.helttunen@jyu.fi

Supporting information for this article is given via a link at the end of the document.

due to their unique properties of self-healing,^[13] stimuliresponsiveness^[14] and shape memory.^[15]

Intermolecular self-inclusion is most often detected in crystal structures. Self-included dimers have been obtained in several crystal structures of calixarene macrocycles, such as deep cavitands,^[16] thiacalix[4]arenes,^[17] and *N*-alkyl resorcinarene halides.^[18,19] In addition, there are few examples of crystalline calixarenes featuring chains with head-to-tail intermolecular self-inclusion behaviour.^[20,21] In contrast, intramolecular self-inclusion requires 180° degree back folding of a part of the compound, typically a covalent host-guest conjugate or a macrocycle equipped with conformationally flexible functional groups. However, crystal structures of intramolecular self-inclusion monomers are relatively rare.^[6,22,23]

Control of intermolecular self-inclusion is important for the preparation of supramolecular materials and self-assembled structures. Few examples of pillararenes show a concentrationdependent transition from intramolecular to intermolecular selfinclusion in solution, which is utilized for reversible self-assembly of dimers or supramolecular polymers.^[6,24] An interesting example of self-inclusion complexation in the solid state is a pillar[5]arene derivative, which breaks when dissolved in a solvent of small molecular size but remains intact in a larger molecular size solvent. [25] Similarly, a pillar[5]arene based pseudo[1]rotaxane that forms a self-inclusion complex in the solid state shows solvent responsive self-inclusion in solution.^[4] Other examples of self-inclusion include cyclodextrins, which exhibit self-inclusion properties when the inclusion of bulky end groups leads to the formation of pseudo[1]rotaxane,[5] cucurbiturils with a pendant residue acting as hydrophobic guest,[11] and monosubstituted resorcinarenes^[26,27] and covalently linked dimeric resorcinarene capsules^[28] displaying intramolecular self-inclusion properties in solution.

Self-inclusion can also be undesired for the designed function of a molecular receptor or the self-assembly of supramolecular aggregates. In the case of a bambusuril anion receptor, solid state intramolecular self-inclusion was observed, and it was expected to lower its affinity for guest binding, even though selfinclusion could not be detected in solution.^[29] Intramolecular selfinclusion of a β -cyclodextrin was prevented by attaching a bridge across the narrow rim thus effectively promoting the competitive supramolecular polymerization.^[30]

Resorcinarene podands are macrocycles in which the upper rim hydroxyl groups of the parent resorcinarene have been functionalized, resulting in conformationally flexible octopus-like structures. In contrast to resorcinarene cavitands with a covalently bridged C_{4v} -symmetrical crown conformation, resorcinarene podands typically exhibit a C_{2v} -symmetrical boat conformation in the solid state.[†] The boat conformation is

defined by two resorcinol rings being almost vertically opposed and the two remaining ones horizontally aligned. Previously, self-inclusion dimers of resorcinarene tetrapodands have been observed by us ^[31,32] and others.^[33–36] Nevertheless, resorcinarene podands tend to display collapsed cavities in the solid state.^[37–45]

Crystal structures of conformationally flexible macrocycles lead to a guestion of how to correlate the solid state structure to the conformation of the molecule in solution. Herein, we have addressed this problem by synthesizing two resorcinarenes bearing four p-toluene podand arms connected with sulfonyl or benzoyloxy linkers to provide similar length but different hydrogen bond donor/acceptor properties. The single-crystal Xray structure of the sulfonyl linked podand 1 displays intriguing self-inclusion complex, where a cavity forms around the included arm, which is bound by weak hydrogen bonds. To the best of our knowledge, this is the first example in which a resorcinarene podand forms a self-inclusion complex stabilized only by weak C-H···O hydrogen bonding and C-H··· π interactions. We envision that this structure is rare since it requires inclusion complexation of a pendant p-tolyl group in a non-preorganized nor permanent aromatic cavity. Indeed, we found only one self-inclusion example of complex of а а tetramethoxyresorcinarene Schiff base stabilized by NH···O hydrogen bonds in the CSD database.^[23] The electron rich and electron poor linker moieties (i.e. sulfonyl and -CH2O- groups) included in the podand arms of resorcinarenes 1 and 2, respectively, provide opposite tendencies to weak electrostatic interactions. This allowed us to carry on extensive structural analysis using computational and experimental methods to model the relationship of the crystal structures of 1 and 2 with their conformations in solution. The results show that the solution structure of 1 correlates well with the conformation adopted by the molecule in its crystal structure, whereas 2 populates different types of low energy conformations with possibility to self-inclusion according to computational structures.

Results and Discussion

Synthesis

Resorcinarene podand **1** was prepared by alkylation of the free hydroxyl groups of racemic tetramethoxyresorcinarene (**3**)^[46] with four (2-tosyloxy)-ethoxy (**6**) podand arms according to the literature procedure.^[47] In the podand arm of **1**, a sulfonyl group (-SO₃-) connects the tolyl ring with the **1**,2-dioxyethane chain. In order to prepare an analogous compound to the resorcinarene podand **1** without the sulfonyl group, resorcinarene podand **2** was synthesized by alkylation of **3** with four 2-((4methylbenzyl)oxy)ethyl tosylate arms (**5**) in 44 % yield (Scheme **1**). In the podand arm of **2**, a -CH₂O- group provides similar length but lacks the hydrogen bond acceptor properties of **1**. The tosylate (**5**) was prepared in two steps from 4-methyl benzylchloride and ethylene glycol. The resorcinarene podands were fully characterized by a complete set of high-resolution NMR spectra, ESI-MS, and single crystal X-ray diffraction.

X-ray crystallography

Resorcinarene podand **1** was isolated after column chromatographic purification and formed single crystals suitable for X-ray diffraction analysis from ethyl acetate/hexane solution. The crystal structure shows that in this case, the resorcinarene macrocycle **1** adopts a boat conformation with two opposed resorcinol rings being almost vertically oriented and the other two horizontally aligned. This conformation is typical for octafunctionalized resorcinarenes lacking a permanent aromatic cavity. Remarkably, in the case of resorcinarene **1** the adopted boat conformation defines an aromatic cavity, which is filled by intramolecular self-inclusion of one of the terminal tolyl sulfonyl substituents of the podand arms.



Scheme 1. Synthesis of tetramethoxy resorcinarene podands 1 and 2 showing NMR assignments. For simplicity, only one enantiomer of the tetramethoxy resorcinarene is shown. Reaction conditions: a) Cs₂CO₃, acetonitrile, dibenzo-18-crown-6; b) KOH, ethylene glycol; c) *p*-toluenesulfonyl chloride, triethylamine, dichloromethane.

WILEY-VCH



Figure 1. X-ray structure of a,b) self-inclusion complex of resorcinarene podand 1 indicating weak hydrogen bonds with dashed lines and OCCO dihedral angles, c) an overlay of XRD (cyan) and DFT energy minimized structure of the lowest energy conformation 1-I, d) resorcinarene podand 2 showing weak hydrogen bonds with dashed lines and C-centroid distances with black arrows, e) an overlay of XRD (cyan) and DFT energy minimized structure (red) of 2-I. Atom colors: C = grey, H = white, S = yellow, O = red. Distances are in Ångströms.

In particular, the self-inclusion takes place with one of the arms attached to one of the two vertically oriented resorcinol rings (Fig. 1). The included tolyl sulfonyl group resides at a distance of 3.10-3.45 Å from the vertical resorcinol walls indicating the presence of C-H… π interactions between them.

The self-inclusion complex is supported by two intramolecular C-H···O bonds from the *p*-methyl group to the resorcinol oxygens of vertical resorcinol rings ($d_{H \cdots O} = 2.57-2.60$ Å). In addition, the oxygen atoms of the sulfonyl group in the included arm reside within 2.73–2.79 Å distance from the methoxy and ethoxy protons of one of the two horizontally oriented resorcinol rings.

The two podand arms attached to the horizontal resorcinol rings are wrapped around the resorcinarene cavity. The arms have, however, different dihedral angles of the ethoxy groups. In one arm OCCO torsion of $+70^{\circ}$ induce an intramolecular 2.62 Å contact between methoxy proton and sulfonyl oxygen on one side (Fig. 1a-b) and rotation of the tolyl group towards the lower rim. On the other side, the OCCO torsion of -72° places the corresponding sulfonyl oxygen away from the cavity where it forms weak intermolecular hydrogen bonds. The fourth podand arm attached to a vertical resorcinol ring folds to the side of the molecule, engaging in weak intermolecular interactions.

In order to compare the role of the sulfonyl group in the crystal structure of the podand **1**, single crystals of resorcinarene podand **2** were grown from an ethanol solution. The crystal structure of **2** contains two resorcinarene molecules per asymmetric unit, both adopting a boat conformation. In contrast to resorcinarene **1**, the vertically aligned resorcinol rings lean towards each other, reducing the size of the aromatic cavity of resorcinarene **2** (Fig. 1d). The podand arms attached to the vertical resorcinol rings fold above the horizontal resorcinol rings placing the benzylic carbons at 3.38–3.77 Å distance from the aryl ring centroids. The cavity is sealed with intramolecular C-H…O contacts between tolyl ring protons (*ortho* to the CH₂O

substituent) and methoxy oxygens of vertical resorcinol rings $(d_{H\cdots O} = 2.65-2.82 \text{ Å})$. The podand arms connected to the horizontal resorcinol rings extend away from the cavity and form edge-to-face $\pi \cdots \pi$ interactions with tolyl arms of adjacent molecules. It should be noted that the second molecule in the asymmetric unit forms a weak intermolecular hydrogen bond from the *p*-tolyl group attached to the vertical resorcinol ring to podand arm oxygen of a neighboring molecule (see SI).

Computational studies

Conformational search and energy minimization with molecular mechanics was performed using OPLS3e force field and implicit solvent model to generate potential conformations for the resorcinarene podands. The search found 460 potential conformations for podand 1. In all of these, one vertical arm was folded inside the cavity similarly to the conformation observed in the crystal structure. The conformations were divided into five categories depending on the folding of the horizontal podand arms and in particular, the OCCO dihedral angles (Fig. 2). In class I) both OCCO torsions are positive giving rise to two Hs...O contacts, in class II) one OCCO torsion is positive and one is negative resulting in one Hs...O contact, in class III) both OCCO torsions are negative, in class IV) horizontal arm proximal to the included vertical sulfonate group does not fold around the cavity, and in class V) the horizontal arm distal to the included sulfonate group does not fold around the cavity.

The lowest energy examples of each class were submitted to DFT geometry optimization using an implicit solvent model to compare the relative energy differences of each representative conformation (1-I–1-V) at a higher level of theory. The order of the relative energies remained the same as in the force field energy minimization (Fig. 2a).

The conformational search for podand **2** found 495 potential conformations. In most of these conformations, a vertical

podand arm was backfolded towards the cavity. These structures were divided in three categories. In class 2-I) one horizontal arm was folded on top of the cavity, in class 2-II) both horizontal arms were folded on sides of the cavity, and in class 2-III) one horizontal arm was backfolded. In addition, the search found 16 open conformations (class 2-IV) without self-inclusion and seven examples of horizontal podand arm folding into the cavity (class 2-V) indicating more versatile range of potential conformations than those found for 1. Interestingly, the benzylic protons of the vertical aryl rings are directed towards the horizontal resorcinol rings both in open (2-IV) and self-inclusion conformations (2-I-2-III). This results in a notable difference in the position and angle of the self-included tolyl group in 2 in contrast to 1. In 2 the tolyl group is positioned higher relative to the aromatic cavity and the p-methyl group is pointing up whereas in 1 it points down.

The order of the relative energies in structures 2-I-2-V changed after DFT optimization with PBE0-D3 functional, however, structure 2-I with self-inclusion of a vertical podand arm remained as the lowest energy conformation. In order to confirm the result, optimization was repeated with another popular DFT functional (B3LYP-D3), which found the same trend in energies but significant discrepancy in absolute values along with some structural changes in optimized geometries (SI). This suggests that the potential energy landscape of podand 2 is more versatile than that of podand 1 containing many local minima.

¹H NMR experiments

The conformational characterization of the resorcinarene podands 1 and 2 in solution was carried out using NMR spectroscopy. Our aim was to assess how the crystal structures of these conformationally flexible molecules reflect into the conformation adopted in solution. The ¹H NMR spectrum of the tetratolyl resorcinarene 2 at 303 K in CD₂Cl₂ (Fig. 3) displays a single triplet for the methine bridges (H_{i,v}), a unique singlet for the methoxy groups (H_{g,s}) and two separate singlets for aromatic protons of the resorcinol rings $(H_{h,t}, H_{i,u})$. The number and

multiplicity of the proton signals is in agreement with a C4vsymmetry, which probably results from the chemical exchange process between two boat conformation being fast on the ¹H NMR chemical shift time scale. The two multiplets observed at δ = 3.7 and 4.0 ppm, respectively, were assigned to the protons of the methylene group alpha to the phenol oxygen atom that resonate as diastereotopic signals (H_{f,r}). An AB quartet at 4.5 ppm was assigned to the -CH2O- methylene protons alpha to the toluene ring (H_{d,p}). In addition to the two singlets of the aromatic resorcinol protons, two sharp doublets corresponding to the protons of the tolyl rings (H_{b,n} and H_{c,o}) appear in the aromatic region of the spectrum.

At room temperature, the tetratosylate resorcinarene (1) exhibited a similar ¹H NMR spectrum. The most significant difference was the observation of the methylene protons alpha to the sulfonyl group in **1** appearing as a well-defined triplet at δ = 4.18 ppm. The analogous signal for the methylene protons alpha to the benzyloxy substituent in 2 resonated slightly upfield shifted (δ =3.65 ppm) owing to a reduction in the inductive effect



5.5 4.5 3.5 7.5 7.0 6.5 6.0 5.0 4.0 3.0 2.5 2.0 1.5 1.0 ppm Figure 3. ¹H NMR spectra of resorcinarene podands in CD₂Cl₂ a) 1 at 193 K, b) 1 at 303 K, c) 2 at 193 K and d) 2 at 303 K. Blue letters refer to protons in the horizontally aligned resorcinol ring and red letters to the vertically opposed ring and attached groups.







WILEY-VCH

We also measured the ¹H NMR spectra of **1** and **2** at different temperatures (303–193 K) to investigate the structural and dynamic properties of the resorcinarene podands at low temperatures, and to determine energy barriers for the conformational exchange (Fig. 3 and SI). In addition, samples with concentrations between 1–12 mM were measured at 193 K to confirm that no dimerization was observed in this concentration range used for the variable temperature experiments.

In case of 2, there were no significant changes either in the shape or in the position of the proton signals when temperature was lowered to 283 K (see SI). As the temperature was further decreased to 263 K the singlet from the lower rim protons (H_{i,u}) broadened significantly due to the slowing of the conformational exchange of the two boat conformations close to the NMR chemical shift timescale. At 243 K, coalescence for the upper rim protons (H_{h,t}) and the methoxy groups was observed.Within the temperature range of 223-193 K new peaks at the aromatic region and at 3.3-4.7 ppm appeared and sharpened thereby giving rise to three singlets for resorcinol rings (fourth signal overlapping with the tolyl signals at 7.12 ppm based on ROESY, see SI), one signal for methine bridges $(H_{i,v})$ and two singlets for methoxy groups. In addition, a broad doublet with integrals of 4 protons at 7.26 ppm and a multiplet of 14 protons at 7.12 ppm were observed for the tolyl groups H_c and H_b/H_n/H_o, respectively. The number and multiplicity of the proton signals at 193 K indicates that the podand adopts a C_{2v}-symmetrical boat conformation.

The results of the ¹H variable temperature experiments of resorcinarene 1 were very similar to those obtained with 2. Coalescence was observed at 243 K suggesting similar energy barrier for the boat-to-boat exchange to the one determined for 2. However, below coalescence temperature, the lower rim methyl signal was split into two broad triplets (H_x and H_i) and methine bridges appeared as two separate signals (H_v and H_i). Interestingly, half of the tolyl ring protons appeared as sharp doublets at 193 K (Hc and Hb) originating from two magnetically equivalent podand arms, whereas two broad signals were assigned for the tolyl protons of the two remaining podand arms. These broad aromatic signals resonated upfield shifted at 6.60 and 7.10 ppm (Hn and Ho) relative to their sharply resolved counterparts. Accordingly, the singlet of the Ar-CH3 (Ha) had an integral equivalent of six protons, and the remaining protons (H_m) were most likely located together with the lower rim CH₂ signals H_w and H_k based on the integral values of these broad resonances.

The line shapes of the NMR signals arising from the lower rim CH₃ protons (H_i, H_x) and upper rim resorcinol protons (H_h, H_t) at different temperatures were modelled with line shape analysis to obtain the exchange rate constants (*k*). The exchange rates were analysed using Eyring plots (SI), which provided Gibbs free energy of activation (ΔG^{\dagger}_{298}) of 55.5 kJ/mol for **1** and 52.0 kJ/mol for **2** (Table 1). The values are similar to the value obtained for octa-acetylated resorcinarene podands (ΔG^{\dagger}_{298} = 54.7 kJ/mol).^[35]

10.1002/chem.201905211

WILEY-VCH

Table 1. Activation energy parameters for the conformational exchange.			
Molecule	$\Delta G^{\ddagger_{298}}$ (kJ mol ⁻¹)	∆H [‡] (kJ mol⁻¹)	ΔS^{\ddagger} (J mol ⁻¹ K ⁻¹)
1	55.5	21.0	-116.0
2	52.0	28.0	-80.7

¹H-¹H COSY and ROESY

¹H-¹H COSY and ROESY NMR were used to investigate the conformation of the resorcinarene podands **1** and **2** in solution, as well as, to confirm the assignment of the protons at low temperature. The ROESY measurements of **2** at 193 K showed strong ROE correlations between aryl protons and methoxy protons, ArH_h to H_g and ArH_t to H_s, as well as, between aryl and ethoxy protons, ArH_h to H_f and ArH_t to H_r (Fig. 4) indicating that these protons were coupled through space. On the other hand, ROE correlations were observed for aryl protons H_i with



Figure 4. ¹H-¹H ROESY of 2 at 193 K in CD_2CI_2 and a DFT minimized structure 2-I showing key contacts (< 4 Å distance) present in this conformation matching with ROESY. Negative ROE cross-peaks are shown in red and positive exchange cross-peaks in blue. The overlap of b, n, o and u protons hinder the assignment of ROEs marked with a green circle.

Positive exchange correlations were also observed between H_d and H_{p} , which were assigned as benzylic protons. The signal H_{d} resonated as an AB quartet with almost identical chemical shift for the A and B protons, whereas in H_p the $\Delta\delta_{AB}$ was 0.12 ppm. The upfield shift in signal Hp in comparison to Hd suggests that the proton is magnetically shielded by the proximity of an aromatic ring. This condition is met for the podand arm attached to the vertical resorcinol ring in the conformation observed in the X-ray structure, where the benzylic protons establish C-H $\cdots\pi$ interactions with the horizontally aligned resorcinol rings. Based on the computational models, the shielding of the protons H_p may result from the inclusion of one of the podand arm into the resorcinarene cavity and from the above-mentioned C-H $\cdots\pi$ interactions with a resorcinol ring. Thus, the protons H_d-H_i arise from the horizontally aligned resorcinol ring in a boat conformation, and the protons Hp-Hu were assigned to the vertically opposed resorcinol ring.

The ROESY spectra of **1** at 193 K (Fig. 5) revealed a similar pattern of exchange cross-peaks between methoxy protons H_g and H_s , and upper rim protons ArH_h and ArH_t as in the spectrum of **2**. Interestingly, the methoxy group H_g showed a ROE correlation with proton assigned as H_t/H_q , which was not observed in **2**. Comparison to the DFT energy minimized structures and the X-ray structure showed that from these two possibilities the distance between H_g and H_q (horizontal-vertical, ~3 Å) is significantly shorter than H_g and H_f (horizontal-horizontal, ~4 Å), and therefore, a more likely source of this correlation. This assignment is made assuming that the similar chemical shifts of the methoxy groups between **1** and **2** allow the assignment of H_g and H_s to horizontally and vertically oriented resorcinol rings also in **1**.

ROE correlations from the sharp tolyl group signals H_c and H_b were observed to the resorcinol lower rim groups. Proton H_b showed weak correlations with methine H_j and methyl H_l . Proton H_c had cross-peaks with the same lower rim protons and interestingly, to the ethoxy H_e/H_f and methoxy H_s . This combination of ROEs was best explained if the tolyl group H_c/H_b is attached to the horizontal resorcinol ring and wraps around the aromatic cavity thereby approaching the vertical methoxy group H_s and the lower rim of the podand. This interpretation is in agreement with our tentative assignment of the vertically and horizontally aligned resorcinol rings, and with the crystal structure of **1**.

The computational structures 1-I–1-V are in excellent agreement with the observed ROEs. Especially structure 1-I, which also has the lowest DFT energy, shows all the expected distances from horizontal podand arm protons H_b and H_c to the lower rim protons and the vertical methoxy protons H_s . In the structures 1-IV and 1-V one of the horizontal arms is folding under the horizontally aligned resorcinol ring. In this conformation the distance between the tolyl group protons and lower rim protons are too long for the observed ROEs, which suggests that these conformations are less populated in solution in accordance with their higher DFT energies.



Figure 5. ¹H-¹H ROESY of 1 at 193 K in CD_2CI_2 and a DFT minimized structure of 1-I showing key contacts (< 4 Å distance) present in this conformation matching with ROESY. Negative ROE cross-peaks are shown in red and positive exchange cross-peaks in blue.

It is important to note that the tolyl groups of the two podand arms, which are attached to the vertical resorcinol rings show broad signals for H_m – H_o at 193 K and appear upfield shifted relative to the corresponding horizontal H_a – H_c . This indicates that the tolyl groups are engaged in a dynamic process that is intermediate on the chemical shift timescale. Based on the most likely conformation of the molecule **1** in solution (ROEs and DFT structures), especially the proximity of vertical podand arm ethoxy protons H_q with the horizontal ring H_g , it can be deduced that the conformation of the vertical podand arm is favorable for tolyl group inclusion into the aromatic resorcinol cavity. The upfield shifted and broadened tolyl group signals are indicative of a second exchange process of low energy barrier involving dynamic inclusion of the tolyl groups in the magnetically shielded environment of the resorcinarene cavity.

Conclusions

In summary, we have presented the synthesis of two conformationally flexible resorcinarene podands without permanent cavities, which were characterized by a complete set of high-resolution spectroscopic techniques and X-ray crystallography. In the solid state, the resorcinarenes exhibit different conformations of the *p*-toluene podand arms, where a sulfonyl linker in **1** promotes self-inclusion complexation of the *p*-toluene group, and a benzoyloxy linker in **2** pinching of the resorcinarene cavity. Variable temperature NMR revealed a 52–55 kJ/mol energetic barrier of the boat-to-boat exchange for both podands, which indicates that the different podand arm linkers do not influence significantly to the exchange rate.

The conformation and intramolecular interactions of the macrocycles were also investigated by ROESY experiments at low temperature. Additionally, conformational search and DFT optimizations were carried out to explore the conformation space of the podands. The observed ROE correlation between the podand arms and resorcinol protons suggest that the tetratosylate resorcinarene podand **1** exhibits similar wrapped conformation of the horizontal podand arms in solution as observed in the solid state. Furthermore, the magnetic shielding of the broad aromatic tolyl group signals assigned to the vertical podand arms, and computational modelling suggest that self-inclusion of the *p*-toluene group is highly favorable conformation also in solution.

For tetratolyl resorcinarene **2**, ¹H NMR and ROESY data suggest that the benzylic protons of the vertical podand arms are involved in C-H··· π interactions with the horizontally aligned resorcinol rings in solution, which was also observed in all computational structures. Computational modelling revealed a more versatile conformation space for resorcinarene **2** than **1**, where self-inclusion of the vertical or horizontal podand arms were identified as the lowest energy structures. However, conformational search also found an open conformation without self-inclusion, which deviates from the crystal structure most significantly in a more compact orientation of the horizontal podand arms. Therefore, it is expected that both types of conformation of the horizontal podand arms is an effect induced by the favorable π ··· π interactions in crystal packing.

The role of the sulfonyl linker in self-inclusion complex of resorcinarene **1** is twofold. On one hand the sulfonyl oxygens are suitable hydrogen bond acceptors for establishing weak hydrogen bonds that support the self-inclusion complex, and on the other hand, the oxygen lone pairs direct the podand arms away from the horizontally aligned resorcinol rings. Comparison to resorcinarene **2** clearly indicates that the presence of the sulfonyl group restricts the range of conformations the podand is likely to adopt. Ultimately, we can conclude that the conformation of podand **1** in solution correlates well with its solid state structure, whereas the conformation of podand **2** changes between self-inclusion complexes and open conformations.

Experimental Section

Solvents and reagents were purchased from commercial suppliers Sigma-Aldrich and VWR. Solvents were dried using an MBraun solvent purification system. The synthesis was performed with dried glassware (at 120 °C overnight) and under nitrogen balloon. Flash chromatography was performed with a Combiflash Companion (Teledyne Isco) and Redisep Gold silica columns. The mass spectrometry was performed with a Micromass LCT ESI-TOF or an ABSciex QSTAR Elite ESI-Q-TOF mass spectrometer. Melting points were measured with a Stuart Scientific SMP30 and are uncorrected.

NMR

NMR spectra were recorded with a Bruker Avance III 500 (500 MHz for ¹H and 126 MHz for ¹³C) spectrometer. The *J* values are given in Hz. Variable temperature measurements of the podands were performed with a BBI probe. The ¹H NMR was obtained in CD₂Cl₂ at different temperatures (303 K, 283 K, 263 K, 243 K, 223 K, 203 K and 193 K) at 9 mM concentration for **1**, and 11 mM concentration for **2**. The ROESY and COSY ¹H-¹H NMR were performed at 193K. Complete lineshape analysis was performed with Bruker TopSpin v. 3.5.

Synthesis

Resorcinarene 1 was synthesized as described previously.^[47] $\delta_{H}(500 \text{ MHz}, \text{CD}_2\text{Cl}_2, +30 ^{\circ}\text{C})$ 7.67 (d, $J = 8.2, 8\text{H}, \text{H}_c, \text{H}_o)$, 7.18 (d, $J = 8.0, 8\text{H}, \text{H}_b, \text{H}_n$), 6.76 (s, 4H, H_i, H_u), 6.11 (s, 4H, d, H_h, H_t), 4.32 (t, $J = 7.9, 4\text{H}, \text{H}_j, \text{H}_v$), 4.17 (t, $J = 4.8, 8\text{H}, \text{H}_e, \text{H}_q$), 4.01–3.93 (m, 4H, H_f, H_r), 3.73–3.62 (m, 4H, H_f, H_r), 3.51 (s, 12H, H_g, H_s), 2.27 (s, 12H, H_a, H_m), 1.87–1.73 (m, 8H, H_w, H_k), 0.82 (t, $J = 6.7, 12\text{H}, \text{H}_i, \text{H}_x$) ppm; $\delta_C(126 \text{ MHz}, \text{CD}_2\text{Cl}_2, +30 ^{\circ}\text{C})$ 156.15, 155.29, 145.65, 133.63, 130.41, 128.29, 127.35, 126.67, 126.45, 98.26, 69.42, 67.54, 55.77, 36.62, 28.82, 21.69, 12.78 ppm.

Resorcinarene 2: Tetramethoxy resorcinarene 3 (0.200 g, 0.304 mmol), Cs₂CO₃ (0.804 g, 2.468 mmol) and dibenzo-18-crown-6 (0.010 g, 0.028 mmol) were mixed with 30 ml of dry acetonitrile under nitrogen atmosphere at 100 °C with stirring. A white suspension formed. The solution was heated at reflux for 15 minutes before the addition of 5 (0.428 g, 1.338 mmol) in 20 ml of dry acetonitrile. The suspension was refluxed for 24 hours. The solution was filtrated while hot through a pad of celite, and the precipitate was washed with hot acetonitrile. The solvent was evaporated with a rotary evaporator, and the residue was dissolved into 50 ml of dichloromethane and washed with 20 ml of water. The organic solution was dried with MgSO₄, evaporated and purified with flash chromatography using SiO2 column and a hexane/ethyl acetate gradient (from 8:2 to 0:1). The product was recovered as a colourless oil and recrystallized from ethanol as white crystalline solid (44 % yield). mp 92—93 °C; $\delta_{H}(500 \text{ MHz}, \text{CD}_2\text{Cl}_2)$ 7.24 (d, $J = 7.9, 8\text{H}, \text{H}_c, \text{H}_o)$, 7.14 (d, J= 7.9, 8H, H_b,H_n), 6.68 (s, 4H, H_i,H_u), 6.33 (s, 4H, H_h,H_t), 4.51 (ABq, $\Delta \delta_{AB} = 0.04, J_{AB} = 11.5, 4H, H_d, H_p), 4.44$ (t, J = 7.2, 4H, H_j, H_v), 4.05–3.93 (m, 4H, H_f,H_r), 3.81-3.71 (m, 4H, H_f,H_r), 3.71-3.59 (m, 8H, H_e,H_q), 3.55 (s, 12H, H_g,H_s), 2.32 (s, 12H, H_a,H_m), 1.93–1.75 (m, 8H, H_w,H_k), 0.89 (t, J = 7.2, 12H, H_I,H_x) ppm; δ_C(126 MHz, CD₂Cl₂) 156.12, 155.67, 137.50, 135.90, 129.17, 128.00, 126.35, 98.24, 73.49, 69.54, 69.40, 55.79, 37.22, 28.12, 21.10, 12.85 ppm; HR-MS (ESI-TOF): m/z calcd. for C₈₀H₉₆O₁₂Na⁺ 1271.6794 [M+Na⁺]; found 1271.6785.

Compound 4: KOH (0.41 g, 7.37 mmol) was dissolved in anhydrous ethylene glycol by heating to 90-100 °C under nitrogen atmosphere. 4-Methylbenzyl chloride (1.00 g, 7.11 mmol) was added dropwise to the yellow solution and heating was continued at 90 °C for 24 hours. The yellow mixture was diluted with 30 ml of Millipore water and extracted three times with 20 ml of dichloromethane. The combined extracts were washed once with water and dried with MgSO4. The organic solvent was evaporated, and the residue was purified with flash chromatography using SiO₂ column and a petrol ether/ethyl acetate gradient (from 65:35 to 0:1). The product was isolated as a colourless liquid (0.63 g, 53 %)

and used as such in the next step. $\delta_{H}(500 \text{ MHz}, \text{ CDCI}_3, +30 \text{ }^\circ\text{C}) 7.24 \text{ }(d, J = 8.0, 2H), 7.17 \text{ }(d, J = 8.0, 2H), 4.52 \text{ }(s, 2H), 3.77-3.72 \text{ }(m, 2H), 3.60-3.56 \text{ }(m, 2H), 2.35 \text{ }(s, 3H) \text{ ppm}; \delta_{C}(126 \text{ MHz}, \text{ CDCI}_3) 137.5, 134.9, 129.1, 127.9, 73.1, 71.1, 61.9, 21.1 \text{ ppm}.$

Compound 5: Tosyl chloride (0.768 g, 4.028 mmol) was dissolved into 30 ml of dry dichloromethane under a nitrogen atmosphere, and the solution was cooled in an ice bath. Triethylamine (0.56 ml, 4.015 mmol) was added. 2-O-(4-Methyl benzoyl)ethyl alcohol 4 (0.56 g, 3.363 mmol) was added in 15 ml of dichloromethane, and stirring was continued for an hour in the ice bath and 24 hours at room temperature. The resulting brown solution was washed twice with 40 ml of water. The yellowish organic solution was dried with MgSO₄, and the solution was evaporated to dryness. The product was purified with flash chromatography using SiO₂ column and a hexane/ethyl acetate gradient (from 8:2 to 0:1). The product was recovered as a colourless liquid (0.494 g, 46 %) with traces of ethyl acetate and was used as such in the next step. $\delta_{H}(500 \text{ MHz},$ CDCl₃, 25 °C) 7.79 (d, J = 8.1, 2H, Ts-H), 7.31 (d, J = 8.1, 2H, Ts-H), 7.14 (br s, 4H, Ar-H), 4.44 (br s, 2H, Ar-CH₂), 4.18 (t, J = 4.7, 2H, SO₃-CH₂), 3.63 (t, J = 4.7, 2H, O-CH₂), 2.43 (s, 3H, Ts-CH₃), 2.34 (s, 3H, Ar-CH₃) ppm; δ_C(126 MHz, CDCl₃) 144.9, 137.7, 134.6, 133.2, 129.9, 129.2, 128.1, 127.9, 73.3, 69.4, 67.4, 21.8, 21.3 ppm; m/z (ESI-TOF) 343.6 (M + Na⁺, 100%).

X-ray crystallography

Single crystal X-ray data were recorded on an Agilent SuperNova, Single source at offset, Eos diffractometer using an Agilent Atlas CCD detector with mirror monochromatized MoK α (λ = 0.71073 Å). The data were processed, and empirical absorption correction was made with CrysAlisPro. The structures were solved with the Superflip structure solution program using Charge Flipping or a ShelXS structure solution program using Direct Methods. The structure refinement was made with Olex2 using SHELXL refinement package with least squares minimization. The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms. EADP and EXYZ constrains, and SADI, DFIX, DELU, SIMU restraints were used in the refinement of disordered fragments in **2**. The crystallographic parameters are shown in SI. CCDC 1963708–1963709 contains the supplementary crystallographic data for this paper.

Computational

Conformational search was performed for individual molecules of **1** and **2** with Maestro package in a mixed torsional low mode sampling mode with 10 000 steps (Schrödinger Release 2019-2: Maestro and MacroModel, Schrödinger, LLC, New York, NY, 2019.) Crystal coordinates were used as a starting point and the energy minimization of the structures was performed with molecular mechanics using OPLS3e force field. The resulting structures were classified in relevant conformations and the lowest energy example of each representative conformation was submitted to DFT structure optimization using Terachem software.^[48,49] DFT calculations were performed using two popular functionals B3LYP-D3^[50,51] and PBE0-D3^[52] with dispersion correction^[53,54], 6-31G** basis set and PCM solvent model^[55] (parameters for chloroform: dielectric constant = 4.806, density = 1.4832 and probe radius = 2.52).

Acknowledgements

We wish to thank M.Sc. Tiina Virtanen for assistance in the synthesis, M.Sc. Esa Haapaniemi for assistance with the NMR experiments, and Prof. Gerrit Groenhof, Dr. Sami Malola and Prof. Petri Pihko for collaboration with the computational studies. We acknowledge grants of computer capacity from the Finnish Grid and Cloud Infrastructure (persistent identifier urn:nbn:fi:research-infras-2016072533) and the CSC-IT center in Espoo. Academy of Finland (grants 309910, 314287, 257246) is gratefully acknowledged for funding.

Keywords: Resorcinarene • Self-inclusion • Solution structure • Supramolecular chemistry • X-ray crystallography

- † CSD version 2019 contained 131 structures identified as Ofunctionalized resorcinarenes or pyrogallolarenes (podands) and all but one were in boat conformation.
- C. Heinzmann, C. Weder, L. M. de Espinosa, Chem. Soc. Rev. 2016, 45, 342–358.
- [2] W. Feng, M. Jin, K. Yang, Y. Pei, Z. Pei, Chem. Commun. 2018, 54, 13626–13640.
- [3] E. Krieg, M. M. C. Bastings, P. Besenius, B. Rybtchinski, *Chem. Rev.* 2016, *116*, 2414–2477.
- [4] M. Bojtár, A. Simon, P. Bombicz, I. Bitter, Org. Lett. 2017, 19, 4528– 4531.
- [5] Y. Liu, C. Chipot, X. Shao, W. Cai, J. Phys. Chem. C 2014, 118, 19380–19386.
- [6] B. Shi, D. Xia, Y. Yao, Chem. Commun. 2014, 50, 13932–13935.
- [7] H. Qian, D.-S. Guo, Y. Liu, *Chem. Eur. J.* 2012, *18*, 5087–5095.
 [8] G. Yu, X. Zhao, J. Zhou, Z. Mao, X. Huang, Z. Wang, B. Hua, Y. Liu, F.
- [6] G. Tu, A. Zhao, S. Zhou, Z. Mao, A. Huang, Z. Wang, D. Huang, T. Liu, T. Zhang, Z. He, et al., J. Am. Chem. Soc. 2018, 140, 8005–8019.
- [9] J. del Barrio, J. Liu, R. A. Brady, C. S. Y. Tan, S. Chiodini, M. Ricci, R. Fernández-Leiro, C.-J. Tsai, P. Vasileiadi, L. Di Michele, et al., J. Am. Chem. Soc. 2019, 141, 14021–14025.
- [10] T. Kakuta, T. A. Yamagishi, T. Ogoshi, Acc. Chem. Res. 2018, 51, 1656–1666.
- [11] Y. Yu, J. Li, M. Zhang, L. Cao, L. Isaacs, Chem. Commun. 2015, 51, 3762–3765.
- [12] C. Y. Goh, T. Becker, D. H. Brown, B. W. Skelton, F. Jones, M. Mocerino, M. I. Ogden, *Chem. Commun.* **2011**, *47*, 6057–9.
- [13] L. M. de Espinosa, G. L. Fiore, C. Weder, J. E. Foster, Y. C. Simon, *Prog. Polym. Sci.* 2015, 49–50, 60–78.
- [14] Y. S. Su, J. W. Liu, Y. Jiang, C. F. Chen, Chem. Eur. J. 2011, 17, 2435–2441.
- [15] W. Lu, X. Le, J. Zhang, Y. Huang, T. Chen, Chem. Soc. Rev. 2017, 46, 1284–1294.
- [16] S. Ma, D. M. Rudkevich, J. Rebek, Jr., J. Am. Chem. Soc. 1998, 120, 4977–4981.
- [17] C. Kabuto, Y. Higuchi, T. Niimi, F. Hamada, N. Iki, N. Morohashi, S. Miyano, J. Incl. Phenom. Macrocycl. Chem. 2002, 42, 89–98.
- [18] N. K. Beyeh, A. Ala-Korpi, M. Cetina, A. Valkonen, K. Rissanen, *Chem. Eur. J.* 2014, 20, 15144–15150.
- [19] N. K. Beyeh, M. Cetina, M. Löfman, M. Luostarinen, A. Shivanyuk, K. Rissanen, Supramol. Chem. 2010, 22, 737–750.
- [20] S. Cecillon, A. Lazar, O. Danylyuk, K. Suwinska, B. Rather, M. J. Zaworotko, A. W. Coleman, *Chem. Commun.* 2005, 2442–2444.
- [21] R. Sekiya, Y. Yamasaki, W. Tada, H. Shio, T. Haino, *CrystEngComm* 2014, 16, 6023–6032.
- [22] P. Amrhein, A. Shivanyuk, D. W. Johnson, J. Rebek, Jr., J. Am. Chem. Soc. 2002, 124, 10349–10358.
- [23] L. Li, J. Sun, L.-L. Zhang, R. Yao, C.-G. Yan, J. Mol. Struct. 2015, 1081, 355–361.

- [24] L. Liu, L. Wang, C. Liu, Z. Fu, H. Meier, D. Cao, J. Org. Chem. 2012, 77, 9413–9417.
- [25] T. Ogoshi, T. Furuta, Y. Hamada, T. Kakuta, T. Yamagishi, *Mater. Chem. Front.* 2018, 2, 597–602.
- [26] Y. Enmi, K. Kobayashi, H. Konishi, M. Morimoto, *Tetrahedron Lett.* 2011, 52, 3367–3370.
- [27] A. R. Renslo, D. M. Rudkevich, J. Rebek Jr, J. Am. Chem. Soc. 1999, 121, 7459–7460.
- [28] O. Morikawa, S. Matsubara, S. Fukuda, K. Kawakami, K. Kobayashi, H. Konishi, *Tetrahedron Lett.* 2007, 48, 7489–7492.
- [29] V. Havel, M. Babiak, V. Sindelar, Chem. Eur. J. 2017, 23, 8963–8968.
- [30] P. Evenou, J. Rossignol, G. Pembouong, A. Gothland, D. Colesnic, R. Barbeyron, S. Rudiuk, A. G. Marcelin, M. Ménand, D. Baigl, et al., *Angew. Chem. Int. Ed.* **2018**, 57, 7753–7758.
- [31] T.-R. Tero, K. Salorinne, M. Nissinen, CrystEngComm 2012, 14, 7360.
- [32] K. Salorinne, D. P. Weimann, C. A. Schalley, M. Nissinen, *Eur. J. Org. Chem.* 2009, 6151–6159.
- [33] J. Han, X. Song, L. Liu, C. Yan, J. Incl. Phenom. Macrocycl. Chem. 2007, 59, 257–263.
- [34] M. J. McIldowie, M. Mocerino, M. I. Ogden, B. W. Skelton, A. H. White, J. Incl. Phenom. Macrocycl. Chem. 2015, 82, 47–51.
- [35] A. Velásquez-Silva, B. Cortés, Z. J. Rivera-Monroy, A. Pérez-Redondo, M. Maldonado, J. Mol. Struct. 2017, 1137, 380–386.
- [36] P. B. Pansuriya, H. B. Friedrich, G. E. M. Maguire, Acta Crystallogr. Sect. E Struct. Reports Online 2011, E67, o2907.
- [37] P. Kumar, P. Venkatakrishnan, Org. Lett. 2018, 20, 1295–1299.
- [38] P. B. Pansuriya, H. B. Friedrich, G. E. M. Maguire, Acta Crystallogr. Sect. E Struct. Reports Online 2012, E68, 097–098.
- [39] J. Han, Y. H. Cai, L. Liu, C. G. Yan, Q. Li, *Tetrahedron* 2007, 63, 2275– 2282.

- [40] R. Zhou, J. C. Ren, C. G. Yan, J. Incl. Phenom. Macrocycl. Chem. 2010, 67, 335–342.
- [41] K.-X. Chang, N. Zhang, P. Du, Y.-Y. Liu, J.-F. Ma, Polyhedron 2017, 138, 287–294.
- [42] L. Li, Y. Yao, J. Sun, C.-G. Yan, RSC Adv. 2015, 5, 102454–102461.
- [43] X. Han, J. Yang, Y.-Y. Liu, G.-H. Xu, J.-F. Ma, Polyhedron 2019, 161, 145–153.
- [44] J. Liu, A. Wei, Chem. Commun. 2009, 1, 4254–6.
- [45] M. Klaes, B. Neumann, H.-G. Stammler, J. Mattay, Eur. J. Org. Chem. 2005, 864–868.
- [46] M. J. McIldowie, M. Mocerino, B. W. Skelton, A. H. White, Org. Lett. 2000, 2, 3869–3871.
- [47] K. Salorinne, E. Nauha, M. Nissinen, *Chem. Asian J.* **2012**, *7*, 809–817.
- [48] I. S. Ufimtsev, T. J. Martinez, J. Chem. Theory Comput. 2009, 5, 2619– 2628.
- [49] A. V. Titov, I. S. Ufimtsev, N. Luehr, T. J. Martinez, J. Chem. Theory Comput. 2013, 9, 213–221.
- [50] A. D. Becke, J. Chem. Phys. 1993, 98, 5648.
- [51] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, J. Phys. Chem. 1994, 98, 11623–11627.
- [52] C. Adamo, V. Barone, J. Chem. Phys. 1999, 110, 6158–6170.
- [53] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys. 2010, 132, 154104.
- [54] S. Grimme, S. Ehrlich, L. Goerigk, J. Comput. Chem. 2011, 32, 1456– 1465.
- [55] F. Liu, N. Luehr, H. J. Kulik, T. J. Martínez, J. Chem. Theory Comput. 2015, 11, 3131–3144.

WILEY-VCH

Entry for the Table of Contents (Please choose one layout) Layout 1:

FULL PAPER

Self-inclusion complex of a flexible resorcinarene podand stabilized by weak C-H…O interactions was observed in crystal structure and in solution.



Małgorzata Pamuła, Maija Nissinen and Kaisa Helttunen*

Page No. – Page No.

Correlating solution and solid state structures of conformationally flexible resorcinarenes – the significance of a sulfonyl group in intramolecular self-inclusion