Title: Simultaneous Endo- and Exo-Complex Formation of Pyridine[4]arene Dimer with Neutral and Anionic Guests

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**Simultaneous Endo- and Exo-Complex Formation of Pyridine[4]arene Dimer with Neutral and Anionic Guests**


Abstract: Complex formation between hexafluorophosphate (PF$_6^-$) and tetrabutyl-octahydroxypyridine[4]arene (1) has been thoroughly studied in gas phase (ESI-QTOF-MS, IM-MS, DFT calculations), solid state (X-ray crystallography) and in chloroform solution (1H, 19F and DOSY NMR). In all states of matter, simultaneous endo-complexation of solvent molecules and exo-complexation of PF$_6^-$ anion within pyridine[4]arene dimer was observed. While similar ternary complex formation is often observed in solid state, this is a unique example of such behaviour in the gas phase that has never been observed so far.

Resorcinarenes, their derivatives, and their dimeric and hexameric assemblies have found numerous applications in molecular recognition as binding motifs for neutral molecules and cations but also for anions.[1] Over the years, however, there have been contradicting reports on the actual binding site for anionic guests: Dimeric capsules, for example, bind separated ion pairs by encapsulating the cation in the cavity of the dimeric capsule with the anion bound at the lower rim via alkyl- and aryl-CH-anion interactions as evidenced by X-ray diffraction analysis.[2] Likewise, a monomeric cavitand was found to bind ion pairs in a similar fashion in solution, with the anion located at the lower rim between the alkyl chains.[3] Such an arrangement was somewhat counterintuitive, especially regarding our previous work on anion binding with functionalized cavatands in the gas phase where computational studies suggested binding of the anions at the upper rim via CH-anion hydrogen bonding involving the H atoms of the acetal bridges.[4] Nevertheless, this study clearly revealed that anion binding is significantly enhanced by functionalizing the cavatand with electron-withdrawing groups. Therefore, the corresponding pyridine[4]arenes[5] derived from the condensation of 2,6-dihydroxypyridine[4] and aldehydes seemed even more promising for this purpose. They are even more electron deficient and present a unique array of hydrogen bond donor and acceptor functions fixing these molecules in cone conformation. Pioneering work by Mattay already suggested octahydroxy-pyridine[4]arene, without lower rim alkyl chains, strongly supported the encapsulation of anionic guests inside the dimer, located in the middle of the cavity close to the hydrogen bonded seam of the dimer. The computational studies showed that anions like tetrafluoroborate and hexafluorophosphate are optimally sized for encapsulation inside the dimer.[6] Moreover, the complexation of carboxylates was experimentally observed, but the mass spectrometric investigation also suggested that the guest could actually be located outside the cavity, with the IRMPD experiments showing the elimination of the guest as the first dissociation step.[7]

Therefore, we decided to thoroughly re-investigate the anion binding behaviour of these interesting but least studied members of the family of resorcinarenes, choosing tetrabutyl-octahydroxy-pyridine[4]arene (1, Scheme 1) to study its binding behavior towards hexafluorophosphate (PF$_6^-$) in solution (NMR), the solid state (X-ray crystallography), and the gas phase (ESI-MS, IM-MS, DFT calculations) as a first example.

Cohen earlier showed by 'H DOSY NMR that the tetraundecyloctahydroxypyridine[4]arene forms an equilibrium of dimeric and hexameric aggregates in chloroform solution.[9] The 'H NMR spectra of 10 mM solution of 1 in chloroform clearly show the formation of dimeric capsule-like aggregates, indicated by the signals at 7.10, 4.28 and 1.90 ppm (Figure 1), which can be assigned to the dimeric species by DOSY NMR. These signals give a diffusion coefficient of 0.411·10$^{-5}$ cm$^2$s$^{-1}$ which is comparable with the 0.37·10$^{-5}$ cm$^2$s$^{-1}$ value measured for tetraundecyloctahydroxypyridine[4]arene dimer by Cohen.[9]

Interestingly, the 'H NMR spectra measured of equimolar solutions of 1 and TBAPF$_6$ in chloroform (Figure 1) show significant, albeit small downfield shifts for the signals of the Ar-H protons H$_A$ and the CH$_2$ protons H$_B$ at the lower rim of the pyridinearene, in accordance with the observations of Diederich and Dalcanale[5] and resulting from weak CH-anion interactions between the PF$_6^-$ anion and the dimer of 1. This is a strong

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**Scheme 1.** Tautomerism of tetrabutyl-octahydroxy-pyridinium[4]arene 1 (only one of the two possible enantiomers of the pyridone tautomer is shown).
indication that the anion is bound on the exterior of the dimeric capsule, and not inside the cavity as suggested by the previous reports.

Additional proof for such exo-interactions came from the comparison of the $^{19}$F NMR spectra of the TBAPF$_6$ and 1+TBAPF$_6$ samples. Significant downfield shift of the fluorine atoms signals (Figure 2) was observed upon binding of hexafluorophosphate. The fact that only a single set of downfield shifted signals of the guests is observed suggests a fast exchange and/or tumbling motion of the almost spherical anion within its binding pocket on the NMR time scale. While the endo-complexation would be expected to result in the shielding of the guests and an upfield shift of the guest signals a downfield shift, however, agrees very well with weak CH-anion interactions, again strongly supporting exo-complexation of the anion with 1.

Single crystals of the 1+TBAPF$_6$ complex were obtained from a chloroform solution of 1 and 3 eq. TBAPF$_6$, by slow evaporation at around 4 °C. The crystal structure (Figure 3) shows 1 in the pyridone tautomeric form (see Table S1). Its cone conformation is stabilized by four intramolecular (hydroxyl)O−H···O(amide) hydrogen bonds with lengths of 2.524(5), 2.553(5), 2.571(6) and 2.609(5) Å, unidirectionally oriented along the upper rim in a clockwise manner. Similarly, the isobutyl groups are aligned unidirectionally along the lower rim with the methane CH groups in an anticlockwise arrangement. Next, two molecules of 1 form a dimeric capsule sustained by eight N−H···O(amide) hydrogen bonds, with the lengths of symmetrically independent hydrogen bonds of 2.822(6), 2.872(6), 3.108(6) and 3.115(8) Å. The latter two hydrogen bonds are elongated due to bifurcation, as both the NH donors and O(amide) acceptors are also engaged in hydrogen bonding with the neighbouring capsule (3.018(6) and 3.040(5) Å long, Figure S1 in SI). Instead of PF$_6^-$ anion, we found the dimer cavity fully occupied by a CHCl$_3$ molecule. On the other hand, the PF$_6^-$ anion was found to reside on the lower rim of 1, in a slightly asymmetric tilted orientation within the pocket formed by the four isobutyl groups. To the best of our knowledge this is the first solid state structure of a pyridinearene host-guest complex and such a motif of simultaneous endo-binding of a solvent molecule and exo-binding of an anion has never been observed for any other resorcinarene system. The apical fluorine atom of the PF$_6^-$ forms short contacts with the four lower rim aromatic CH protons, with respective C−H···F hydrogen bond lengths of 3.445(8), 3.516(8), 3.566(7) and 3.616(7) Å, as well as with the isobutyl groups. Equatorial fluorine atoms further form a number of C−H···F hydrogen bonds with the isobutyl groups. The PF$_6^-$ anion is further surrounded by two CHCl$_3$ molecules and the tetrabutyl ammonium (TBA$^+$) cation, also forming a number of C−H···F hydrogen bonds (Figure S2 in SI).

The spontaneous self-assembly of 1 into dimeric ions was also clearly observed in ESI-MS spectra. In addition to the deprotonated ion [1+H]$^+$ at m/z 1432 and anion complex [1+PF$_6$]$^-$ at m/z 1578, abundant formation of solvent adduct [1+PF$_6$+S]$^-$ (S = solvent, e.g., acetone, acetonitrile or CH$_2$Cl$_2$, depending on sample solvent) and ternary complex [1+PF$_6$+S]$^-$ were clearly detected (Figure 4).[10] Even though the formation of solvent adducts or even inclusion of solvent molecules is relatively common in condensed phase where the solvent often fills the void space, this phenomenon is extremely surprising and novel in gas phase and has – to the best of our knowledge – never been described in any anion- or cation-binding study with resorcinarenes before. It is important to note that the monomer region of the mass spectra did not show any peaks corresponding to solvent adducts such as [1+H+S]$^-$ or [1+PF$_6$+S]$^-$, implying that the phenomenon is indeed a feature of the dimer via inclusion, and not adduct formation.
When ternary complex, \([\text{12}+\text{PF}_6\text{+acetone}]^-\), was isolated in gas phase and activated in collision-induced dissociation (CID) experiment, \(\text{PF}_6^-\) anion was eliminated in the initial dissociation step. CID is an ergodic activation technique and due to energy randomization the weakest bond or interaction is generally broken first. Elimination of the anion as the initial dissociation step, implies to weak and exo-complexation of \(\text{PF}_6^-\) with pyridinearene 1, since only small amounts of other dissociation products were observed. In the case of endo-complexed \(\text{PF}_6^-\) and exo-complexed solvent, elimination of solvent or pyridinearene monomer would be expected as the first step. Definitive proof for the exo-complexation of anion in the gas phase was obtained by drift tube ion-mobility mass spectrometry (DTIM-MS) experiments.[12,13] IM-MS is still rarely utilized tool in supramolecular chemistry despite its benefits in the detection of host-guest complexes and the analysis of conformers and structural features.[14] As the drift tube of the IM-MS instrument is operated at atmospheric pressure, it allows high resolution calibration, which often severely complicates the analysis when used. The ion mobilograms (Figure 4a) show very similar but clear larger DTCCS\(_2\) values for ions \([\text{12+PF}_6\text{+acetone}]^-\) and \([\text{12+PF}_6\text{+acetone}]^-\) compared to ions \([\text{12-H}^-]\) and \([\text{12-H+acetone}]^-\). In terms of collision cross sections (CCS), the \(\text{PF}_6^-\) complexes are \(-8\) Å\(^2\) larger compared to the deprotonated dimer (Table 1).

Table 1. Experimental DTCCS\(_{2+}\) values and comparison of approximated diameters (nm) obtained by IM-MS, 1H DOSY NMR and X-ray diffraction.

<table>
<thead>
<tr>
<th>Ion</th>
<th>(m/z)</th>
<th>DTCCS(_{2+}) (Å(^2))</th>
<th>IM-MS(^a) (d) (nm)</th>
<th>DOSY (d) (nm)</th>
<th>X-ray (d) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{1-H}]^-)</td>
<td>715</td>
<td>254.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>([\text{1-H}^+])</td>
<td>1432</td>
<td>350.8</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>([\text{1-acetone-H}^-])</td>
<td>1490</td>
<td>388.6</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>([\text{1-PF}_6^-])</td>
<td>1578</td>
<td>369.9</td>
<td>2.3</td>
<td>2.0</td>
<td>1.9(^b)</td>
</tr>
<tr>
<td>([\text{1-PF}_6^-\text{+acetone}]^-)</td>
<td>1636</td>
<td>377.6</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Diameters calculated on basis of CCS by assuming a spherical conformation.
\(^b\) Diameters for 1H DOSY NMR and X-ray diffraction apply generally to dimers.

Therefore, it is reasonable to conclude that, also in the gas phase, the dimers of 1 contain endo-complexed solvent and exo-complexed anion and can thus be denoted as \([\text{12+PF}_6\text{+exocomplex}\text{+endo}]^-\). Assuming the spherical shape for dimer of 1, the obtained CCS values can be roughly compared with the hydrodynamic radii from the 1H DOSY NMR and the crystal structure (Table 1). Each of the methods results in very similar diameters (1.9 to 2.3 nm), demonstrating structural similarity of dimers in solid state, gas phase, and solution and also highlighting the potential of IM-MS technique for structural chemistry purposes of host-guest systems.

To further analyse the gas phase structures of the observed ternary complexes, we performed density functional theory (DFT) calculations for the dimer and its inclusion complexes in vacuo at the RIMPBE/PBE/def2-TZVP and RIMPBE/PBE/def2-TZVP-D3 levels of theory.[16-18] As mentioned above, previous computational studies suggested the encapsulation of \(\text{PF}_6^-\) within the octahydroxypyridine[4]arene capsule.[9] However, the lower rim alkyl chains were truncated and the solvent molecules were not modelled explicitly in this earlier study, with the solvent effects included using the COSMO-model only. Therefore, both the endo- and exo-complexes of \(\text{PF}_6^-\) with and without acetone were re-examined by simulating the complete structures.

Optimized structures of the inclusion complexes are in good agreement with solid state structures, with the exo-complexed \(\text{PF}_6^-\) showing several F···H interactions with the lower rim alkyl chains of 1, in \([\text{1+PF}_6\text{+exo}]^-\), \([\text{12+PF}_6\text{+exo}]^-\), and \([\text{1+PF}_6\text{+exo+acetone}]^-\) (Table S3 and Figure S4).

The calculated interaction energies, given in Table 2, reveal that the exo-complexation of \(\text{PF}_6^-\) is favoured over the endo-complexation in all studied systems, except in \([\text{1+PF}_6\text{+exo}]^-\), when the dispersion correction is applied. The dispersion-corrected calculation predicts the interaction energy for \([\text{1+PF}_6\text{+exo}]^-\) to be \(-10\) kJmol\(^{-1}\) more favourable compared to the one for \([\text{12+PF}_6\text{+exo}]^-\). However, this is reversed in case of the ternary complexes, where the \([\text{12-PF}_6\text{+exo+acetone}]^-\) is significantly more favoured (by \(-20\) kJmol\(^{-1}\)) compared to \([\text{1+PF}_6\text{+exo+acetone}]^-\). Interestingly, the dispersion-corrected
interaction energies are much higher (40-120 kJmol⁻¹) than the non-corrected energies underlining the important role of dispersion forces in the formation of the inclusion complexes at hand.

Table 2. Calculated interaction energies for 1 and complexes at the RI-PBEPBE/def2-TZVP (E₁a) and RI-PBEPBE/def2-TZVP-D3 (E₁a-D3) levels of theory.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ΔE₁a</th>
<th>ΔE₁a-D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1+PF₆₋(exo)]⁻</td>
<td>−122.49</td>
<td>−161.27</td>
</tr>
<tr>
<td>[1+PF₆₋(endo)]⁻</td>
<td>−116.90</td>
<td>−155.55</td>
</tr>
<tr>
<td>[1+PF₆₋(exo)+acetone(endo)]⁻</td>
<td>−117.03</td>
<td>−239.3</td>
</tr>
<tr>
<td>[1+PF₆₋(endo)+acetone(exo)]⁻</td>
<td>−105.70</td>
<td>−217.56</td>
</tr>
</tbody>
</table>

To visualize the reason for the exo-complexation of PF₆⁻ we mapped the electrostatic potential (ESP) surfaces of the 1₂ dimer and its complexes with acetone and/or PF₆⁻ (Figure 5). The cavity of the dimer itself does not show any significant positive partial potential. Instead, the seam of hydrogen bonds is clearly polarized and contains electron-rich surfaces implying poor affinity of the cavity towards anions. In contrast to the cavity, however, the lower rim alkyl chains show an electron-poor area that is more suitable for anion binding. The computational data not only supports the experimental finding that the exo-complexation of PF₆⁻ is more favourable than the endo-complexation but it also indicates that the guest encapsulation is largely governed by dispersion forces, making the solvent molecules better guests for the endo-complexation.

In conclusion, we have unambiguously shown the anion complexation by an exo-binding site of pyridine[4]arene 1 through CH-anion interactions in gas phase, solid state, and in solution. This is rationalized by the computed electrostatic potential surfaces which, in contradiction to previous reports, show partial positive potential located between the lower rim alkyl chains, not in cavity. In contrast to earlier assumptions, it is clear that the pyridine[4]arene cavity is not particularly well suited to anion binding. Instead, efficient endo-complexation of neutral molecules by dispersion interactions and formation of ternary complexes is detected. Even though the anion binding (exo-)site is similar in pyridine[4]arenes and classical resorcinarenes, the binding mode in pyridine[4]arene dimer deviates from that of the latter and is unrepresented. Whereas resorcinarenes complex separated ion pairs (cations in cavity and anions at lower rim), the pyridine[4]arene complexes neutral molecules within the cavity and anion on lower rim. Although common in the solid state, similar ternary complex formation has not been previously observed in any gas phase studies of resorcinarenes. This study also shows the importance of utilising novel techniques and...
approaches, such as IM-MS to study the structural chemistry of host-guest complexes in gas phase. Preliminary results,[10,11] concerning binding of other anions in variety of other solvents indicate that this binding motif is a unique feature of the pyridinearenes but it is not limited to the combination of the PF6- anion and chloroform or acetone but is more general in terms of both the anion, the solvent and the pyridinearene lower rim alky chains. We are currently investigating the potential of pyridinearenes in host-guest chemistry in more detail and these results will reported in due course.

Experimental Section

Experimental details for synthesis, NMR, mass spectrometry, DFT calculations and X-ray crystallography are presented in supporting material.

Acknowledgements

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Keywords: pyridinearenes • resorcinarenes • molecular recognition • anion binding • ion mobility mass spectrometry


[6] Please note, that it is actually more efficient to use 2,6-dimethoxypyridine instead of 2,6-dihydroxypyridine for the synthesis of pyridine[4]arenes. For more details see SI.


[10] Preliminary studies show that a similar exo-binding is also found with other anions like BF4- and I- as revealed by NMR and mass spectrometry.

[11] Preliminary studies show that a similar encapsulation of solvent molecules is also found with other solvents like THF and CH2Cl2 as revealed by XRDA-analysis and mass spectrometry.


