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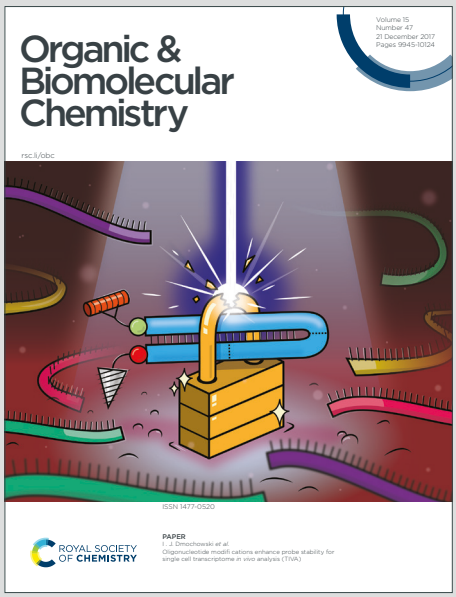

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ARTICLE

Host-guest interaction of nitroxide radicals with water-soluble pillar[6]arene

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The host-guest interaction of nitroxide radicals with water-soluble pillar[n]arenes was for the first time studied by electron paramagnetic resonance spectroscopy and NMR spectroscopy. Our results showed that this interaction strongly depended on the 4-substituents of nitroxides and the cavity size of pillar[n]arene. The host-guest interaction with water-soluble pillar[6]arene **WP6** effectively increased the thermodynamic and kinectic stability of nitroxide radical **4-AT** toward ascrobic acid, thus expanding its potential biomedical applications.

Introduction

Macrocycles such as crown ether,[1,2] cyclodextrin (CD),[3,4] calixarene,[5,6] and cucurbit[*n*]uril (CB[*n*])[7,8] have been widely used in supramolecular chemistry. Recently, pillar[*n*]arenes[9] including pillar[5]arenes[10] and pillar[6]arenes[11] have accepted intense attention as a new type of macrocyclic hosts which are composed of phenolic units linked by methylene bridges at the *para*-position. Owing to their electron-rich cavities, pillar[*n*]arenes can efficiently complex with electron-deficient guest molecules such as methyl viologen[12] and their analogues,[13,14,15] as well as neutral guests.[16,17,18] The host–guest interaction of pillar[*n*]arenes has found wide applications in development of sensors,[19,20] supramolecular polymers,[21,22] artificial transmembrane channels,[23,24,25] liquid crystals[26] and drug delivery systems.[27,28] In this work, we report the host-guest interaction between a water-soluble pillar[6]arene **WP6** and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-based nitroxide radicals (Chart 1).

Nitroxide radicals have found wide applications as spin labels or probes,[29,30,31] spin traps[32,33] and antioxidants[32,34,35] owing to their unique redox properties. The host-guest interaction of TEMPO-based nitroxide radicals with β-CDs[36,37] and CB[7]s[38,39,40] have been well studied due to the suitable cavity sizes of these macrocycles (6.0 Å for β-CD[41] and 7.3 Å for CB[7][42]). These host-guest complexes exhibit enhanced applications in electron paramagnetic resonance (EPR) spectroscopy and imaging due to improved biostability toward reducing agents,[36,43] and also show the potential as paramagnetic gyroscopes and rolling nanomachines.[44] On the other hand, the host-guest interaction with TEMPO radicals and its tetraradical derivatives has been used to probe the cucurbituril assemblies and the homotropic allosteric binding of cucurbituril in water.[45] Since the pillar[6]arene **WP6** has a comparable cavity size (7.7 Å) as β-CDs and CB[7]s, **WP6** may form host-guest complex with TEMPO radicals. However, no related study has been reported except for a TEMPO-linked pillar[5]arene.[46] Unfortunately, the TEMPO moiety was determined to be located outside the cavity of pillar[5]arene due to its small cavity size (5.6 Å).[46] Herein, we investigate the complexation of **WP6** with three 4-substituted TEMPO radicals including **4-AT**, **4-HT** and **4-OT** (Chart 1) by EPR spectroscopy. To confirm the host-guest interaction, NMR spectroscopy is used to study the complexation of **WP6** with the diamagnetic hydroxylamine derivative of **4-AT** (i.e., **4-ATH**, Chart 1). In addition, the effects of the host-guest interaction on the redox potential and stability of **4-AT** toward ascorbic acid are also investigated.

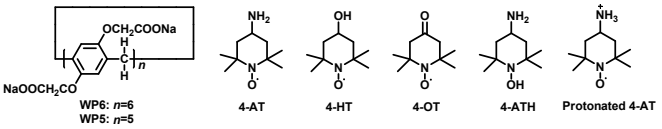

Chart 1. Molecular structures of water-soluble pillar[n]arenes (**WP6** and **WP5**), nitroxide radicals as well as the hydroxylamine and protonated derivatives of **4-AT**.

Results and discussion

EPR spectroscopy is a unique method to study the host-guest interaction of nitroxide radicals since their EPR spectra are highly sensitive to the environmental polarity and molecular motion. As shown in Fig. 1a, upon addition of **WP6** (500 μM), the high-field EPR line of **4-AT** (20.0 μM) is significantly broadened with the weak signal intensity as compared to the other two peaks, indicating its slow motion possibly due to its

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complexation with **WP6.** On the contrary, addition of **WP6** to the solutions of **4-HT** or **4-OT** did not lead to any spectral change, indicating that neither **4-HT** nor **4-OT** is complexed with **WP6** (Fig. 1b,c). Similar study was also carried out using **WP5**. No host-guest interaction was observed for **4-AT** (Fig. 1d) due to the small cavity size of **WP5** (5.6 Å) as compared to **WP6** (7.7 Å).[47] As a result, the host-guest interaction strongly depends on the substituent at the 4-position of nitroxide radical and the cavity size of pillar[*n*]arene.

Now that **4-AT** can form the host-guest interaction with **WP6**, we next investigated the concentration effect of **WP6** on EPR spectra of **4-AT**. Two-dimensional (2D) EPR spectral simulation was used to decompose the overlapping spectra of various species.[48] To increase the spectral resolution, the EPR spectra were recorded under anaerobic conditions to eliminate the oxygen-induced line broadening (Fig. 2a). Results showed that three species coexist in the solution of **4-AT** and **WP6**, including free **4-AT** (G), **4-AT** associated with one **WP6** molecule (GH) and **4-AT** associated with two **WP6** molecules (GH_2) (Fig. 2b-2d). Similar results were also observed for the host-guest interaction of TEMPO radicals with CB[7].[43] GH represents the real inclusion inside **WP6** as evidenced by the significantly smaller α_N ($\Delta\alpha_N$ = -0.450 G) (Fig. 2c) and the increased g-factor (Δg = 0.00014) (Table S1). The 91-fold larger β and 37-fold larger γ relaxation parameters reflect a strongly hindered rotation of **4-AT** in the complex of GH (Table S1). The complexation in the GH broadens the EPR lines and makes the hyperfine splittings unresolved (Fig. 2c). Comparatively, GH_2 has the similar α_N and g values with free **4-AT**, suggesting that **4-AT** may not be located into the cavity of **WP6**. However, the 10-fold larger β relaxation parameter for GH_2 than that of free **4-AT** indicates an external association of **4-AT** with two **WP6** molecules possibly through the electrostatic interaction. Fig. 2e shows the plot of the relative populations of three species as a function of [**WP6**]/[**4-AT**]. Clearly, the population of GH rapidly increases with [**WP6**]/[**4-AT**] at the ratio of < 20 and then slightly decreases. On the other hand, the population of GH_2 gradually increases with [**WP6**]/[**4-AT**] and the formation of GH_2 competes with that of GH. However, GH is a dominant species relative to GH_2 throughout the ratios studied. Association constant (K) of **4-AT** with **WP6** was calculated by 2D-EPR simulation to be 3.1×10^3 M^{-1}, larger than that of β-CD with TEMPO-like nitroxides (607 M^{-1})[43] but smaller than that of CB7 (2.5×10^4 M^{-1}).[44]

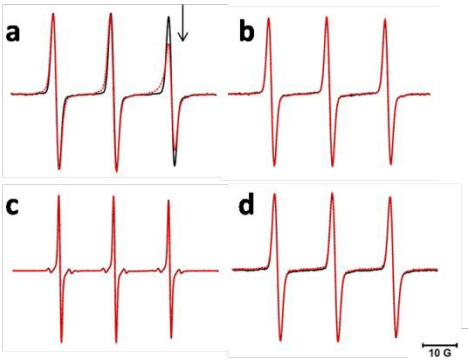

Fig. 1 EPR spectra of aqueous solutions of **4-AT** (a), **4-HT** (b) and **4-OT** (c) before (black solid line) and after (red dotted line) addition of **WP6**; (d) EPR spectra of aqueous solution of **4-AT** before (black solid line) and after (red dotted line) addition of **WP5**. Nitroxide radical (20 μM) and **WP6**/**WP5** (500 μM) were used in these experiments and EPR spectra were recorded under aerobic conditions.

In general, **WP6** prefers forming the complex with electron-deficient guest molecules owing to its electron-rich cavity. [9] Since the amine group in **4-AT** can be protonated to result in the corresponding ammonium in aqueous solution, pH titration experiments of **4-AT** in the presence of **WP6** were carried out by EPR. EPR spectra of **4-AT** in the presence of **WP6** (25 equiv.) were recorded at pHs from 10.5 to 8.0. As shown in Fig. S1, **4-AT** was not included into the cavity of **WP6** at high pH (e.g., 10.5) as evidenced by three equal-height peaks. However, the intensity of the high-field peak decreases as pH decreases (Fig. S1), implying the complexation of **4-AT** with **WP6**. Therefore, the protonated form of **4-AT** (see Chart 1) is responsible for this complexation. Assuming that the complexation does not change the protonation of **4-AT,** the binding constant of the protonated **4-AT** with **WP6** can be also estimated to be 4.1×10^3 M^{-1} according to the reported pKa (9.5) of **4-AT**,[49] pH value (9.0) used in the experiment as well as the apparent binding constant (3.1×10^3 M^{-1}) which was calculated by 2D-EPR simulation.

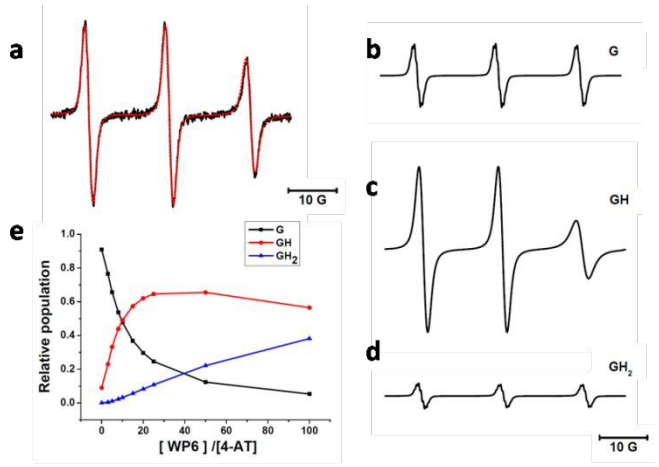

Fig. 2 (a) Experimental (black solid line) and simulated (red dotted line) EPR spectra of **4-AT** (20 μM) ⊂ **WP6** (500 μM) under anaerobic conditions in water (pH 9.0). Simulated spectrum in (a) is decomposed into (b) non-associated **4-AT** (G, 24.6%), (c) the complex GH (**4-AT**:**WP6**, 1:1; 64.6%) and (d) the complex GH_2 (**4-AT**:**WP6**, 1:2; 10.8%). (e) Plot of the relative populations of three species (G, GH and GH_2) as a function of the concentration ratios ([**WP6**]/[**4-AT**]).

Since the information on the molecular tumbling of the complex can be also extracted from low-temperature EPR spectra,[30,50] EPR spectra of **4-AT** and **4-AT**⊂ **WP6** were recorded at 250 K. As shown in Figure 3, both rigid (R, 54.9%) and mobilized (M, 45.1%) components exist in the system of **4-AT**⊂ **WP6**, while there is only one mobilized component for free **4-AT**. EPR simulation[51] showed that the τ_c value (19.6 ns) of M is significantly smaller than that of free **4-AT** (62.0 ns). This mobilized species is most likely due to the complex of **4-AT** with **WP6** since the complexation with **WP6**

prevents/attenuates the interaction of **4-AT** with solvents and increase its molecular motion in solid state, as observed from the interaction of the nitroxide radical bPTO with CB[7].[44] On the other hand, the rigid component may be due to the external interaction which leads to the formation of the cluster between **4-AT** and **WP6** through the electronic interactions.

Subsequently, NMR experiments were also carried out at room temperature to investigate the host-guest interaction between **4-AT** and **WP6**. Due to the paramagnetism of **4-AT**, its NMR signal was too broad to be detectable (Fig. S2c). The host-guest interaction with **4-AT** significantly broadened the NMR signals of **WP6** through paramagnetic relaxation enhancement (Fig. S2b).[52] Full widths at half maxima (FWHM) of the three peaks from **WP6** were 2.0-13.0 fold higher than those in the absence of **4-AT** (Table S2). No signal broadening in the systems of **4-AT ⊂ WP5** and **4-HT ⊂ WP6** (Fig. S3) excludes the possibility of the random interaction between **4-AT** and **WP6** and further confirms their host-guest interaction.

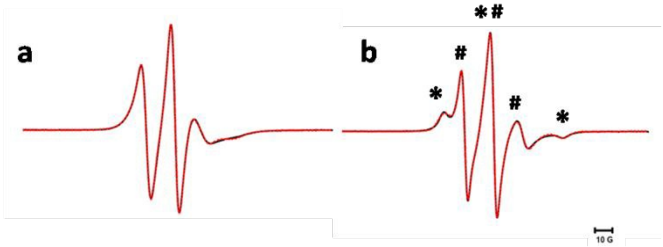

Fig. 3 Experimental (black) and simulated (red) EPR spectra of (a) **4-AT**, (b) **4-AT ⊂ WP6** (10 eq) at 250K in 1:1 (w/w) water: glycerol. The pH value in 1:1 (w/w) water: glycerol was determined to be 8.0 at room temperature. Note: #, mobilized component; *, rigid component.

To further reveal the host-guest interaction of **4-AT** with **WP6**, NMR experiments were also carried out using a diamagnetic hydroxylamine derivative of **4-AT** (named as **4-ATH**, Chart 1). To enhance the host-guest interaction with **WP6**, the protonated form of **4-ATH** was used in this experiment. As shown in Fig. 4a, upon complexation with **WP6**, the ^{1}H-NMR signals of **4-ATH** are slightly broadened and shifted upfield due to the shielding provided by the electron-rich macrocyclic structure. For instance, the chemical shifts of the protons α, β and γ are shifted from 3.76, 2.21 and 1.85 ppm to 2.50, 0.82 and 0.67 ppm, respectively. Interestingly, a single peak at 1.35 ppm from 4 methyl groups was splitted into two peaks at 0.36 and 0.08 ppm possibly due to the inhibition of the conformational interconversion.[53] On the other hand, the host-guest interaction of **4-ATH** with **WP6** resulted in the downfield shifts of the aromatic protons (Δδ = 0.06 ppm) and methylene (OCH_2) protons (Δδ = 0.04 ppm), as shown in Fig. 4b. These results consistently suggested that the cationic **4-ATH** is encapsulated into the cavity of **WP6**.

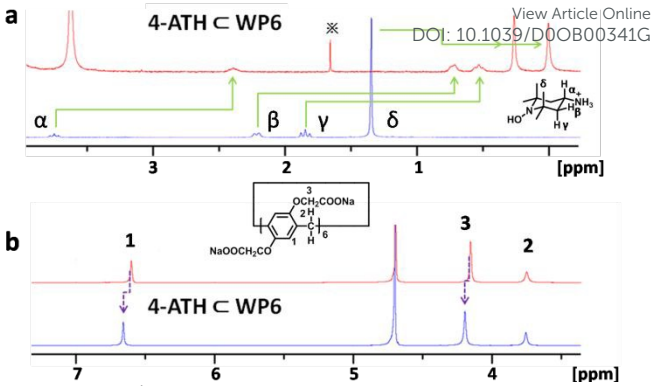

Fig. 4 (a) Partial ^{1}H NMR spectra of **WP6** and **4-ATH ⊂ WP6** at high-field region (※, undefined); (b) partial ^{1}H NMR spectra of **4-ATH ⊂ WP6** and **4-ATH** at low-field region. **WP6** (2.5 mM) and **4-ATH** (1 mM) was used in these NMR experiments in D_2O (pH 9.1)

Cyclic voltammetric experiments of **4-AT** were performed in the absence and presence of **WP6**. As shown in Fig. 5a, **4-AT** underwent a reversible one-electron oxidation at the half-wave potential ($E_{1/2}$) of *ca.* + 670 mV *vs.* Ag/AgCl. The one-electron oxidation of **4-AT** turned to be irreversible in the presence of **WP6** with only an anodic peak at *ca.* 100 mV *vs.* Ag/AgCl, suggesting the relatively high thermodynamic tendency for oxidation upon complexation with **WP6**. A broad one-electron irreversible reduction peak was observed for both free **4-AT** and **4-AT ⊂ WP6.** Comparatively, the complexation led to weaker reduction tendency with the more negative cathodic peak (-897 mV) for **4-AT ⊂WP6** than that of free **4-AT** (-883 mV). Then, we investigated the ascorbic acid (AsA)-induced decay of **4-AT⊂ WP6**. As shown in Figure 6, 67 % of the EPR signal intensity of **4-AT** remained in the presence of AsA (2eq) after 20 min, while only 14 % of the signal intensity remained for free **4-AT** (Fig. 6). These results consistently suggest that the complexation of **4-AT** with **WP6** can significantly increase the stability of **4-AT** towards reducing agents such as AsA.

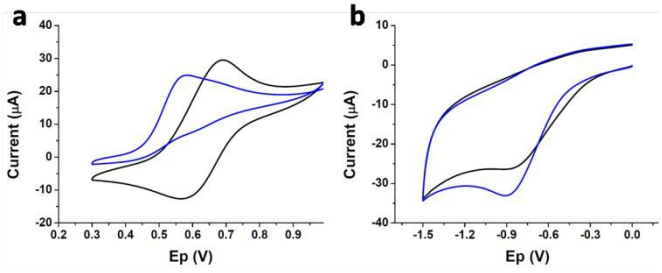

Fig. 5 Cyclic voltammograms of **4-AT** (1mM) (black), **4-AT** (1mM) **⊂ WP6** (5mM) (blue) in 0.15M KCl.

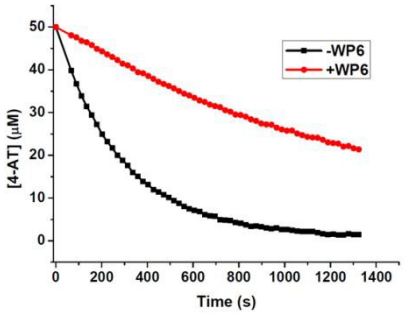

Fig. 6 Effect of **WP6** (1.25 mM) on the reduction of **4-AT** (50 μM) by ascorbic acid (100 μM).

Conclusions

In summary, we for the first time demonstrate that the 4-amino-TEMPO radical (**4-AT**) can be complexed into the cavity of the water-soluble pillar[6]arene **WP6**. The host–guest interaction of **4-AT** with **WP6** effectively increases the stability of 4-AT towards reducing agents such as ascorbic acid, thus expanding its biomedical applications. This host-guest interaction will also be suitable for other amine-containing nitroxide radicals due to their similar electrostatic interactions with **WP6** as observed for **4-AT**. The use of other water-soluble pillar[6]arene derivatives[54,55] may further enhance the host-guest interaction with nitroxide radicals, thus providing high binding constants. Our present study indicates that pillar[6]arenes are a new type of macrocycles for nitroxide radicals besides CDs and CB[*n*], and nitroxide radicals could be used to explore the host-guest interaction of pillar[6]arenes by EPR.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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