# Monomeric, dimeric and hexameric resorcin[4]arene assemblies with alcohols in apolar solvents†‡§

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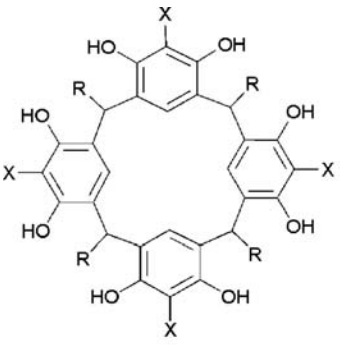
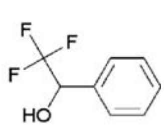
**Resorcin[4]arenes in an apolar solvent containing alcohols exist in three forms of self-assembled aggregates which have been characterised by the technique of diffusion NMR spectroscopy.**



**1a** X = H, R = (CH$_2$)$_{10}$CH$_3$
**1b** X = H, R = CH$_3$
**1c** X = H, R = (CH$_2$)$_2$Ph
**2a** X = OH, R = CH$_2$CH(CH$_3$)$_2$



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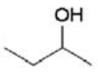

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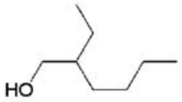

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Since Högberg developed a practical synthesis of the resorcin[4]arenes in 1980,[1] numerous articles have been published on these macrocyclic hosts and their molecular recognition and self-assembling behavior. The bowl shaped structure of resorcinarenes was one of the origins of the host–guest study made by Aoyama *et al.*[2] on the complexation of non-ionic polar compounds in 1988, which was followed by Kobayashi *et al.*[3] Regarding the self-assembly of resorcin[4]arene **1a**, Aoyama also suggested in the same work that higher aggregates such as pentamers or hexamers could possibly be formed. The first evidence of higher supramolecular structures in the solid state was discovered by Atwood and MacGillivray[4], and Mattay *et al.*[5] in the late 1990s. Both reported independently and almost simultaneously the first X-ray crystal structures of cubic hexameric nano-capsules of resorcin[4]arene **1b** and pyrogallo[4]arene **2a**. Studies on these hexameric species in solution have almost primarily been made by the groups of Cohen,[6] Rebek[7] and Atwood[8] using NMR spectroscopy techniques including NOE and diffusion coefficient determination. Later, Atwood[9] suggested the formation of the smaller self-assembled resorcin[4]arene **1c** dimer facilitated by hydrogen-bond bridges involving eight 2-propanol molecules, which was characterised by X-ray diffraction analysis. More recently Ugono and Holman[10] discovered an achiral hexameric capsule related to the chiral form reported by Atwood. In contrast to the water bridged chiral assembly, this capsule is held together by a hydrogen-bonding network with six 2-ethylhexanol molecules and additionally two water molecules on the edges of the formed cube.

The aggregation phenomenon controlled by one compound (*e.g.* alcohol) in a three-component system (*e.g.* solvent, resorcin[4]arene and alcohol) is not very well studied. The works of Holman, Aoyama and Atwood prompted us to elucidate the controlled molecular assembling processes of 1 : 1 complexes, dimers and hexamers in apolar solvents by addition of selected alcohols. In order to visualize such interactions, at first we attempted to detect and characterise such species by mass spectrometry methods such as MALDI-TOF, ESI and CSI. None showed evidence supporting the formation of aggregates that survived in the gas phase. Also, Williams *et al.*[11] reported that neither variable temperature $^1$H NMR spectroscopy nor GPC measurements yielded coherent information concerning the aggregation of similar systems in solution. However, diffusion NMR spectroscopy provided useful data concerning the solution states of aggregated species. Based on the diffusion coefficients, it is possible to conclude the particle size in solution. In our NMR experiments,¶ we used a solution of undecylresorcin[4]arene **1a**‖ in dry CDCl$_3$, to which alcohols **3–5** were added.

We first determined the diffusion coefficients of species existing in the NMR sample (0.7 mL) of **1a** (25 mM) and racemic **3** (**1a** : **3** ≈ 1 : 10) in dry CDCl$_3$. Because of the high acidity of the alcoholic proton that should support the necessary hydrogen-bonding network of such an aggregate, we expected the formation of a hexameric capsule. However, the diffusion coefficient (Table 1) of 0.42 ± 0.01 × $10^{-5}$ cm$^2$ s$^{-1}$ indicated a monomeric species in accordance with the reports of Cohen *et al.*[6] Considering the studies of Kobayashi *et al.*[3] we propose a 1 : 1 complexation of 2,2,2-trifluoro-1-phenylethanol

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‡ Electronic supplementary information (ESI) available: $^1$H NMR spectra of **1a·3** 1 : 1 complex, **1a·4** dimer, and **1a·5** hexamer. See DOI: 10.1039/b803890b

§ Dedicated to Professor Ernst-Ulrich Würthwein (University of Münster) on the occasion of his 60th birthday.

**Table 1** Effect of the addition of alcohols **3–5** on the diffusion coefficient $D$ ($\times$ $10^{-5}$ in $cm^2\ s^{-1}$) of **1a** at 6.12 ppm in dry $CDCl_3$ at 296 K

| System | $D/10^{-5}$ $cm^2\ s^{-1}$) | Aggregation state |
|---|---|---|
| **1a·3** | 0.42 ± 0.01 | 1 : 1 Complex |
| **1a·4** | 0.32 ± 0.01 | Dimer |
| **1a·5** | 0.25 ± 0.01 | Hexamer |
| Free $CHCl_3$ | 2.56 ± 0.02 | — |

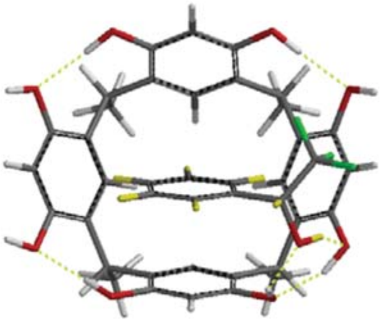

**Fig. 1** Stick model of the **1a·3** complex. The alkyl chains are omitted for clarity. The hydrogen-bonding network is described by the green dotted lines.

in the cavity of resorcin[4]arene (Fig. 1). The driving force for this complexation is apparently the π–π interaction between the aromatic residue of the alcohol and the cavity. Moreover the association may be assisted by the hydrogen-bonding network formed by the alcohol and two resorcinol units. In addition, solvophobic forces may also play a minor role in strengthening the complexation.

Next we treated the NMR sample of the stock solution of **1a** with racemic **4** (**1a** : **4** ≈ 1 : 10) and determined the diffusion coefficient. In good agreement with the results of Atwood *et al.* in the solid state, we found a diffusion coefficient of 0.32 ± 0.01 × $10^{-5}$ $cm^2\ s^{-1}$ which is typical for a dimer.[6] This aggregate is formed by 24 delocalized hydrogen bonds between two molecules of **1a** and eight molecules of **4** (Fig. 2). The effective van der Waals volume of the resorcin[4]arene's cavity was calculated by Barbour[12] to be 230 $Å^3$. In order to maintain structural stability, we assume that the capsule contains an undefined number of alcohol molecules.

Finally we treated the NMR sample of **1a** with racemic **5** (**1a** : **5** ≈ 1 : 10). We expected a lower diffusion coefficient compared to our previous experiments since the formation of the hexameric nano-capsule has been reported by Holman and Ugono[10] (Fig. 3) and formulated as $\mathbf{1a}_6\cdot(\mathbf{5})_6\cdot(H_2O)_2$. In fact, we determined a diffusion coefficient of 0.25 ± 0.01 × $10^{-5}$ $cm^2\ s^{-1}$ respective to the signal at 6.12 ppm. This result is consistent with the observed diffusion coefficients of several experiments in related systems reported by Cohen *et al.*[6] In contrast to the solid state, in our experiments under absolutely dry conditions we assume the complete "substitution" of all water molecules by racemic 2-ethylhexanol resulting in the hexameric complex $\mathbf{1a}_6\cdot\mathbf{5}_8$ in solution.

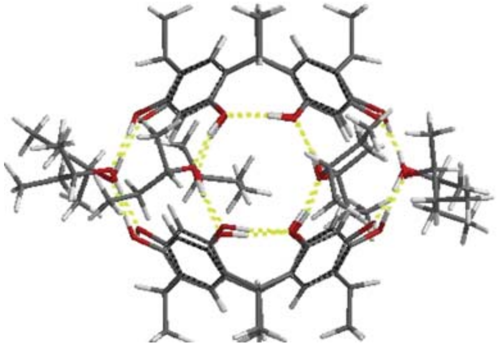

**Fig. 2** Tube model of the butan-2-ol bridged resorcin[4]arene dimer.

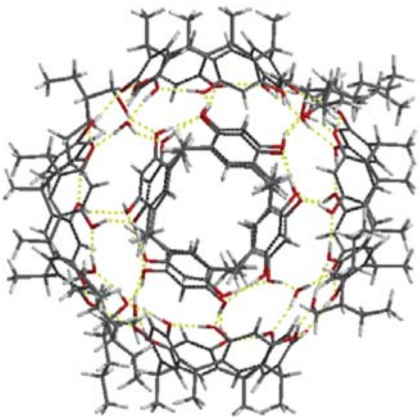

**Fig. 3** Stick model of the hexameric nano-capsule of $\mathbf{1a}_6\cdot(\mathbf{5})_6\cdot(H_2O)_2$.

Moreover under the solid state conditions it is likely that three additional molecules of **5** are essential to stabilize the aggregate's inner volume (1290 $Å^3$) by encapsulation.

Depicted in Fig. 4 are the signal decays as a function of the gradient strength combined for each experiment. It is apparent that the system **1a·5** has the strongest effect of all, whereas the differences in the signal decay between the systems **1a·3** and **1a·4** are not so strong. This may be due to the moderate increase in the particle size from monomeric to dimeric species ($V_{inner}$ = 230 $Å^3$) and then dramatic increase in the case of hexameric species ($V_{inner}$ = 1290 $Å^3$). Filling the inner volume of these

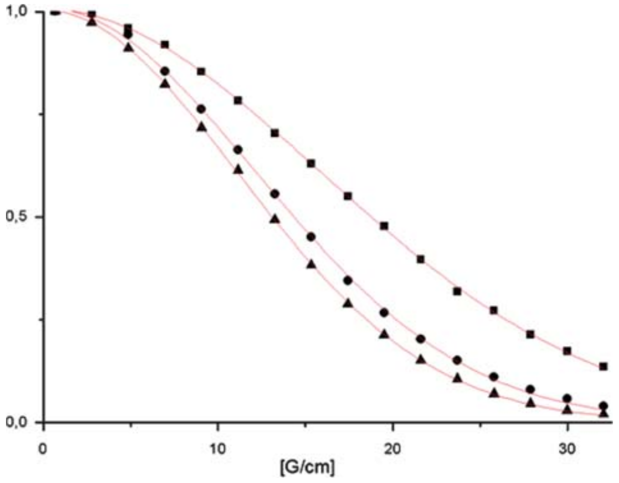

**Fig. 4** $^1H$ NMR signal decays as a function of the gradient strength ($G$) (600 MHz, 296 K) of **1a·5** (■), **1a·4** (●) and **1a·3** (▲) at 6.12 ppm in dry $CDCl_3$.

aggregates is of main interest in all of these experiments. We suggest that the formation of these complexes is strongly dependent on the shape and structure of the alcohol employed and the resulting van der Waals interactions in the inner cavity.

In summary, we have elucidated the origin of the puzzling aggregation behavior of resorcin[4]arenes with various alcohols by revealing the dramatic influence of bridging molecules on the multicomponent aggregation in solution under fixed conditions (concentration, pH, *etc.*). Further studies with enantiomerically pure alcohols are currently in progress and the results will be reported in due course.

## Notes and references

¶ NMR diffusion measurements were performed on a Bruker Avance 600 MHz FT-NMR spectrometer. The diffusion experiments were performed using an LED pulse sequence with bipolar gradients as delivered by the manufacturer. The gradient length ($\delta$) was set to 4000 ms and was varied linearly from 5 to 95%. The diffusion delay ($\Delta$) was set to 85 ms. 16 data points per diffusion experiment were collected and 32 scans were applied per increment. Prior to the measurements the heater and the airflow were switched off. and the sample was left in the magnet for an additional 4 h in order to have constant temperature conditions (296 K). In all measurements, we used the signal of **1a** at 6.12 ppm to determine the diffusion coefficients. All spectral data showed only averaged resonances of the alcohol signals on the NMR timescale, because the formation of the different species is subjected to a fast thermodynamic equilibria.

‖ Resorcinol and *n*-dodecanal were obtained from Aldrich and used as supplied.

**Synthesis of undecylresorcin[4]arene**, **1a**: concentrated hydrochloric acid (25 ml) was added to an ethanolic solution (125 ml) containing *n*-dodecanal (33.2 g, 180 mmol) and resorcinol (19.8 g, 180 mmol). The mixture was heated to reflux for 3 h. Upon cooling, the product precipitated as a fine colourless solid. The crude product was collected and washed with methanol and recrystallized from ethanol. Yield 75%.

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