Encapsulation of secondary and tertiary ammonium salts by resorcinarenes and pyrogallarenes: the effect of size and charge concentration†

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The binding of different categories of alkyl ammonium (secondary and tertiary mono- and di-ammonium) salts with resorcinarenes and a pyrogallarene through weak interactions was analysed in all phases. 1H NMR spectroscopy and electrospray ionisation mass spectrometry were utilized in analysing the complexes in solution and in the gas phase, respectively. The 1H NMR titration studies in methanol-d4 reveal that the association constants for the 1:1 complexes vary according to the electronic properties of the hosts as well as the size, geometric orientation and charge concentration of the guest cations with binding constants of up to 950 M⁻¹ in some cases. Mass spectrometry reveals 1:1 monomeric and 1:2 dimeric complexes in the gas phase. Six co-crystals, three of which are dimeric host-guest capsular assemblies, two open inclusion complexes and a pseudocapsular methanol solvate, were analysed in the solid state through single-crystal X-ray diffraction. The crystal structures confirm that the complexes are held together by multiple cation⋯π, CH⋯π and hydrogen bond interactions.

Introduction

The discovery of new receptors with new properties such as high selectivity or versatility is a continuous quest for supramolecular researchers.1–3 Modifying known receptors in most cases increases their binding efficiency and in some cases increases the variety of guests.2 Resorcinarenes and pyrogallarenes constitute a class of phenolic macrocyclic receptors.4–7 The bowl-shaped electron rich cavity of the C₄ᵥ of resorcinarenes and pyrogallarenes has been vastly explored in the binding of a variety of different guests through multiple weak interactions.8–12 The eight and twelve hydroxyl groups on the upper rim of the resorcinarenes and pyrogallarenes, respectively, play a key role in maintaining their conformation.13 These hydroxyl groups also aid the formation of many supramolecular assemblies and in co-crystallization studies.5,14 The electron rich interior is particularly suitable to bind guests through cation⋯π and CH⋯π interactions with a distinct preference for the size and orientation of the guests.5,15 Host–guest complexes of unfunctionalized resorcinarenes with a variety of guests have resulted in supramolecular assemblies such as 1:1 open inclusion complexes,16,17 dimeric5,14,17–21 and hexameric22–24 capsular as well as tubular assemblies.25,26

The ammonium group is particularly important in biotechnology since it constitutes part of many active pharmaceutical compounds.27–29 A recent trend is the co-crystallization of some pharmaceutical compounds with receptors like resorcinarenes and pyrogallarenes with the hope of improving their pharmaceutical properties,30,31 making crystal engineering12 a useful tool in analysing supramolecular assemblies. A recent example is the co-crystallization of the pharmaceutical drug gabapentin, a primary amine widely used for the treatment of epilepsy and neuropathic pain,33–34 with pyrogallarenes, which was studied by Atwood et al.35

Secondary and tertiary ammonium salts possess the hydrogen bond donating groups –NH₂ and –NH, respectively, and these can further enhance their complexation through intermolecular hydrogen bonds. Rissanen et al.35 reported one example of this type of complex whereby a dimeric capsule is formed between resorcinarene and triethylammonium chloride. In this complex, the –NH group is hydrogen bonded to a water molecule and this mini-assembly acts as a template for the larger dimeric capsule.35

The ability of resorcinarenes to bind both symmetrical and unsymmetrical quaternary ammonium salts is well reported.5–21
The tetramethyl ammonium (TMA) cation is of optimum size and orientation to template dimeric capsular assemblies. Complexes of resorcinarenes and diquaternary ammonium \([N,N\text{-diaryl-1,4-diazabicyclo[2.2.2]octane \left( \text{alkyl}_2\text{-DABCO} \right)}]\) dications show a higher binding constant in alcoholic solvents than the quaternary ammonium analogues due to the higher charge concentration of the diquaternary ammonium cations. The orientation of the alkyl\(_2\)DABCO dication in the cavity of the resorcinarene influences the final structure of the complex, as seen in several X-ray crystallographic studies. Dimethylpiperazine has been shown to deprotonate resorcinarenes and templates a directly hydrogen bonded assembly. Despite the multitude of reported structures involving quaternary ammonium salts and unfunctionalized resorcinarenes and pyrogallarenes, there are limited reports on host–guest complexes with primary and tertiary ammonium cations. Only one co-crystal structure of a secondary ammonium salt viz. proline is reported by Aoki et al.

In this contribution, we report several supramolecular co-crystals of two resorcinarenes and a pyrogallarene, acting as the receptors, with a series of secondary and tertiary mono- and di-ammonium salts (Fig. 1) in the solid state via single crystal X-ray diffraction analyses. These assemblies were studied in solution through \(^1\)H NMR titration analyses and in the gas phase via electrospray ionization mass spectrometry (ESI-MS). The ammonium salts all possess a hydrogen bond donating NH/NH\(_2\) group and are of different sizes and orientations compared to quaternary TMA and diquaternary alkyl\(_2\)-DABCO cations. The interactions and template effects of these salts in the final assemblies are analysed.

### Results and discussion

#### Solid state analyses

Single crystals were obtained from several host–guest systems and structurally characterized as the pseudo-capsular solvate \(2\text{MeOH}@2\), the dimeric host–guest capsules \(5a@2, 5b@2, 5b@3, \) and the host–guest inclusion complexes \(4a@2\) and \(5c@1\).

\(2\text{MeOH}@2\) is the crystallization product of \(2\) in methanol by slow evaporation. Despite the absence of an ammonium ion template, the solvate forms a pseudo capsule with two MeOH solvent molecules in the cavity and another two MeOH molecules outside the cavity. The role of methanol in the formation of the pseudocapsule is crucial. The two in-cavity MeOH interact with one of the resorcinarene molecules in the pseudocapsule via OH···π interactions and through O···HO hydrogen bonds (donated by the host –OH) with the second resorcinarene molecule (Fig. 2A and B), while the two out-of-cavity MeOH act as a hydrogen bond donor and a hydrogen bond acceptor bridging adjacent resorcinarene pseudo capsules (Fig. 2C). In addition, along the crystallographic \(b\) direction, the pseudo capsules hydrogen bond with each other by O···HO interactions, thus extending the structure to a two dimensional network (Fig. 2C).

The structures of \(5a@2, 5b@2, \) and \(5b@3\) are observed in the solid state as dimeric capsules with the ammonium cation sitting in each capsular assembly (Fig. 3). Among them, both \(5a@2\) and \(5b@2\) crystallize in the orthorhombic space group \(Pnnn\), where the guest cations are located around...
The intersection of three 2-fold axes. However, $5b@3_2$ crystallizes in the triclinic space group $P\bar{1}$, with the $N_{TEA}$ atom lying exactly on the centre of inversion. The symmetries of the ammonium cations are lower than those of the cavities in all the cases and are accordingly disordered in the cavities. The sizes of the cavities and the ammonium cations also reflect the disorders. The volumes of the cavities in $5a@2_2$, $5b@2_2$ and $5b@3_2$ are approximately 200, 212 and 274 Å$^3$, respectively, as calculated by PLATON, whereas those of the corresponding ammonium cations are much smaller. In the structures of $5a@2_2$ and $5b@2_2$, the $Cl^-$ anions generally prefer to sit in the middle of the lower rim of the ethyl chains stabilized by weak $CH\cdots Cl^-$ interactions (the mean $C_{methylen}e\cdots Cl^-$ distances are 3.835 in $5a@2_2$ and 3.743 in $5b@2_2$) similar to structures with quaternary salts. However, the hydroxyl groups of the resorcinarenes also compete for the $Cl^-$ ions, therefore some chloride anions are located beside the OH groups participating in the capsule formation. The competition of the hydroxyls is overwhelming in the case of pyrogallarene, whereby all the $Cl^-$ ions form $OH\cdots Cl^-$ hydrogen bonds, with no $Cl^-$ anion located between the lower rim of the ethyl chains.

In the two host-guest complexes $5a@2_2$ and $5b@2_2$, four $OH\cdots O$ intramolecular hydrogen bond interactions support the $C_{4v}$ conformation of the resorcinarene, while the other four OH groups interact with either the guest water, MeOH or $Cl^-$ anions. The guests link each half of the dimeric capsule equally, thus templating the capsule formation. The two resorcinarene molecules in the capsule are arranged in a staggered orientation. Such an arrangement further stabilizes the capsule through weak $CH\cdots O$ interactions. In the capsule $5b@3_2$, the four central OH groups break the staggered arrangement due to

![Fig. 3](image-url) Dimeric capsules formed via multiple cation-π, $CH\cdots\pi$ and hydrogen bond interactions with ammonium cations in the cavities: (A) $5a@2_2$, (B) $5b@2_2$, (C) $5b@3_2$.

![Fig. 4](image-url) Packing of the capsules in the crystals of $5a@2_2$ (A) and $5b@3_2$ (B). The packing in $5b@2_2$ is the same as that in $5a@2_2$. 

Published on 05 December 2014. Downloaded by Jyvaskylan Yliopisto on 09/07/2015 09:49:36.
the direct OH⋯O intermolecular hydrogen bond interactions between the two pyrogallarene molecules. As a result of these two intermolecular hydrogen bonds, the two pyrogallarene molecules are pushed further away from each other with a bottom-to-bottom distance of 11.964 Å compared to 10.382 Å in 5a@2_2 and 10.441 Å in 5b@2_2 (the bottom centres are defined by the centroid of the four H atoms attached to the aromatic rings). The other two central hydroxyl groups of the first pyrogallarene are indirectly connected via H_2O molecules to the hydroxyl groups of the second one within the capsule.

Fig. 4A illustrates the packing of the capsules in 5a@2_2, as viewed from the crystallographic c direction. Direct OH⋯O hydrogen bonds between resorcinarene groups connect the dimeric capsule along the a axis, whereas along the b axis direction, two water molecules bridge the adjacent capsules by OH⋯O hydrogen bond interactions. Four neighbouring capsules in the same layer are further joined by hydrogen bonds with disordered water, MeOH and Cl^− molecules. The packing of the capsules in 5a@2_2 and 5b@2_2 is quite similar, contrary to that in 5b@3_2. Fig. 4B displays the arrangement of 5b@3_2 in the ab plane. Intermolecular OH⋯O hydrogen bond interactions between adjacent capsules extend the structure along a and b directions to two-dimensional layers. Solvent water molecules and chloride anions squeeze into the inter-space and further glue the capsules through hydrogen bonds.

In the structure of 4a@2, due to the small volume of dimethyl ammonium chloride, the salt is entirely captured by one resorcinarene. In addition to the NH⋯Cl^− hydrogen bonds, cation⋯π interactions and in-cavity OH⋯Cl^− hydrogen bonds between the Cl^− and resorcinarene are also observed (Fig. 5A). The Cl^− anion further bridges two more host molecules by two out-of-cavity OH⋯Cl^− hydrogen bonds. Solvent molecules are not crystallized in the lattice, thus adjacent resorcinarene molecules interact with each other via OH⋯O hydrogen bonds along the b direction (Fig. 5C).

In the complex 5c@1, despite the dication 5c connecting two resorcinarenes via cation⋯π interactions (the average distance between C_methyl and aromatic centre is 3.425 Å), two cations share the same resorcinarene cavity (Fig. 5B). The ratio of the host and guest in 5c@1 is therefore 1:1. One of the two

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**Fig. 5** Projections to show the structures in 4a@2 (A and C) and 5c@1 (B and D). A and B: the unit structures with thermal ellipsoids at 30% probability; C and D: the 2-D layers formed by the intermolecular interactions.

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**Fig. 6** A) 1H NMR spectral changes observed (A) upon the addition of 5b (50 mM) to pyrogallarene 3 (5 mM) and (B) upon the addition of 5c (50 mM) to resorcinarene 1 (5 mM). Measurements were done in CD_3OD at 303 K.
chlorides, Cl1, is captured by the positive nitrogen through electrostatic interaction while the other chloride, Cl2, is involved in linking two adjacent resorcinarene molecules. In such way, a 2-D hydrogen bond network is formed in 5c@1 (Fig. 5D).

**Solution studies**

A series of 1H NMR titration studies were performed to probe the binding capabilities of the different hosts 1–3 and the ammonium guests 4a–5c. The presence of the NH and NH2 groups on the guests has the potential of adding a direct hydrogen bond motif between the hosts and the guests. The 1H NMR titration experiments between the hosts 1–3 and the guests 4a–5c were done in methanol-d4 at 303 K. In the experiment, increasing amounts of the ammonium salts (50 mM) were added to a solution of each of the hosts 1–3 (5 mM). Complication induced shifts of the 1H NMR resonances of the guest protons were observed (Fig. 6). These result from the shielding effects of the aromatic rings of the bowl-shaped host cavity upon the addition of the guests. This phenomenon clearly reveals a fast guest exchange on the NMR time scale.

A close observation of the chemical shifts reveals that the pyrogallarene 3 shields the guests better than the methyl-resorcinarene 2 and the resorcinarene 1 (Fig. S6, ESI†). The presence of the extra hydroxyl group on the pyrogallarene 3 and the methyl group on the resorcinarene 2 can explain this observation since they enhance the electron density of the host cavity by electron donation. Job plots experiments reveal mainly 1:1 binding stoichiometry (see the ESI†). In the case of 5c, the Job plots showed the possible formation of 2:1 species (see the ESI†). Signals from the guests were successfully determined and the binding constants were obtained by non-linear least square titration curve fitting of the respective titration data based on 1:1 and 2:1 (for 5c) host–guest binding modes using the winEQNMR2 computer program.44 The binding constants and the signals obtained are presented in Table 1.

A significantly higher binding constant K1 for the tertiary di-ammonium salt 5c as compared to the tertiary mono-ammonium salts 5a-b as well as the secondary mono-ammonium salts 4a-b was observed. The high affinity of the hosts towards the di-tertiary ammonium salt 5c could be explained by the high charge concentration and the suitable size of the guest 5c. The second binding constant K2 was much lower in all cases compared with that of 5c, highlighting the well known14,16,20 interference of the bulk methanol. The titration study was not possible for the dication 4c due to its extremely low solubility in methanol. The binding constant K1 of the dication 5c is equally higher than the values reported for its diquaternary Me2-DABCO analogue (145 M−1 at 288 K and 105 M−1 at 313 K for host 1).14 The high binding constant K1 can be explained by the presence of the NH groups on 5c. The crystal structure of the host-guest complex 5c@1 (Fig. 5b) shows that the guest ion-pair is located in the cavity of the resorcinarene held together by NH···Cl hydrogen bonds. This complex process is believed to be responsible for the increase in the binding affinity of 5c.

Comparatively, the binding constants of the secondary 4a–4b and tertiary 5a–5b ammonium cations are lower than the values reported for the quaternary TMA analogue (195 M−1 at 288 K, 93 M−1 at 298 K and 170 M−1 at 303 K for host 1, 121 M−1 at 303 K for host 2 and 478 M−1 at 303 K for host 3).14,16 The dimethyl 4a and trimethyl 5a cationic analogues are relatively smaller and tumble freely within the cavity of the resorcinarene and pyrogallarene hosts, resulting in lower binding constants as compared to that of the quaternary TMA analogue. The small size of 4a for example was highlighted in the crystal structure of 4a@2 where the entire ion pair was bound in the cavity of the resorcinarene (Fig. 5a). The ethyl groups of the diethyl 4b and triethyl 5b ammonium cations are slightly longer as compared to quaternary TMA, thus resulting in lower binding constants.

### Table 1. Binding constants K1 [M−1] and K2 [M−2] for hosts 1–3 with guests 4a–5c in CD3OD at 303 K

<table>
<thead>
<tr>
<th>Host</th>
<th>K1 M−1</th>
<th>K2 M−2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a@1</td>
<td>4±1.3</td>
</tr>
<tr>
<td></td>
<td>4a@2</td>
<td>51±1.6</td>
</tr>
<tr>
<td></td>
<td>4a@3</td>
<td>59±8.2</td>
</tr>
<tr>
<td>2</td>
<td>4b@1</td>
<td>23±2.7</td>
</tr>
<tr>
<td></td>
<td>4b@2</td>
<td>19±3.5</td>
</tr>
<tr>
<td></td>
<td>4b@3</td>
<td>25±2.7</td>
</tr>
<tr>
<td>3</td>
<td>4c@1</td>
<td>4±1.3</td>
</tr>
<tr>
<td></td>
<td>4c@2</td>
<td>4±1.3</td>
</tr>
<tr>
<td></td>
<td>4c@3</td>
<td>4±1.3</td>
</tr>
<tr>
<td>Tertiary ammonium salts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5a@1</td>
<td>65±11</td>
</tr>
<tr>
<td></td>
<td>5a@2</td>
<td>23±4.3</td>
</tr>
<tr>
<td></td>
<td>5a@3</td>
<td>48±3.0</td>
</tr>
<tr>
<td>2</td>
<td>5b@1</td>
<td>23±1.7</td>
</tr>
<tr>
<td></td>
<td>5b@2</td>
<td>37±2.0</td>
</tr>
<tr>
<td></td>
<td>5b@3</td>
<td>24±1.3</td>
</tr>
<tr>
<td>3</td>
<td>5c@1</td>
<td>676±22</td>
</tr>
<tr>
<td></td>
<td>5c@2</td>
<td>778±35</td>
</tr>
<tr>
<td></td>
<td>5c@3</td>
<td>413±96</td>
</tr>
</tbody>
</table>

a Obtained from monitoring the guests’ CH3 signals. b K could not be determined due to the low solubility of 4c in methanol.

gas phase analyses

The complexation of the ammonium guests 4a–5c with the hosts 1–3 was investigated in the gas phase via electrospray ionization mass spectrometry (ESI-MS).45–47 Using methanol as the spray solvent in the positive ion mode, the complexes can be observed in the gas phase. Samples containing combinations of the hosts 1–3 and the ammonium guests 4a–5c were prepared and analysed.†

† The resorcinarene and pyrogallarene hosts 1–3 were synthesized according to reported procedures.11 The ammonium salts 4a, 4b, 5a and 5b were commercially available. The ammonium salts 4c and 5c were obtained from the corresponding piperazine and 1,4-dimethylpiperazine through protonation with HCl. 1H and 13C NMR spectra were recorded on a Bruker Avance DRX 500 (500 MHz for 1H and 126 MHz for 13C) and a Bruker Avance DRX 400 (400 MHz for 1H and 100 MHz for 13C) spectrometers. The mass spectrometric studies were performed with a QSTAR Elite ESI-Q-TOF mass spectrometer equipped with an API 200 TurbolonSpray ESI source from AB Sciex (former MDS Sciex) in Concord, Ontario (Canada). All experiments were performed on positive polarization. The parameters of the ion source, ion optics and quadrupole were optimized to get maximum abundance of the ions under study. Single-crystal X-ray diffraction studies on 2MeOH@12, 5a@22, 5b@32 and 4a@2 were conducted at 173 K on an Agilent SuperNova diffractometer using mirror-monochromatized Mo Kα (λ = 0.71073 Å) radiation. The single crystal data for 5b@2 and 5c@1 were collected at 123 K using an Agilent SuperNova dual wavelength diffractometer with a micro-focus X-ray source and multilayer optics monochromatized Cu Kα (λ = 1.54184 Å) radiation. All the data collection and reduction were performed using the program CrystAlisPro.48

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were all analysed. The cations act as templates in the construction of the assemblies. The complexes are held together by multiple cation⋯π, CH⋯π and hydrogen bond interactions. The anions in some cases assist the capsular formation and together with solvent molecules connect the complexes, resulting in complex three-dimensional architectures. The size and electronic properties of the alkyl groups of the guests had a direct effect on the binding strength of the assembly, as shown by $^1$H NMR titration studies. Due to a higher charge concentration and a better fit, the guest 5c showed the strongest binding in solution. The other ammonium salts that were either too small or slightly larger and unsymmetrical as compared to TMA showed lower binding constants. The substituent on the 2-position of the benzene ring also had an influence on the shielding effects of the guest with the most shielding observed with pyrogallarene 3. Positive-ion mass spectrometric studies also confirmed that the 1:1 monomeric and 1:2 dimeric complexes prevail in the gas phase. This work adds substantial information on the recognition abilities of resorcinarenes to secondary and tertiary mono- and di-ammonium salts in all phases. It supplements the literature on the binding of quaternary ammonium salts and also contributes to our understanding of non-covalent interactions, which are very important in supramolecular chemistry and can be applied in other areas of chemistry.

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Notes and references


Conclusions

This study reports the complexation of several secondary and tertiary mono- and di-ammonium salts 4a–5c with resorcinarenes and pyrogallarene 1–3 in the solid state, in solution and in the gas phase. Co-crystals of several host-guest assemblies were all analysed. The cations act as templates in the construction of the assemblies. The complexes are held together by multiple cation⋯π, CH⋯π and hydrogen bond interactions. The anions in some cases assist the capsular formation and together with solvent molecules connect the complexes, resulting in complex three-dimensional architectures. The size and electronic properties of the alkyl groups of the guests had a direct effect on the binding strength of the assembly, as shown by $^1$H NMR titration studies. Due to a higher charge concentration and a better fit, the guest 5c showed the strongest binding in solution. The other ammonium salts that were either too small or slightly larger and unsymmetrical as compared to TMA showed lower binding constants. The substituent on the 2-position of the benzene ring also had an influence on the shielding effects of the guest with the most shielding observed with pyrogallarene 3. Positive-ion mass spectrometric studies also confirmed that the 1:1 monomeric and 1:2 dimeric complexes prevail in the gas phase. This work adds substantial information on the recognition abilities of resorcinarenes to secondary and tertiary mono- and di-ammonium salts in all phases. It supplements the literature on the binding of quaternary ammonium salts and also contributes to our understanding of non-covalent interactions, which are very important in supramolecular chemistry and can be applied in other areas of chemistry.

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