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Intramolecular binding site organization by Pd(II) complexation with a resorcin[4]arene derivative

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Abstract

Intramolecular assembly of a binding site by Pd(II) ion complexation with a resorcin[4]arene derivative has led to a water-soluble resorcin[4]arene receptor. The bowl-shaped cavitand host **2** shows a good binding affinity to aromatic carboxylates with alkyl moiety of an appropriate length in D_2O. The guest inclusion within the host cavity was confirmed by ^1H NMR spectroscopy. Hydrophobic and electrostatic interactions turned out to act as cooperative binding force for a strong complex formation with appropriate anionic guests in water. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: self-assembly; hydrophobic interaction; electrostatic interaction; resorcin[4]arene.

Hydrophobic binding of aromatic groups is the crucial element for modeling molecular recognition events in biological systems.[1] Water-soluble cyclophanes[1,2] with large hydrophobic cavities and cyclodextrins[3] are among the major class of receptors capable of effectively mimicking the hydrophobic effect of biomolecular recognition in aqueous solution. Other approaches to water-soluble receptors use a bowl-shaped molecular scaffold such as the calix[4]arenes and resorcin[4]arenes as a potential hydrophobic binding site.[4] Unlike previous covalent bond based synthetic approaches, the strategy of self-assembly has recently been exploited to generate new recognition sites.[5] The ability of a metal ion to assemble flexible ligands around its coordination sphere into highly organized structures has led to the development of hydrophobic binding site for the recognition of aromatic guests in aqueous solution.[5b–e]

Since there are only a few examples of water-soluble resorcin[4]arene based receptors which have been prepared by the traditional chemical bond synthesis,[6] the strategy of recognition site self-assembly using resorcin[4]arenes as a basic skeleton of the receptor is of particular interest. We present herein intramolecular assembly of a binding site by Pd(II) ion complexation with a resorcin[4]arene derivative and describe the complexation behavior of the resorcin[4]arene based receptor **2** toward aromatic carboxylates in water.

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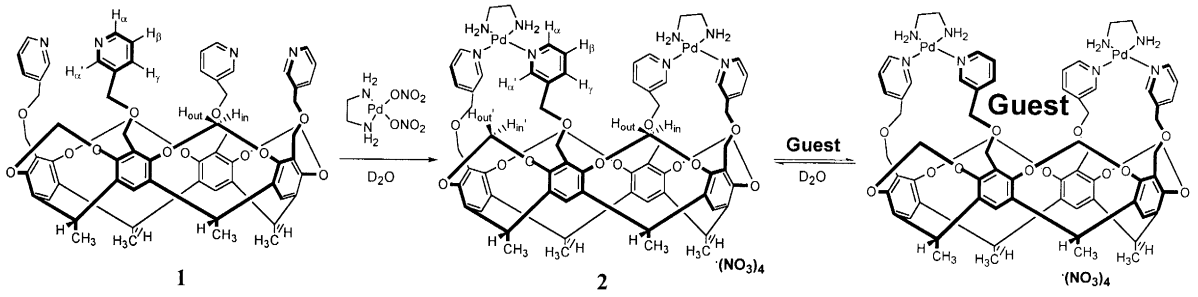
Scheme 1 shows Pd(II) ions induce intramolecularly organized recognition site. Since the four pyridyl groups on the upper rim of the resorcin[4]arene cavitand **1**[7] can be intramolecularly assembled with Pd(II) ions to generate a monomeric molecular receptor **2**[8,5f] with a hydrophobic binding site, complementary-sized nonpolar guests can be bound inside the hydrophobic recognition site in aqueous solution. Formation of **2** was confirmed by ^{1}H NMR spectroscopy and ESI-MS.[8] The intermolecular self-assembly to give rise to a dimeric cage-like metallocyclophane turned out to be entropically unfavorable.



Scheme 1.

Fig. 1 shows the NMR spectra before and after Pd(II) ion complexation. H_α and $H_{\alpha'}$ experience downfield shift indicative of complexation of pyridines with Pd(II). Methylene protons (H_{out}) on the upper rim pointing outside the aromatic cavity splitted into two signals ($H_{out'}$ and H_{out}). One ($H_{out'}$) existing between two pyridine ligands interacting with a Pd(II) ion moved far upfield compared to the other protons (H_{out}). Methylene protons (H_{in}) pointing toward the aromatic cavity also divided into two signals ($H_{in'}$ and H_{in}). One ($H_{in'}$) between two pyridyl groups also moved upfield. This clearly indicates these protons ($H_{out'}$ and $H_{in'}$) experience shielding effect by two pyridyl groups organized by metal-templated self-assembly. Benzylic protons (ArCH_2O−) on the upper rim of **2** become diastereotopic upon complexation with Pd(II). They split each other and appear in the spectrum as a pair of doublets. This implies formation of the rigid structure resulting from metal–ligand interaction. Methyl protons (CHCH_3) on the lower rim appear as two doublets showing that complexation results in C_2 symmetry.

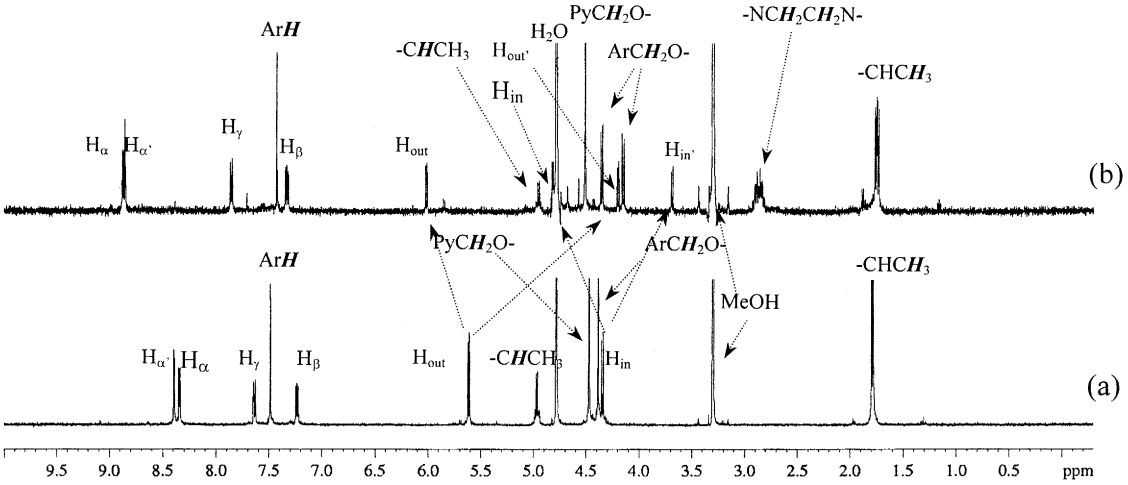


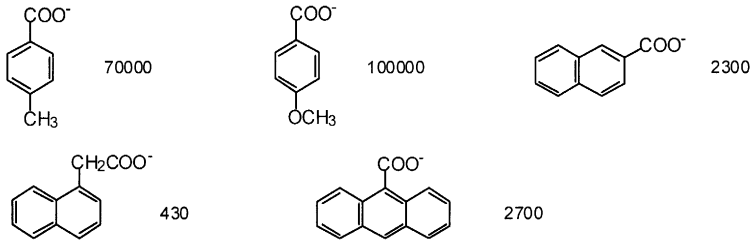
Fig. 1. ^{1}H NMR spectra (500 MHz) of (a) **1** and (b) **2** in CD_3OD at 25°C. See Scheme 1 for proton labeling

An energy-minimized structure of the self-assembled monomeric molecular host **2** shows the hydrophobic binding site generated by Pd(II)-induced self-assembly.[9] Those methylene protons ($H_{out'}$ and

$H_{in'}$) on the upper rim of **2** turned out to be located in the magnetically shielded region formed by two pyridyl groups complexed with Pd(II).

The host–guest complexation is demonstrated by the complexation-induced changes in chemical shift observed in the ^{1}H NMR binding titrations in D_2O. Analysis of titration data of **2** with aromatic carboxylates shows that the binding isotherms fit well to a 1:1 binding model. The 1:1 stoichiometry of the complex between **2** and *p*-anisic acid sodium salt was further confirmed by Job analysis. The calculated association constants are collected in Table 1. *p*-Toluic acid sodium salt and *p*-anisic acid sodium salt containing methyl and methoxy groups which can properly reside inside the resorcinarene hydrophobic cavity show much larger binding constants compared to other aromatic carboxylates which do not have the alkyl moiety for deep inclusion inside the host cavity. This suggests the importance of hydrophobic interaction for the strong complex formation in aqueous media. It is thought that aromatic alkyl moiety of an appropriate length shows the most effective hydrophobic interaction in the apolar cavity. The degree of participation of the electrostatic interaction between the cationic metal center of **2** and guest anionic site in complexation was checked by binding study for 1,4-dimethoxy benzene as a neutral analog of *p*-anisic acid sodium salt. Compound **2** was found to bind 1,4-dimethoxy benzene with K_a value of 4,500 M^{-1}, which corresponds to more than 20-fold decrease compared to that of *p*-anisic acid sodium salt. This implies that the cationic metal center of **2** might strongly influence on binding when combined with appropriate hydrophobic interaction.[10]

Table 1
Binding constants (M^{-1}) of the 1:1 host–guest complexes in D_2O[a]



[a] Binding constants were obtained by ^{1}H NMR titrations on the basis of the 1:1 binding model at 300 K. All counterions are Na^+.

Fig. 2 shows NMR titration of **2** with *p*-toluic acid sodium salt in D_2O. The methyl group of toluic acid appeared at far upfield ($\Delta\delta_{Hc} < -3.2$ppm) upon binding and turned out to be pointing inside the aromatic cavity. Similarly, significant upfield shifts ($\Delta\delta_{Hb}$ (protons on the *ortho* position of the methyl group) < -1.5 ppm, $\Delta\delta_{Ha}$ (protons on the *meta* position of the methyl group) < -0.8 ppm) of the aromatic proton resonances were observed on complexation with **2**. In the presence of excess guest, because of fast exchange of the guest in and out of the cavity, the methyl and aromatic signals of the guest gradually moved to downfield as shown in Fig. 2. The advantage of intramolecular assembly of a hydrophobic binding site by Pd(II) complexation was corroborated by comparing the binding properties of **2** with those of a tetra *N*-methyl pyridinium derivative **3**[11] of **1**. *p*-Anisic acid sodium salt and *p*-toluic acid sodium salt turned out to bind **3** with K_a=7900 and 1900 M^{-1}, respectively. These values are comparable to K_a of **2** with 1,4-dimethoxy benzene. This indicates that the binding site organization of **2** by Pd(II)-induced self-assembly not only contributes to hydrophobic interaction but also electrostatic interaction in complexation with proper anionic guests such as *p*-anisic acid sodium salt and *p*-toluic acid sodium salt.

In summary, we have synthesized a monomeric molecular host **2** with a hydrophobic binding site by

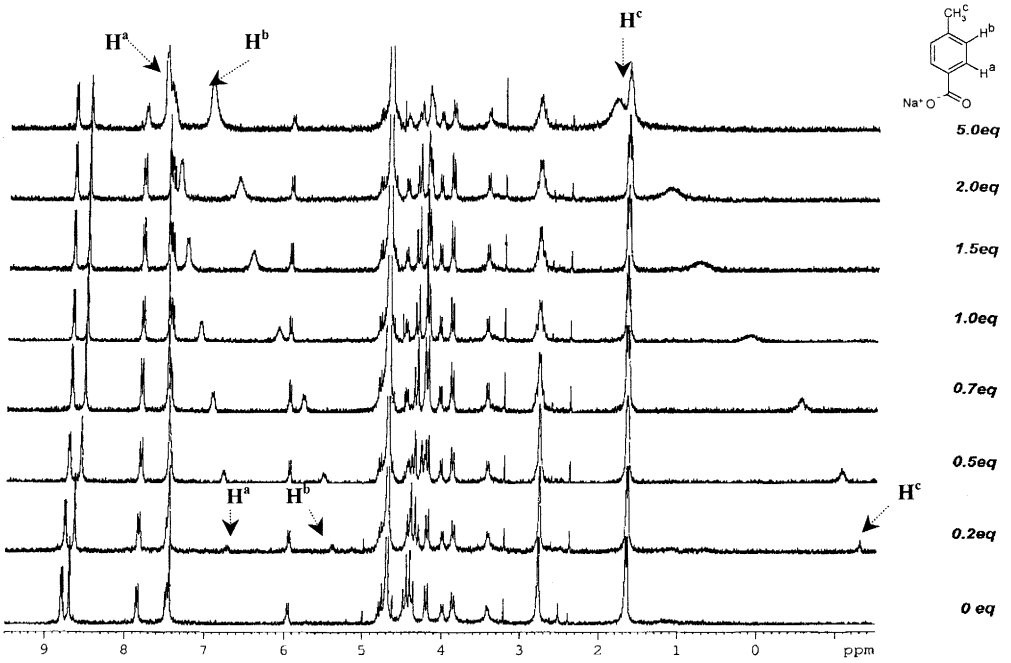


Fig. 2. ^{1}H NMR (300 MHz) titration of **2** with *p*-toluic acid sodium salt in D_2O at 25°C. The amount of added guest is indicated (equiv.)

intramolecular binding site organization using metal–ligand interaction. The water-soluble host **2** shows a good binding affinity to aromatic carboxylates with an appropriate length of the alkyl chain for the most effective hydrophobic interaction in the host cavity in D_2O. Hydrophobic interaction and electrostatic interaction act as cooperative binding force for a strong complex formation with appropriate anionic guests in water.

Acknowledgements

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7. Selected spectral data for **1**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.39 (s, 4H, Py$H_{\alpha'}$), 8.34 (d, J=5.4 Hz, 4H, PyH_{α}), 7.63 (d, J=7.8 Hz, 4H, PyH_{γ}), 7.48 (s, 4H, Ar*H*), 7.23 (dd, J=5.4, 7.8 Hz, 4H, PyH_{β}), 5.61 (d, J=7.3 Hz, 4H, ArOCH_{out}H$_{in}$OAr), 4.96 (q, J=7.5 Hz, 4H, C*H*CH$_3$), 4.47 (s, 8H, PyCH_2O), 4.38 (s, 8H, ArCH_2O), 4.34 (d, J=7.3 Hz, 4H, ArOCH$_{out}H_{in}$OAr), 1.78 (d, J=7.5 Hz, 12H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 150.0, 149.6, 139.2, 136.4, 133.8, 123.8, 120.5, 99.8, 70.7, 62.6, 51.0, 31.5, 16.4; FAB-MS (NBA) *m/z* 1077 (M+H$^+$).
8. Selected spectral data for **2**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.86 (d, J=5.6 Hz, 4H, PyH_{α}), 8.84 (s, 4H, Py$H_{\alpha'}$), 7.85 (d, J=7.8 Hz, 4H, PyH_{γ}), 7.42 (s, 4H, Ar*H*), 7.33 (dd, J=5.6, 7.8 Hz, 4H, PyH_{β}), 6.01 (d, J=7.2 Hz, 2H, ArOCH_{out}H$_{in}$OAr), 4.95 (q, J=7.6 Hz, 4H, C*H*CH$_3$), 4.81 (d, J=7.2 Hz, 2H, ArOCH$_{out}H_{in}$OAr), 4.51 (s, 8H, PyCH_2O), 4.35 (d, J=9.1 Hz, 4H, ArCH_aH$_b$O), 4.19 (d, J=7.2 Hz, 2H, ArOC$H_{out'}$H$_{in'}$OAr), 4.15 (d, J=9.1 Hz, 4H, ArCH$_a$$H_b$O), 3.68 (d, J=7.2 Hz, 2H, ArOCH$_{out'}$$H_{in'}$OAr), 2.86 (m, 8H, NC$H_2CH_2$N), 1.74 (q, J=7.6 Hz, 12H, CHCH_3); ^{1}H NMR (300 MHz, D_2O) δ 8.79 (d, J=5.4 Hz, 4H, PyH_{α}), 8.70 (s, 4H, Py$H_{\alpha'}$), 7.84 (d, J=7.2 Hz, 4H, PyH_{γ}), 7.48 (dd, J=5.4, 7.2 Hz, 4H, PyH_{β}), 7.43 (s, 4H, Ar*H*), 5.95 (d, J=7.0 Hz, 2H, ArOCH_{out}H$_{in}$OAr), 4.77 (q, J=7.0 Hz, 4H, C*H*CH$_3$), 4.42 (q, J=12.6 Hz, 8H, PyCH_2O; d, 2H, ArOCH$_{out}H_{in}$OAr), 4.19 (d, J=9.8 Hz, 4H, ArCH$_a$$H_b$O), 3.98 (d, J=7.0 Hz, 2H, ArOC$H_{out'}$H$_{in'}$OAr), 3.87 (d, J=9.8 Hz, 4H, ArCH_aH$_b$O), 3.43 (d, J=7.0 Hz, 2H, ArOCH$_{out'}$$H_{in'}$OAr), 2.77 (s, 8H, NC$H_2CH_2$N), 1.66 (d, J=7.0 Hz, 12H, CHCH_3); ESI-MS m/z 1596 [M−(NO$_3$)]$^+$, 767 [M−2(NO$_3$)]$^{2+}$, 489 [M−3(NO$_3$)]$^{3+}$, 351 [M−4(NO$_3$)]$^{4+}$.
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11. Selected spectral data for **3** (tetra *N*-methyl pyridinium nitrate derivative of **1**): ^{1}H NMR (300 MHz, D_2O) δ 8.62 (d, 4H, PyH_{α}), 8.60 (s, 4H, Py$H_{\alpha'}$), 8.27 (d, J=8.1 Hz, 4H, PyH_{γ}), 7.86 (dd, 4H, PyH_{β}), 7.42 (s, 4H, Ar*H*), 5.83 (d, J=7.6 Hz, 4H, ArOCH_{out}H$_{in}$OAr), 4.39 (s, 8H, ArCH_2O), 4.27 (s, 12H, PyCH_3), 4.07 (d, J=7.5 Hz, 4H, ArOCH$_{out}H_{in}$OAr), 1.68 (d, J=7.3 Hz, 12H, CHCH_3); FAB-MS (glycerol) *m/z* 1385 (M+H$^+$).