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A self-assembled Pd$_2$L$_4$ cage that selectively encapsulates nitrate

Inspiration of the artwork is from an Ancient Chinese Story, i.e., ‘Four Dragons Playing Bead’ (Si Long Xi Zhu’ in Chinese). In this picture, the dragon represents the bidentate benzimidazole ligand, with an anthracene spacer. Four dragons twist (right- or left-handed, here right-handed) into a quadruple helicate conformation, defining a concise hydrophobic pocket. The ball represents the nitrate anion, which is selectively encapsulated inside.
A self-assembled Pd$_2$L$_4$ cage that selectively encapsulates nitrate$^\dagger$

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Nitrate anion is ubiquitous and important in biology, the environment, and the food industry.$^1$ Although nitrate is probably benign, it can be reduced to nitrite or other nitric oxides, which react with thiols, amines and amides to form carcinogenic compounds. Other health concerns associated with NO$_3$ amines include diabetes, thyroid disorders, respiratory infections and congenital malformations.$^2,3$ Therefore, the design of a specific nitrate receptor is still very challenging.

Many artificial hosts that can bind nitrate have been documented, including pyrrole-$^4$, amide-$^5$, ammonium-$^6$, guanidinium-$^7$, based tripod-$^8$, macrocycle-$^9$, rotaxane-$^{10}$ catenane-$^{11}$ or cage-$^{12}$ like receptors. Because of the intrinsic properties of nitrate, the reported receptors have several common problems. First of all, large hydration energy and weak basicity of the nitrate anion result in that NO$_3^-$ is weakly coordinative and it is difficult to form robust hydrogen bonds with the host,$^1$ although hydrogen-bonding interaction plays a crucial role in the anion recognition process.$^{13,14}$ As a result, nitrate anion recognition has been mostly studied in less-polar solvents to favour the hydrogen bonding interactions, and in general poor binding affinity has been reported in polar solvents. Secondly, NO$_3^-$ has a $D_{3v}$ symmetry with equivalent N–O bonds. Based on the principle of geometrical matching,$^{15}$ the hydrogen bond donors were limited to a complementary trigonal arrangement in the reported systems.$^{15,21}$ Thirdly, these receptors usually show limited selectivity for NO$_3^-$.$^{17}$ Particularly, due to the negligible difference in ionic radii and charge densities between nitrate and halide anions, it is difficult to selectively recognize nitrate from halide anions.$^{13,15}$ Fourth, the most reported organic hosts generally require tedious multistep synthesis and in most cases give low yield. This means the design of a specific nitrate receptor is still very challenging.

The coordination cages,$^{22-28}$ readily self-assembled from simple organic ligand and metal components, have distinct advantages for the design of new ion receptors. Supramolecular organometallic cages avoid tedious synthesis; still they can be regulated easily via a rational symmetry consideration regarding the shape of the ligand, the coordination geometry of the metal, and the relative spatial orientation of the ligand and metal components. Although numerous coordination cages have been designed and synthesized for the encapsulation of anions in the literature,$^{29-36}$ to the best of our knowledge, an example where the differentiation between nitrate and halides by the host has never been reported due to the difficulties raised above.

Herein, we succeeded in designing a cationic M$_2$L$_4$ cage by a quantitative self-assembly of four anthracene-bridged benzimidazole ligands and two Pd$^{10}$ ions (Fig. 1A). The cage showed a $D_4$ symmetry, but exhibited excellent capability in the selective encapsulation of nitrate. The binding constant ($K_{\text{anion}}$) for the inclusion of NO$_3^-$ was at least two orders of magnitude higher than all the other anions screened.

Bidentate benzimidazole ligand 1, with an anthracene spacer, was synthesized in two steps according to an established method.$^{37}$ After treating ligand 1 (18 µmol) with a half equivalent of Pd(NO$_3$)$_2$·H$_2$O (9 µmol) in 700 µL $d_6$-DMSO (dimethyl sulfoxide) for 2 h at 70 °C, the turbid solution turned limpid. The signals of the protons on the complex (2a) strongly split and shifted in comparison with those of the free ligand in the $^1$H NMR spectrum (Fig. 1B and C). All the signals were assigned carefully based on the correlation constants, integrals along with the correlations obtained from the $^1$H–$^1$H COSY spectrum (Fig. S5, ESI$^\dagger$). H$_4$ and H$_9$ of benzimidazole...
Fig. 1 (A) Self-assembly of complex 2: the $^1$H NMR (400 MHz, $d_6$-DMSO, 298 K) spectrum of (B) ligand 1 and (C) complex 2a. (D) $^1$H DOSY spectrum of complex 2a.

were significantly shifted downfield (from 7.62 ppm and 7.21 ppm to 8.70 ppm and 7.95 ppm, respectively), which is diagnostic for the metal coordination. Diffusion-ordered NMR spectroscopy (DOSY) showed a single product with a single band at the diffusion coefficient $D = 1.321 \times 10^{-6}$ m$^2$ s$^{-1}$ ($\log D = -9.879$) (Fig. 1D). The radius of the complex calculated from the $D$ value was 8.42 Å, in accordance with the crystal structures of the complex (see discussion below).

Solid structural confirmation of 2a was provided by X-ray crystallographic analysis.‡ Suitable single crystals were obtained by slow diffusion of 1,4-dioxane vapour into a solution of 2a in DMSO after about one week. Crystallographic data showed that four ligands in 2a are arranged in a quadruple helicate conformation due to the steric repulsion between the anthracene panels, resulting in a $D_4$ symmetry of the host framework with inherent $P$ or $M$ helicity (Fig. 2A). Such helical chirality of the host must be maintained in solution to account for the observed diastereomeric splitting for proton $H_{f,g,h}$ signals on the complex (Fig. 1C).

More interestingly, the four anthracene walls of the ligand wrap up a very concise hydrophobic cavity where all the benzimidazole protons are pointing inward, forming a perfect bind pocket that is occupied by a nitrate anion. Though the nitrate anion is in-plane disordered into four different orientations due to a mismatch of the symmetry, at each orientation its oxygen atoms are involved in at least six hydrogen bonding interactions with the benzimidazole $H_e$ (Fig. 2B), with bonding distances of around 2.124–2.637 Å.

We happened to note that only three out of the four NO$_3$ in 2a could be replaced by BF$_4$ after anion exchange by addition of an excess amount of NaBF$_4$ in a typical anion exchange procedure, as revealed by ESI-Q-TOF mass spectroscopy (Fig. 3), which showed prominent peaks observed at $m/z$ 2202.5594, 1057.7774, 676.1837, corresponding to the [([NO$_3$]<2)(BF$_4$)$_{n-a}$]$^{m+}$, ($n = 1$–3) respectively. The finely resolved isotopic distribution at each MS signal was also in perfect agreement with the simulated pattern. The IR spectrum also confirmed that the nitrate occupied in the cavity of helicate (Fig. S8, ESI†). This finding inspired us to estimate that cage 2 has a much stronger binding affinity for NO$_3^{-}$ than BF$_4^{-}$.

When Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ was used as the metal source, $^1$H and DOSY NMR spectra also suggested the quantitative formation of a similar metal-coordination cage (Fig. S9 and S12, ESI†). However, the $^1$H NMR spectrum (complex 2b) changed dramatically in comparison with that of 2a (Fig. S23, ESI†). This was the result of the encapsulation of BF$_4$-, which was clearly confirmed by the $^{19}$F NMR spectrum (Fig. S11, ESI†) and the ESI-Q-TOF mass spectrum (Fig. S14, ESI†). In the $^{19}$F NMR spectrum, the signals corresponding to the encapsulated ($\sim 145.18$ ppm) and the free ($\sim 148.24$ ppm) BF$_4$- anions were both observed.‡ When the bulkier guest BF$_4$-, with a radius of 2.27 Å, which is larger than NO$_3^{-}$ (1.79 Å), was encapsulated in situ during the complexation, the cage had to adopt a more twisted configuration. So the difference of $\delta_{H_{f1}}$ with $\delta_{H_{f2}}$ increased, and $H_b$ and $H_c$ are more...
downfield shifted. The difference in distortions was also suggested by the coordination conditions. It was necessary to prolong the reaction time or increase the temperature to 110 °C for the formation of 2b, meaning that it had to overcome a higher energy barrier when BF$_4^-$ was trapped into the cavity.

Though both NO$_3^-$ and BF$_4^-$ could be encapsulated, the cage showed distinct binding affinities between them. After treating 2b with one equivalent of KNO$_3$ at 110 °C, the $^1$H and $^{19}$F NMR spectrum revealed that 2b converted to 2a almost quantitatively with the encapsulated BF$_4^-$ released (Fig. S24 and S25, ESI$^†$), which confirmed that cage 2 bound NO$_3^-$ more strongly than BF$_4^-$.

These observations urged us to make the empty cage 2 for further studies of its specific anion binding properties. We chose Pd(PF$_6$)$_2$ (0.10 M solution in $d_6$-DMSO, prepared by reacting PdCl$_2$ with AgPF$_6$ in a 1:2 ratio at room temperature for 10 h under dark conditions, the AgCl precipitate was then removed by filtration) as the metal source. In contrast to NO$_3^-$ and BF$_4^-$, PF$_6^-$ with an ionic radius of 2.54 Å$^{18}$ is significantly larger, and thus should not be encapsulated in the cavity. After treating ligand 1 with Pd(PF$_6$)$_2$ for 2 h at 70 °C, $^1$H and DOSY NMR spectra all suggested the quantitative formation of a similar metal-coordination cage 2c (Fig. S16 and S19, ESI†). The $^{19}$F NMR spectrum also confirmed that the PF$_6^-$ was not encapsulated by the cage (Fig. S18, ESI†). However, the ESI-Q-TOF mass spectrum revealed that a chloride ion was trapped into the cavity (Fig. S21, ESI†). The contamination of Cl$^-$ possibly comes from the preparation process of the Pd(PF$_6$)$_2$ solution. This was also confirmed by the anion exchange reactions (Fig. S26 and S27, ESI†) by treating 2b with 1.1 equivalent of N(C$_4$H$_9$)$_4$Cl at 110 °C, where new emerging signals attributed to 2c were observed. The equilibrium constant, calculated by integrating the $^1$H NMR spectra, was around 40. The $^{19}$F NMR spectrum, showing that BF$_4^-$ was replaced from the cavity by Cl$^-$, further proved the presence of Cl$^-$ in 2c. Cl$^-$, an ionic radius of 1.65 Å, is smaller than NO$_3^-$ and BF$_4^-$, so 2c twisted less. This was also supported by the $^1$H NMR spectrum, where a smaller diastereomeric splitting between $\delta_{HH}$ with $\delta_{HH}$ was observed in comparison to 2a (Fig. S23, ESI†).

Nevertheless, the presence of Cl$^-$ in the cavity of 2c had no influence on the study of anion binding properties. Though the binding constants ($K_{anion}$) could not be obtained, the relative binding ability (versus Cl$^-$) could be exhibited. A series of anions available in the lab were screened for binding ability measurement by treating with cage 2c (Fig. 4 and Fig. S28, ESI†), from which the equilibrium constants ($K$, i.e., $K_{anion}$/K$_{Cl}$) (Table 1) for the inclusion of anions, determined by the integration of the characteristic encapsulation signals in the $^1$H NMR experiments, were calculated.

For bulky anions, such as CF$_3$SO$_3^-$, H$_2$PO$_4^-$, and HSO$_4^-$, no signals referenced to the anion-cage complex were observed. The binding affinity is weaker than Cl$^-$ because they are too bulky to enter the cavity. For Br$^-$, the equilibrium constant was less than 1, meaning that the binding affinity is weaker than Cl$^-$.

Table 1. The equilibrium constants$^a$ of anion exchange of 2c

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<th>Anion</th>
<th>$K$</th>
<th>Anion</th>
<th>$K$</th>
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<tr>
<td>NO$_3^-$</td>
<td>2.56 × 10$^2$</td>
<td>NO$_3^-$</td>
<td>4.12 × 10$^3$</td>
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<tr>
<td>Br$^-$</td>
<td>2.86 × 10$^2$</td>
<td>F$^-$</td>
<td>--$^c$</td>
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<tr>
<td>I$^-$</td>
<td>2.33 × 10$^{-2}$</td>
<td>Ac$^-$</td>
<td>--$^c$</td>
</tr>
<tr>
<td>BF$_4^-$</td>
<td>2.5 × 10$^{-2}$</td>
<td>CO$_3^{2-}$</td>
<td>--$^c$</td>
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$^a$ Determined by the integration of the H$_2$ signals except for the case of BF$_4^-$ where the integration of H$_2$ takes place because of signal overlapping.$^b$ Determined by the exchange of 2b with N(C$_4$H$_9$)$_4$Cl.$^c$ No distinct exchange peaks appeared.

Fig. 4 $^1$H NMR (400 MHz, $d_6$-DMSO, 298K) spectra showing the encapsulation of different anions by cage 2c. (1.1 equivalent of anions were added to the solution of 2c in $d_6$-DMSO, * represents the new encapsulation signals.)

size made its spatial orientation inappropriate, so no distinct peaks appeared. The binding of cage 2 towards Ac$^-$ where the integration of H$_2$ takes place because of signal overlapping was much weaker than Cl$^-$ though they have similar size and geometry compared to nitrate anions.

Notably, for NO$_3^-$, the equilibrium constant was up to 256, in other words, cage 2 shows two orders of magnitude higher binding affinity toward NO$_3^-$ than Cl$^-$. Moreover, in the kinetic experiments, the encapsulation of NO$_3^-$ was faster than Br$^-$ (Fig. S29–S31, ESI†). We attributed such a big difference to the presence of maximal hydrogen bonding interactions between the nitrate and the host cage in spite of the mismatching on symmetry. In contrast, the lack of hydrogen bonding weakens this binding between anions and the host even if their symmetries are better matching when single-atom halide anions were placed in the $D_3$ symmetrical host. Similarly, little exchange for NO$_3^-$ was observed.

In conclusion, a chiral M$_2$L$_4$ cage was constructed from the coordination-driven self-assembly of the bidentate ligand 1 and Pd$^{4+}$ and showed distinct inclusion behaviour for different anions where unprecedented selective binding toward nitrate was observed.

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Notes and references

‡ Crystal data for 2a: space group C2, a = 13.7980 (14) Å, b = 32.546 (4) Å, c = 13.7267 (16) Å, α = 90°, β = 100.330 (10)°, γ = 90°. V = 6064.3 (12) Å³, Z = 2, T = 102 K. R1 = 0.0971, wR2 = 0.2481, and goodness of fit = 1.075. CCDC 1048711.