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Metal coordination to a deep cavitand promotes binding selectivities in water

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ABSTRACT

One goal of supramolecular chemistry is the creation of synthetic receptors that have a high affinity for hydrophilic molecules in water. We found that cavitands with upper rims extended by pyridyl groups coax hydrophilic guests into the cavity where they are shielded from the aqueous environment. The ability of Pd(II) to coordinate adjacent pyridyl groups leads to increased selectivity for highly hydrophilic solvent molecules such as acetone, 1,4-dioxane and tetrahydrofuran in water. Analysis of the binding behavior indicated that metal-coordination restricts the container entrance, shrinks the effective cavity volume and increases the energetic barrier to guest exchange.

Host/guest sequestration in water has become a popular research area as a probe for intermolecular forces involved in biological recognition processes [1]. In the last decades, most attention has been paid to recognition of cations, anions and hydrophobic molecules in water [2,3]. Macrocyclic receptors with preorganized binding sites such as crown ethers [4], cyclodextrins [5,6], cucurbit[*n*]urils [7], calix[*n*]arenes [8–10], pillar[*n*]arenes [11–13], naphthotubes [14], metal cages [15] and many others [16] have been well-developed. However, few synthetic receptors can recognize hydrophilic molecules in aqueous solution [17,18].

Deep cavitands can confine many small molecules and show applications in molecular recognition, sensing and biomimetic catalysis [19–23]. Most of them are derived from shallow resorcinarenes that are deepened through covalently added aromatic walls. They typically exist in two conformations: a receptive vase-like shape and unreceptive kite-like shape. The kite shape is self-complementary and often dimerizes to a velcrand through solvophobic forces [24]. Additional non-covalent interactions such as a cyclic array of intramolecular hydrogen bonds [25] and metal coordination have been used to stabilize the vase conformation and enhance guest binding [26]. For small molecule guests, these cavitands can provide a hydrophobic surrounding, but the open end provides exposure to solvent. The in/out exchange rates of small molecule guests are often too fast to observe the signals for the bound guest in the ^{1}H NMR spectra [27]. Metal coordination such as Pd(II) to a quinoxaline-rimmed cavitand can alter the shape of the cavity and constrict the size of its opening; this can enhance the binding of hydrophobic and even hydrophilic guests in water [28]. Here we describe the synthesis of a deep cavitand **1** with benzimidazole rims extended four 3-pyridinyl functions. We find that metal coordination to the pyridyls enhances selective recognition of hydrophilic molecules in water.

We prepared the deep cavitand **1** with 2-(3-pyridinyl)benzimidazole arms from the well-known precursor, octanitro cavitand [29] through three reaction steps. The octanitro cavitand was reduced to octaamine cavitand and condensation with ylide (2-(pyridin-3-ylmethylene)malononitrile) to afford the 2-(3-pyridinyl)benzimidazole tethered cavitand [30]. Water soluble cavitand **1** was obtained by attaching *N*-methyl imidazole groups to the feet (Scheme 1a and Scheme S1 in Supporting information). Cavitand **1** was characterized by analytical techniques such as ^{1}H, ^{13}C NMR and HRMS. The ^{1}H NMR spectra of cavitand **1** in D_2O (Fig. 1a) showed broad and undefined peaks which are attributed to the interconversion process between its *vase* and *velcrand* conformations [31].

Cavitand **1** displays good affinity for some small amphiphilic molecules (Fig. 1) and forms a kinetically stable complexes in "*vase*" conformations with these guests in D_2O. The *vase* conformation is deduced from its methine proton's characteristic signal observed around 5.5 ppm [32]. We studied the binding of **1** with several cyclic, amphiphilic small molecules like thiane,

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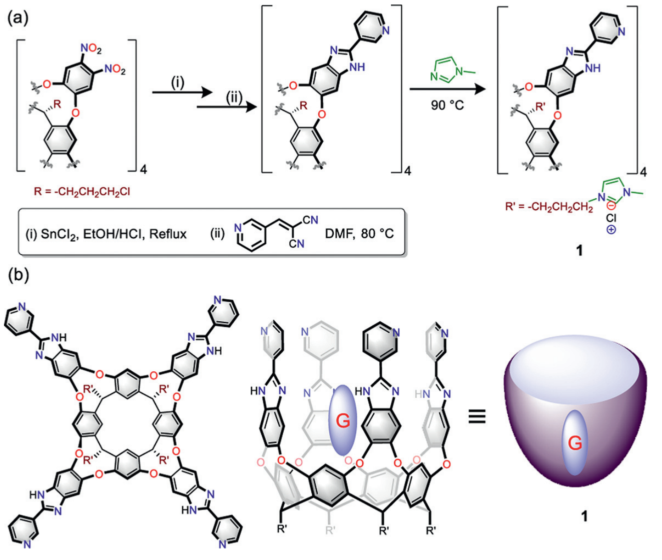


Scheme 1. (a) Synthesis of the water-soluble cavitand **1** containing 2-(3-pyridinyl)benzimidazole. (b) Chemical structure and "*vase*" shape of **1** and cartoon representation of guest binding.

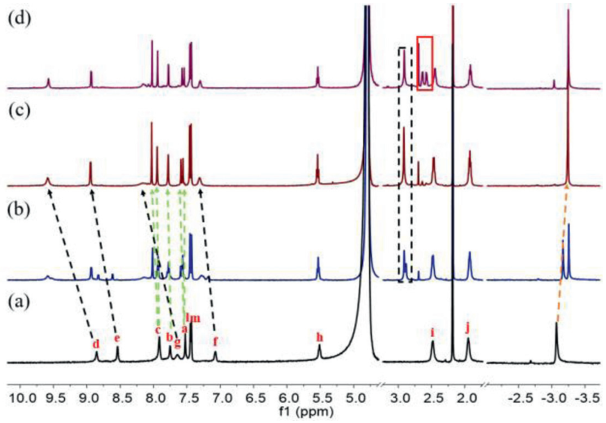


Fig. 2. ^{1}H NMR spectra of **1** and excess cyclohexane in the presence of increasing equivalent of Pd(EDA)$(H_2O)_2 \cdot NO_3$ (a) 0 equiv., (b) 1 equiv., (c) 2 equiv., (d) 3 equiv. Black rectangles mark the chemical shift of Pd(EDA)$(H_2O)_2 \cdot 2NO_3$ coordinated to **1**; the red rectangle shows the chemical shift of the free Pd(EDA)$(H_2O)_2 \cdot NO_3$. Shifts of the proton peaks in **1** are shown, marked by arrows. Proton labeling is given in Scheme 2.

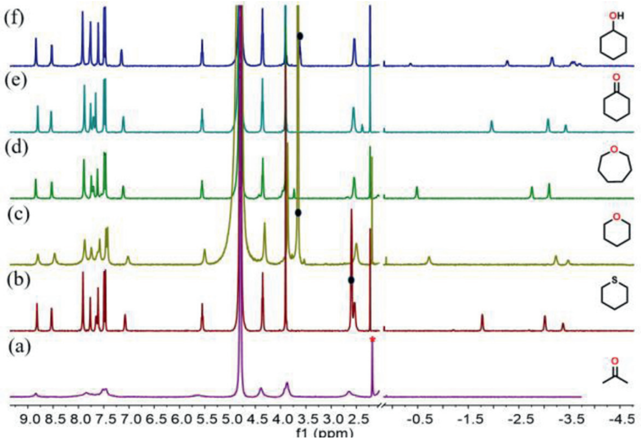


Fig. 1. Partial ^{1}H NMR spectra of the cavitand **1** at 1 mmol/L in D_2O. (a) Before the addition of guest, and in the presence of about 1 equiv. of (b) thiane, (c) tetrahydropyran, (d) hexamethylene oxide, (e) cyclohexanone and (f) cyclohexanol. Free acetone protons are marked with red asterisk symbol. Free guest proton signals are marked with black circular dots, and bound guest proton signals are shown in the upfield region between 0 and −4.0 ppm.

tetrahydropyran (THP), hexamethylene oxide, cyclohexanone, and cyclohexanol by ^{1}H NMR in D_2O (Figs. S9–S13 in Supporting information). The ^{1}H NMR integration indicated 1:1 (stoichiometric) complexes in all cases. The encapsulated guests' proton signals were shifted upfield and appeared between 0 and −4.0 ppm. The binding depth can be evaluated by comparing the changes in chemical shift ($-\Delta\delta$) with respect to the free guests [33]. The calculated maximum $-\Delta\delta$ of these guests are *ca.* −5.0 ppm when bound in the deepest part of the cavity and positioned near the aromatic panels. This is the case for the methylenes of these cyclic amphiphilic small molecules: the hydrophobic part of these guests is bound deep within the cavity, while the polar groups are directed toward the openings near the pyridyl rim.

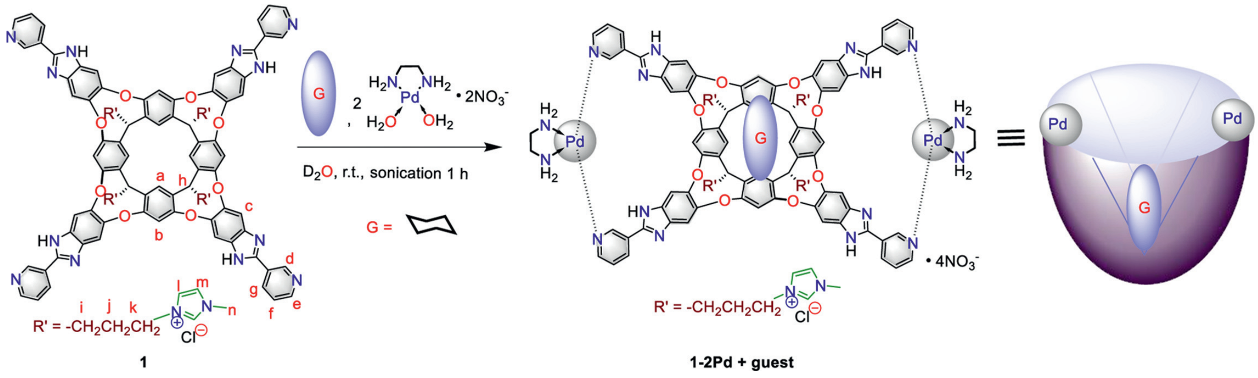
However, highly hydrophilic molecules such as 1,4-dioxane, THF, 1,4-dioxene and other small molecules (isopropanol and diethyl ether) were not observed inside the cavity (Figs. S33–S38 in Supporting information).

Our previous studies showed that metal coordination to Pd(II) with quinoxaline-rimmed cavitands can alter the shape and size of the cavity and enhance the binding properties in water [34]. In cavitand **1** the donor nitrogens can be favorably arranged to chelate Pd(II), so we studied metallo cavitand formation and it's effect on binding properties in water.

Monomeric metallo receptor complexes are known to assemble in the presence of adaptive guest molecules [35]. The assembly process of cavitand **1** and Pd(II) precursor [Pd(EDA)$(H_2O)_2 \cdot 2NO_3$] (EDA = ethylenediamine) was monitored by ^{1}H NMR titration in D_2O (Fig. 2) in the presence of cyclohexane. Upon addition of Pd(II) precursor (1–3 equiv.) to a solution of **1** and cyclohexane in D_2O, new proton signals appeared in the upfield region (Fig. 2b). When 2–3 equiv. of the Pd(II) precursor were added, the proton peaks became a set of well-resolved signal patterns (Fig. 2c), indicating the formation of metallo cavitand **1–2Pd**. The signals of the pyridyl H-atoms (d, e, f, g) shifted downfield, as expected for coordination of the pyridyl nitrogen with Pd(II) [36]. The signals of the resorcinarene and benzimidazole H-atoms (a, b, c) appear as two doublets showing that complexation results in C_{2v} symmetry. The guest cyclohexane's chemical shifts indicated it was deeper in the cavity in the presence of Pd(II) (Figs. 2c and d).

We also treated **1** with different quantities of the Pd(II) precursor in the presence of about 1 equiv. acetone, and sonicated the mixture for 1 h in D_2O. Acetone is a very poor guest for **1** due to the high hydrophilic and small size, and the corresponding ^{1}H NMR spectrum was broad, indicating that cavitand **1** is flexible in D_2O. But in the presence of 1 to 3 equiv. of the Pd(II) precursor, the cavitand **1** quickly shifts to the *vase* conformation and takes up acetone (Fig. S18 in Supporting information). The new proton signal at −2.6 ppm indicates acetone bound within the cavity (calculated chemical shift, $-\Delta\delta = 4.8$ ppm). Apparently, Pd(II) coordination stabilizes the "*vase*" conformation of the cavitand which can better capture the guest. This implies that Pd coordination can shrink the cavity volume of host **1** and it simultaneously preorganizes the cavity to take up small hydrophilic molecules in water [37,38].

Several small solvent molecules are hazardous environmental pollutants and their detection and removal are highly desirable [39]. We studied the competitive binding of small hydrophilic solvent molecules including acetone, isopropanol, DMF and diethyl ether to **1–2Pd** (Figs. S20–S23 in Supporting information). The results show that acetone, diethyl ether and isopropanol bind better to **1–2Pd** than does DMF. The sharp proton signals of aromatic



Scheme 2. Schematic representation of **1–2Pd** complex formation in water is in the presence of adaptive guest (**G**, Cyclohexane).

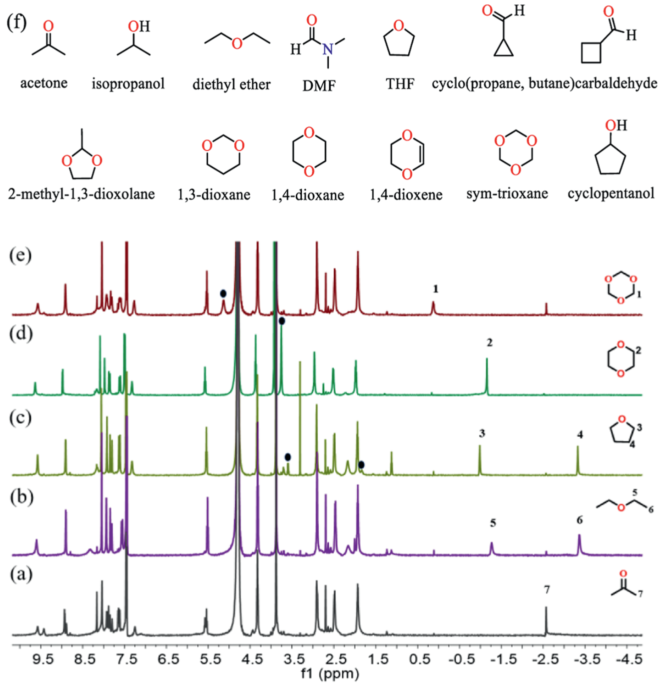


Fig. 3. ^1H NMR spectra of the cavitand **1–2Pd** at 1 mmol/L in D_2O (a) before the addition of guest, and in the presence of about 1 equiv. of (b) diethyl ether; (c) tetrahydrofuran; (d) 1,4-dioxane; (e) sym–trioxane. Signals arising from free guest protons are marked with black circular dots, and bound guest protons are shown in the upfield region between 0 and −4.0 ppm. (f) Chemical structures of the small molecules are studied as guests.

Table 1
Calculated binding constants (K_A) for representative guests in **1–2Pd**.[a]

Entry	Guest	K_A (L/mol)
1	THF	4.26×10^3
2	1,4-dioxane	2.48×10^3
3	1,3-dioxane	2.85×10^3
4	THP	5.53×10^3

[a] Binding constant were calculated using ^1H NMR titration *via* adding guest to **1–2Pd** in solution (see details in Supporting information). Dimethylsulfoxide was used as an internal standard.

protons and upfield shifted signals confirm that the complexes are stable at room temperature.

Cavitand **1–2Pd** showed a good selective binding for hydrophilic molecules in water, forming 1:1 complexes with 1,4-dioxane, THF and sym–trioxane (Fig. 3). Binding of THF to **1** results in a broad peak in the ^1H NMR spectra, but large upfield shifts and very sharp signals were observed when it binds to **1–2Pd**. Likewise, the 1,4-dioxane rapidly tumbles or spins at room temperature in **1–2Pd**, leading to an averaging of the chemical shifts to give only one sharp singlet in the ^1H NMR spectra in the upfield region [40]. Cavitand **1–2Pd** showed a low affinity for sym–trioxane-signals when competing with bound acetone. 1,3-Dioxane, tetrahydropyran, cyclopentanol and others are also guests in **1–2Pd** in water (Figs. S27–S32 in Supporting information). Binding constants (K_A) of the guests to **1–2Pd** were calculated from the ^1H NMR titrations (Table 1). The K_A values often reflect the kinetics of the guests in–out rates of complexation; high K_A values often correspond to slow release of the guests by **1–2Pd** [41]. THP shows a K_A value (5.53×10^3 L/mol) of an order of magnitude larger than the binding to **1** (330 L/mol, Fig. S43 in Supporting information).

In conclusion, we have shown a new method to introduce pyridyl groups to the upper rim of deep cavitand **1**. Chelation of Pd(II) by the pyridyls gave 2:1 metal:cavitand derivatives **1–2Pd**. The Pd(II) coordination holds the walls together and decreases the volume of the cavitand. Accordingly, small molecule guests experince more favorable packing coefficients [42]. Even small hydrophilic solvent molecules show good binding affinity to **1–2Pd** in aqueous solution.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.03.039.

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