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Molecular Binding Behaviors and Thermodynamics of Ferrocenyl Dimethylaminium Derivatives by Anionic Pillar[5]arene

Cui-Fang Zhang, Sheng-Hua Li, Cai-Cai Zhang, and Yu Liu

A novel anionic water-soluble pillar[5]arene (4C-WP5A) was synthesized via a convenient synthetic strategy of the direct cyclization of functionalized hydroquinone monomer. The alkyl chains dependent affinities of ferrocenyl aminiums (FCA, n: carbon number) with 4C-WP5A are driven by hydrophobic interactions and desolvations with assisted C–H···π interactions and electrostatic interactions.

As a new class of cyclophanes, pillar[n]arenes have received more attentions in supramolecular chemistry due to their intrinsic characteristics and properties since reported by Nakamoto and Ogoshi. Unlike other meta-bridged and ortho-bridged aromatic rings, pillar[n]arenes are para-bridged aromatic rings by methylene which make their shapes like cylinders rather than cones. Furthermore, pillar[n]arenes could be functionalized including monofunctionalization, difunctionalization, rim-differentiation, perfunctionalization, and phenylene substitution. Benefiting from easy accessibility and versatile functionality of pillar[n]arenes, the first watersoluble pillar[n]arene (WP[n]A) with ten carboxylate ions at their rims was reported by Ogoshi in 2010, and then WP[n]As have been developed numerous applications for molecular recognition and sensing, functional materials, biological applications and so on. Among those ionic water-soluble pillar[n]arenes, anionic series have attracted more popularity for their good biocompatibilities in chemical biology and good host–guest properties.

Based on the extensive studies of anionic carboxylatopillar[5]arene, to find a facile way for preparing WP[n]A is vital for further applications. So far, the reported carboxylatopillar[5]arene was synthesized by means of cyclisation of 1,4-dialkoxybenzene precursor then removal of alkyl groups with BBr₃ to obtain pillar[5]arene, then functionalized the phenolic groups on both rims of pillar[5]arene with ethyl bromoacetate following by hydrolysis the ester groups to afford percarboxylatopillar[5]arene (Scheme 1).

However, the corrosive and toxic BBr₃ was used for the deprotection of alkyl aryl ethers and the yield of functionalization of pillar[5]arene was relatively low. Meanwhile, the length of columnar conformation of the carboxylate WP[n]A was relatively shorter. In order to supplement the defect of the synthesis and extend the length of WP[n]A, we propose a convenient synthetic strategy for the preparation of a novel carboxylatopillar[5]arene with extended alkyl chains (Scheme 2). In this synthetic strategy, the direct cyclization of monomer precursor is in satisfactory yield for percarboxylatopillar[5]arene, and the BBr₃ is avoided because of no deprotection process involved in this strategy.
The host–guest complexation for $\text{FC}_n^-$ and 4C-WPSA was firstly investigated by $^1$H NMR experiment in $\text{D}_2\text{O}$ at 25°C. As shown in Fig. 2, the methylene proton signals of H-2–H-8 in $\text{FC}_n^-$ are shifted upfield in the presence of 1 equiv. 4C-WPSA, which is the consequence of the inclusion-induced shielding effects by the aromatic ring in 4C-WPSA. Nevertheless, no obvious chemical shift changes is observed for methyl H-1, that indicates the methyl group at the end of alkyl chains thread out of the pillararene’s cavity. On the other hand, all of the proton signals on the pillararene are shifted downfield attributes to deshielding effect of the guest $\text{FC}_n^-$. Interestingly, the single methylene proton (Hc) peak splits into multiple peaks when $\text{FC}_n^-$ is in the presence of 1 equiv. 4C-WPSA, but this phenomenon does not appear for $\text{FC}_n^-$ of the short alkyl chain, which could be ascribed to obvious immobilization of the alkyl substituents in 4C-WPSA after complexation with $\text{FC}_n^-$. And the other reason is that the protons of the upper or lower edges are in the different environment aroused by the asymmetry guest threading into the host.\textsuperscript{30,11} To find the binding stoichiometry of 4C-WPSA $\supsetarrow \text{FC}_n^-$, the job plot was performed by monitoring the chemical shift of Hi on the $\text{FC}_n^-$. As shown in Fig. 3, the inflection point corresponds to the molar ratio of 0.5, which has revealed a 1:1 complexation.

The same $^1$H NMR experiments were carried out for the different $\text{FC}_n^-$ with 4C-WPSA. Comparison of the chemical shift changes ($\Delta\delta$) of methyl H-1 on the different $\text{FC}_n^-$ in the absence / presence of the host 4C-WPSA could find the different inclusion of 4C-WPSA $\supsetarrow \text{FC}_n^-$ (see Figs. S14–S17†). As shown in Table 1, for $\text{FC}_2^-$, the proton signal is shifted from 3.026 to 2.923. This slight change indicates the methyl group is not in the pillararene’s cavity. For $\text{FC}_4^-$ and $\text{FC}_8^-$, the proton signals are shifted from 0.902 to −0.408 and 0.920 to −0.334, respectively, which indicates the methyl group locates in pillarene’s cavity. For $\text{FC}_n^-$, the signal is shifted from 0.747 to 0.446, the relative weak shielding effect partly because the methyl group thread out of the pillarene’s cavity. Meanwhile, the signals of some methylene protons in $\text{FC}_n^-$ are greatly upfield shifted to $\delta < 0$.
by the investigation of the Job plot of 4C-WP5A.

The association constants for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_4\) is \((3.30 \pm 0.35) \times 10^4\ \text{M}^{-1}\), which is a little larger than that for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_3\) because of the uncharged FC\(_4\) is more hydrophobic than FC\(_3\) (see Fig. S29†).

![Job plot for the complexation of (a) FC\(_1\)\(^+\), (b) FC\(_3\)\(^+\), (c) FC\(_4\)\(^+\), (d) FC\(_5\)\(^+\), (e) FC\(_6\)\(^+\), and (f) FC\(_7\)\(^+\), with 4C-WP5A in D\(_2\)O.](image)

As shown in the Fig. 4, the 1:1 stoichiometry was confirmed by the investigation of the Job plot of FC\(_1\)\(^+\), FC\(_3\)\(^+\), FC\(_4\)\(^+\), FC\(_5\)\(^+\), FC\(_6\)\(^+\), and FC\(_7\)\(^+\), with 4C-WP5A. The binding stoichiometry and association constants for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) were listed in Table S1†. Nevertheless, the average association constant for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) was too small to calculate accurately.\(^{10c}\) Concretely, the Ka values for these host–guest complexes became smaller followed the decreasing length of alkyl chains \((\text{FC}_{n}^+ > \text{FC}_{n-1}^+ > \text{FC}_{n-2}^+ > \text{FC}_{n-3}^+)\)\(^{15}\) (see Figs. S25–S28†). The smaller binding affinity for FC\(_1\)\(^+\) and 4C-WP5A was attributed to the single electrostatic interaction between quaternary ammonium salt in FC\(_1\)\(^+\) and carboxyl anions in 4C-WP5A. The maximum C–H⋯\(\pi\) interactions were only up to quadrupole owning to a fixed aromatic cavity in pillararene.\(^{10c}\) So we rationalized the greater affinity of 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) were mainly driven by the increasing hydrophobic interactions, and the C–H⋯\(\pi\) interactions and the electrostatic interactions made the minor contribution to the stability of these host-guest complexes. This speculation was supported by the investigation of complexation for 4C-WP5A with the uncharged FC\(_n\). The \(^1\)H NMR experiments showed that the proton signals of the alkyl chains in FC\(_n\) shifted upfield (see Fig. S18†) and the binding stoichiometry of 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\) is 1:1 (see Fig. S24†). The association constants for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\) is \((3.30 \pm 0.35) \times 10^4\ \text{M}^{-1}\), which is a little larger than that for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_3\) because of the uncharged FC\(_4\) is more hydrophobic than FC\(_3\) (see Fig. S29†).

![Job plot for the complexation of (a) FC\(_1\)\(^+\), (b) FC\(_3\)\(^+\), (c) FC\(_4\)\(^+\), (d) FC\(_5\)\(^+\), (e) FC\(_6\)\(^+\), and (f) FC\(_7\)\(^+\), with 4C-WP5A in D\(_2\)O.](image)

Considering the Ka determined by \(^1\)H NMR titration experiments have relatively big deviations, especially that the Ka values are larger than \(10^5\ \text{M}^{-1}\).\(^{16}\) the microcalorimetric titration was used to ensure the quantitative accuracy of the titration data and gave a deep insight in thermodynamics for the host–guest complexation.\(^{17}\) A typical titration curve is shown in Fig. 5a, the association constant for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) is up to \((6.51 \pm 0.29) \times 10^5\ \text{M}^{-1}\) with a good “N” value of 0.932 in the curve fitting by computer simulation using the “one set of binding sites” model and repeats as 1:1 complex formation. The host–guest complexation for 4C-WP5A and FC\(_n\)\(^+\) except FC\(_1\)\(^+\) have been verified in the same ways which are shown in Figs. 5a–d. The Ka values and thermodynamic parameters (such as enthalpy change \(\Delta H^\circ\) and entropy change \(T\Delta S^\circ\)) are listed in Table 2.

Table 2. Association constant (Ka), standard enthalpic (\(\Delta H^\circ\)), and entropic changes (\(T\Delta S^\circ\)) for inclusion complexations of FC\(_n\) with 4C-WP5A in deionized water at 298 K obtained by ITC.

<table>
<thead>
<tr>
<th>Guests</th>
<th>H-1 ((\delta), ppm)</th>
<th>H-1 ((\Delta\delta), ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC(_1)(^+)</td>
<td>3.026 – 2.923</td>
<td>0.093</td>
</tr>
<tr>
<td>FC(_3)(^+)</td>
<td>0.902 – 0.408</td>
<td>1.310</td>
</tr>
<tr>
<td>FC(_4)(^+)</td>
<td>0.920 – 0.334</td>
<td>1.254</td>
</tr>
<tr>
<td>FC(_5)(^+)</td>
<td>0.747 – 0.446</td>
<td>0.301</td>
</tr>
<tr>
<td>FC(_6)(^+)</td>
<td>0.839 – 0.757</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Fig. 3 \(^1\)H NMR spectra \((\{4C-WP5A\} + [FC\(_n\)\(^+\)] = 2.0 \text{mM}, \text{D}_2\text{O}, 298\ K, 400 \text{MHz}\) of the chemical shift changes of H-1 on FC\(_n\) with the molar ratio of FC\(_n\)\(^+\): (a) individual FC\(_1\)\(^+\), (b) 0.9, (c) 0.8, (d) 0.7, (e) 0.6, (f) 0.5, (g) 0.4, (h) 0.3, (i) 0.2, (j) 0.1, and (k) individual 4C-WP5A. Insert: Job plot showing the 1:1 stoichiometry of the complex between 4C-WP5A and FC\(_n\)\(^+\) by \(^1\)H NMR titration.

As shown in the Fig. 4, the 1:1 stoichiometry was confirmed by the investigation of the Job plot of FC\(_1\)\(^+\), FC\(_3\)\(^+\), FC\(_4\)\(^+\) with 4C-WP5A. The binding stoichiometry and association constants for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) were listed in Table S1†. Nevertheless, the average association constant for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) was too small to calculate accurately.\(^{10c}\) Concretely, the Ka values for these host–guest complexes became smaller followed the decreasing length of alkyl chains \((\text{FC}_{n}^+ > \text{FC}_{n-1}^+ > \text{FC}_{n-2}^+ > \text{FC}_{n-3}^+)\)\(^{15}\) (see Figs. S25–S28†). The smaller binding affinity for FC\(_1\)\(^+\) and 4C-WP5A was attributed to the single electrostatic interaction between quaternary ammonium salt in FC\(_1\)\(^+\) and carboxyl anions in 4C-WP5A. The maximum C–H⋯\(\pi\) interactions were only up to quadrupole owning to a fixed aromatic cavity in pillararene.\(^{10c}\) So we rationalized the greater affinity of 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\)\(^+\) were mainly driven by the increasing hydrophobic interactions, and the C–H⋯\(\pi\) interactions and the electrostatic interactions made the minor contribution to the stability of these host-guest complexes. This speculation was supported by the investigation of complexation for 4C-WP5A with the uncharged FC\(_n\). The \(^1\)H NMR experiments showed that the proton signals of the alkyl chains in FC\(_n\) shifted upfield (see Fig. S18†) and the binding stoichiometry of 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\) is 1:1 (see Fig. S24†). The association constants for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_n\) is \((3.30 \pm 0.35) \times 10^4\ \text{M}^{-1}\), which is a little larger than that for 4C-WP5A \( \supset \supset \supset \supset \) FC\(_3\) because of the uncharged FC\(_4\) is more hydrophobic than FC\(_3\) (see Fig. S29†).

Fig. 4 Job plot for the complexation of (a) FC\(_1\)\(^+\), (b) FC\(_3\)\(^+\), (c) FC\(_4\)\(^+\), (d) FC\(_5\)\(^+\), (e) FC\(_6\)\(^+\), and (f) FC\(_7\)\(^+\), with 4C-WP5A in D\(_2\)O.
Guests  
\[ \text{Ka (M}^{-1}\text{)} \]  
\[ \Delta H^\circ(\text{kJ} \cdot \text{mol}^{-1}) \]  
\[ \Delta S^\circ(\text{kJ} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}) \]  

\begin{array}{|c|c|c|c|}
\hline
\text{FC}^+_1 & \text{---} & \text{---} & \text{---} \\
\text{FC}^+_2 & (7.94 \pm 0.09) \times 10^3 & -8.27 \pm 0.05 & 13.89 \pm 0.17 \\
\text{FC}^+_3 & (2.54 \pm 0.15) \times 10^3 & -16.27 \pm 0.09 & 8.86 \pm 0.23 \\
\text{FC}^+_4 & (1.96 \pm 0.03) \times 10^3 & -21.55 \pm 0.10 & 8.66 \pm 0.14 \\
\text{FC}^+_8 & (6.51 \pm 0.29) \times 10^3 & -26.8 \pm 0.21 & 6.38 \pm 0.32 \\
\hline
\end{array}

(a. For FC\text{+}_1, the exotherm of the complexation is too little to measure.)

![Fig. 5 ITC experiments on complexation of (a) 4C-WPSA \(\supset\) FC\text{+}_4, (b) 4C-WPSA \(\supset\) FC\text{+}_3, (c) 4C-WPSA \(\supset\) FC\text{+}_4, and (d) 4C-WPSA \(\supset\) FC\text{+}_3, respectively, in neat water at 25°C.]

It is generally accepted that favorable enthalpic changes aroused by noncovalent interactions between host and guest including the vander Waals, ion-dipole, hydrogen bond, π-π, C-\(\cdot\)-π and hydrophobic interactions, are driven by noncovalent interactions between host and guest molecules by the increasing two methylene in alkyl chains. So we conclude that increasing favorable enthalpic changes of 4C-WPSA \(\supset\) FC\text{+}_4 with growing \(n\) numbers are mainly driven by the more remarkable hydrophobic interactions.

Also as shown in Table 2, the positive entropy changes of 4C-WPSA \(\supset\) FC\text{+}_n can be observed which hints the increased perplexity during the complexation process, and the values of \(\Delta S^\circ\) have followed the sequence of \(\Delta S^\circ_{\text{FC}^+_4} > \Delta S^\circ_{\text{FC}^+_3} > \Delta S^\circ_{\text{FC}^+_4} > \Delta S^\circ_{\text{FC}^+_8}\). In general, the desolvation results in solvent liberation which makes the positive contributions to the entropy change, and immobilization of conformation makes the negative contributions. So especially for 4C-WPSA \(\supset\) FC\text{+}_3, the feature of \(|\Delta S^\circ| > |\Delta H^\circ|\) indicates that the desolvation of inclusion for 4C-WPSA \(\supset\) FC\text{+}_3 makes more contributions than exothermic effect, while the declension of favorable entropic changes (\(\Delta S^\circ > 0\)) accompanied by the growing length of alkyl chains in FC\text{+}_n can be rationalized in terms of the offset desolvation by the restricted conformations of alkyl chains in 4C-WPSA \(\supset\) FC\text{+}_n, which is deduced from the aforementioned \(^1\)H NMR experiments.

In conclusion, a novel anionic water-soluble pillar[5]arene (4C-WPSA) with extended alkyl chains was conveniently synthesized via the cyclization of functionalized precurors. The relatively high binding affinities of 4C-WPSA with FC\text{+}_n are attributed to the remarkable hydrophobic interactions with minor C-\(\cdot\)-π interactions and electrostatic interactions, which is deduced by mutually supported investigations on \(^1\)H NMR titrations and microcalorimetric titrations. Furthermore, the molecular binding affinity in the 4C-WPSA \(\supset\) FC\text{+}_n is much greater than that in the 4C-WPSA \(\supset\) FC\text{+}_3, which is \(K_{a_{\text{FC}^+_3, \text{FC}^+_3}} = 82.0\). This facile synthesis of 4C-WPSA and its increasing higher affinities with the growing length of alkyl chain aminiums would pave a way for investigating the supramolecular assemblies of different functions based on 4C-WPSA in water. Further works on the aggregations of 4C-WPSA with organic cations are in process in our laboratory.

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Notes and references

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