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Anion Receptors

Synthetic Receptors with Micromolar Affinity for Chloride in Water

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Abstract: A water-soluble coordination cage was obtained by reaction of $Pd(NO_3)_2$ with a 1,3-di(pyridin-3-yl)benzene ligand featuring a short PEG chain. The cavity of the metal-organic cage contains one nitrate anion, which is readily replaced by chloride. The apparent association constant for chloride binding in buffered aqueous solution is $K_a = 1.8(\pm 0.1) \times 10^5\ M^{-1}$. This value is significantly higher than what has been reported for other macrocyclic chloride receptors. The heavier halides Br^- and I^- compete with binding or self-assembly, but the receptor displays very good selectivity over common anions such as phosphate, acetate, carbonate, and sulfate. A further increase of the chloride binding affinity by a factor of 3 was achieved using a fluorinated dipyridyl ligand.

The development of synthetic receptors for the complexation of anions in neutral aqueous solutions represents a formidable challenge. While substantial progress has been made over the years, few synthetic receptors are able to bind anions in water with high affinity and selectivity.[1]

The recognition of chloride is of particular relevance because this anion is ubiquitous in biology and in the environment. Exceptionally good receptors for the binding of chloride in organic solvents have been reported,[2] but as soon as water is added to the mixture, the association constants tend to drop significantly.[3] Only a few receptors are able to bind chloride in pure water at neutral pH.[1,4–16]

The bambusuril[4] macrocycle **A** (Figure 1), developed by Sindelar and co-workers, is able to bind chloride with an association constant of $K_a(Cl^-) = 1.2 \times 10^3\ M^{-1}$, as determined by isothermal titration calorimetry (ITC).[5] However, receptor **A** and other bambusurils are promiscuous anion receptors, and monoanions such as NO_3^-, BF_4^-, ReO_4^-, PF_6^-, Br^-, and I^- are bound stronger than Cl^-.[4–6] The structurally related biotin[6]uril **B** was synthesized by the group of Pittelkow.[7] It is able to bind chloride with an association constant of $K_a(Cl^-) = 63\ M^{-1}$ (D_2O, NMR), but its selectivity for chloride is also poor.[8]

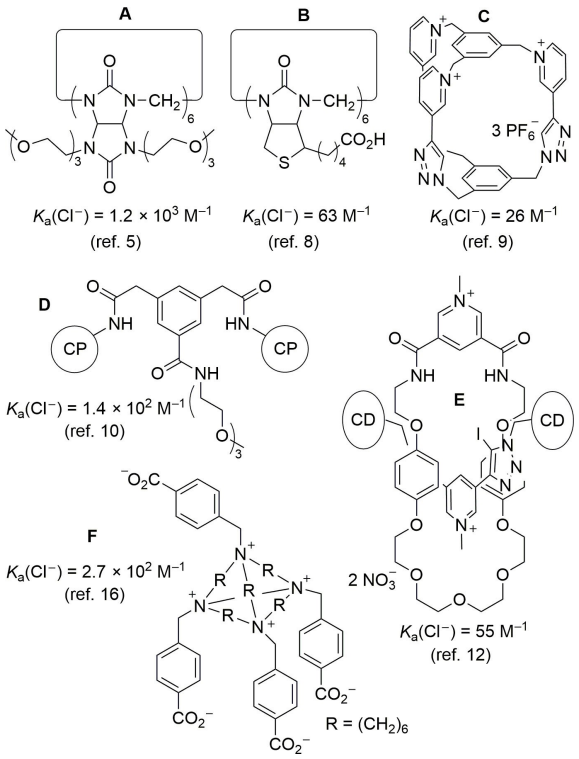

Figure 1. Macrocyclic receptors for chloride binding in water and the corresponding binding constants (CP = cyclopeptide; CD = β-cyclodextrin).

The macrobicyclic receptor **C** was developed by Li and co-workers.[9] Its rigidity imparts good selectivity. However, the affinity of **C** for chloride is lower than what was reported for the macrocycles **A** and **B**.

Kubik and co-workers have investigated extensively the anion binding properties of cyclopeptide-based receptors.[1b] The bridged dicyclopeptide **D** was found to bind chloride with an association constant of $K_a(Cl^-) = 1.4 \times 10^2\ M^{-1}$ (ITC).[10] Stronger binding was observed for Br^-, I^-, and SO_4^{2-}.

The anion-binding properties of receptors relying on halogen bonding have been studied by Beer and co-workers.[11] Rotaxane **E** was found to bind chloride in water with an association constant of $K_a(Cl^-) = 55\ M^{-1}$ (D_2O, NMR).[12] Interestingly, the replacement of the halogen-bonding C–I group with a hydrogen-bonding C–H group diminished the affinity of the receptor.[12,13]

Macrocyclic polyammonium compounds were among the first halide receptors described in the literature,[14] and they have been studied widely over the years.[15] While receptors

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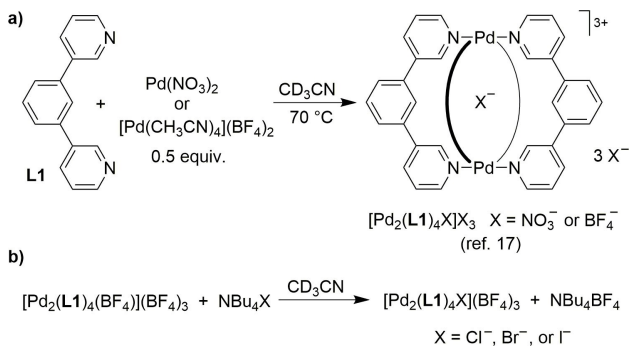
with tertiary ammonium groups require a low pH, the use of quaternary ammonium groups allows binding studies under neutral conditions. Worm and Schmidtchen have investigated chloride binding to the zwitterionic receptor **F**, and an association constant of $K_a(Cl^-) = 2.7 \times 10^2\ M^{-1}$ was determined (D_2O, NMR).[16]

Below, we describe two Pd-based coordination cages, which are able to bind chloride in buffered aqueous solution. An unprecedented low micromolar affinity was observed by ITC.

Recently, we have reported the syntheses of the coordination cages $[Pd_2(\mathbf{L1})_4(NO_3)](NO_3)_3$ and $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$.[17] The dinuclear complexes were obtained by thermal equilibration of $[Pd(CH_3CN)_4](BF_4)_2$ or $Pd(NO_3)_2$ with two equivalents of 1,3-di(pyridin-3-yl)benzene (**L1**) in acetonitrile (Scheme 1). A crystallographic analysis of the complex formed from $Pd(NO_3)_2$ showed that the cavity of the cage is occupied by one nitrate anion.[18] The ^{19}F NMR spectrum of the cage obtained from $[Pd(CH_3CN)_4](BF_4)_2$ suggests that one BF_4^- anion is also encapsulated (see the Supporting Information, Figure S28). Despite the similarities, the assembly of the nitrate complex was found to be "cleaner" and less susceptible to variations in the Pd^{2+} concentration.[17] Most likely, nitrate is better suited as a template. Intrigued by the encapsulation of NO_3^- and BF_4^-, we investigated whether $[Pd_2(\mathbf{L1})_4]^{4+}$ could encapsulate other small anions.



Scheme 1. a) Synthesis of the coordination cages $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$ and $[Pd_2(\mathbf{L1})_4(NO_3)](NO_3)_3$. b) Formation of the halide adducts $[Pd_2(\mathbf{L1})_4X](BF_4)_3$.

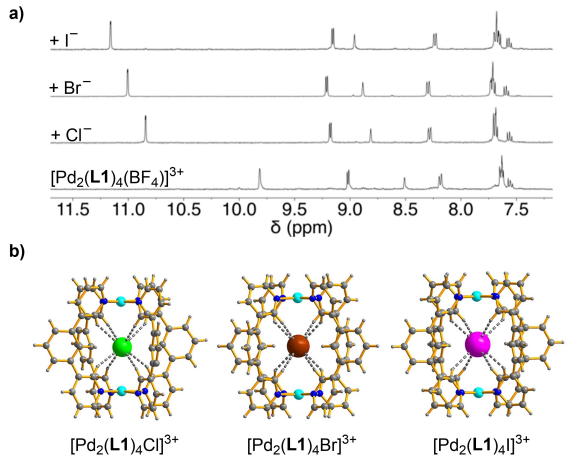


Figure 2. a) Aromatic part of the ^1H NMR spectra (400 MHz, CD_3CN) of $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$ and of solutions containing equimolar amounts of $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$ and NBu_4X (X = Cl, Br, or I). b) Molecular structures of the halide adducts $[Pd_2(\mathbf{L1})_4X](BF_4)_3$ as determined by X-ray crystallography. The BF_4^- anions are not shown for clarity.

When one equivalent of NBu_4Cl was added to a solution of $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$ in CD_3CN (1.0 mM), the clean formation of a new complex was observed by ^1H NMR spectroscopy (Figure 2a). Similar results were obtained when using NBu_4Br or NBu_4I, even though adduct formation was accompanied by the formation of some precipitate.

The ^1H NMR spectra of the adducts showed noticeable differences, in particular for the signals of the NCH protons pointing to the cage interior (Figure 2a). The addition of sub-stoichiometric amounts of NBu_4X indicated that the binding of the halides is slow on the NMR time scale (see the Supporting Information, Figure S27). Further confirmation for the formation of host–guest complexes was obtained by high-resolution mass spectrometry (HR-MS). Dominant peaks for $[Pd_2(\mathbf{L1})_4X]^{3+}$ species were observed in all three cases (see the Supporting Information, Figures S29 to S31).

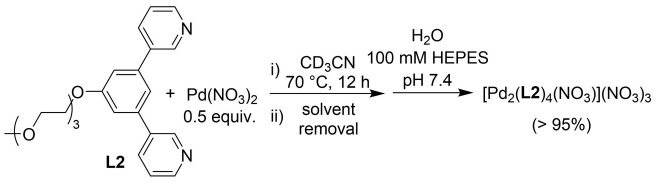
Crystallographic analyses[19] of the three halide adducts revealed that the anions are bound in the cavity of the lantern-shaped[20] $[Pd_2(\mathbf{L1})_4]^{4+}$ host (Figure 2b). For all three complexes, we observed eight C–H···X^- contacts involving the pyridyl NCH protons, with $d_{H\cdots X}$ distances below 3 Å.[21,22] The hydrogen atoms of the central phenylene spacers, on the other hand, are too far away for efficient interaction with the halide ($d_{H\cdots X} > 3.2$ Å). The Pd···X^- distances of around 3.7 Å exclude direct coordination bonds.[23] Nevertheless, the presence of two Pd^{2+} ions will promote anion binding via electrostatic interactions.

First evidence for the high chloride affinity of $[Pd_2(\mathbf{L1})_4]^{4+}$ was provided by a failed attempt to remove chloride with a silver salt. The addition of 500 equivalents of $AgBF_4$ to a solution of $[Pd_2(\mathbf{L1})_4Cl](BF_4)_3$ in CD_3CN did not result in the decomplexation of chloride, as shown by ^1H NMR spectroscopy. The high chloride affinity was further evidenced by the extraction of chloride from water using a solution of $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$ in CD_3NO_2 (for details, see the Supporting Information Figures S32 and S55).

Chloride encapsulation by palladium-ligand assemblies[24] and by other metallasupramolecular structures[25,26] has been described before. These studies were mostly performed in organic solvents. In view of the high apparent chloride affinity of $[Pd_2(\mathbf{L1})_4(BF_4)](BF_4)_3$, we wanted to explore if dinuclear Pd cages could also act as chloride receptors in water.[27,28]

Attempts to use $[Pd_2(\mathbf{L1})_4]X_4$ complexes in water were hampered by solubility problems. Therefore, we synthesized ligand **L2**, featuring a short PEG chain (Scheme 2).

The new ligand **L2** was combined with $Pd(NO_3)_2$ in CD_3CN (Scheme 2). After verifying the success of the self-assembly process by ^1H NMR spectroscopy and HR-MS, we removed the solvent under reduced pressure. The residue was then dissolved in H_2O containing 100 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer with a pH of 7.4 (Scheme 2). The ^1H NMR spectrum of the



Scheme 2. Synthesis of a buffered aqueous solution containing receptor $[Pd_2(\mathbf{L1})_4(NO_3)](NO_3)_3$.

resulting solution showed the presence of $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ in high purity (>95%; see the Supporting Information, Figure S36). A solution of the cage was stable over a prolonged period of time (see the Supporting Information, Figure S38).

The template effect of the nitrate anion was found to be important. Attempts to prepare cages using $Pd(OAc)_2$ or $[Pd(CH_3CN)_4](BF_4)_2$ instead of $Pd(NO_3)_2$ were met with limited success. When $Pd(OAc)_4$ was equilibrated with **L2** (2 equiv) in CD_3CN, the ^{1}H NMR spectrum of the solution showed free **L2** to be the main species present. Analysis by HR-MS indicated that $[Pd_2(\mathbf{L2})_3](OAc)_4$ had formed along with $[Pd_2(\mathbf{L2})_4](OAc)_4$. With $[Pd(CH_3CN)_4](BF_4)_2$, on the other hand, the reaction gave $[Pd_2(\mathbf{L2})_4](BF_4)_4$ and $[Pd_4(\mathbf{L2})_8](BF_4)_8$ as the major products (see the Supporting Information, Figures S13 to S17).

The binding of anions by $[Pd_2(\mathbf{L2})_4(NO_3)]^{3+}$ was first investigated by ^{1}H NMR spectroscopy using a water suppression pulse sequence. The addition of one equivalent of NaCl to a solution of $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ in H_2O/D_2O (95:5, [cage] = 1.0 mM, 100 mM HEPES, pH 7.4) gave a new set of signals for the adduct $[Pd_2(\mathbf{L2})_4Cl]^{3+}$. By integration of the signals, we were able to deduce that the apparent binding constant for chloride complexation is higher than $10^4\ M^{-1}$ (see the Supporting Information, Figure S36). Attempts to use UV/Vis spectroscopy for quantifying the binding affinity were not successful because only minor spectral changes were observed upon complexation of chloride (see the Supporting Information, Figure S54).

The utilization of NaBr gave similar results: a tight host–guest complex between the cage and the halide was formed. The addition of NaI resulted in the slow formation of a yellow precipitate. Nevertheless, the formation of the corresponding adduct could be observed by ^{1}H NMR spectroscopy. Likely, iodide competes with the pyridyl ligand for coordination to the Pd^{2+} ions, resulting in a partial rupture of the cage structure. Similar behavior has been observed for Pd-based cages in organic solvents.[24e,g,h,29]

The addition of one equivalent of NaF, Na_2SO_4, NaOAc, Na_2CO_3, or Na_3PO_4 to a solution of $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ in H_2O/D_2O (95:5, [cage] = 1.0 mM, 100 mM HEPES, pH 7.4) did not result in changes in the ^{1}H NMR spectrum, indicating that the bound nitrate is not exchanged by fluoride, sulfate, acetate, carbonate, or phosphate under these conditions.

To determine the binding constants for chloride and bromide complexation, we performed ITC measurements (T = 298 K).[30] The measurements were carried out in buffered water at pH 7.4 (10 mM HEPES). The solution of $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ was prepared as described above. Solutions of NaCl or NaBr were titrated to a solution of the cage (0.1 mM). The data could be fitted to a 1:1 binding model resulting in apparent association constants of $K_a(Cl^-) = 1.8(\pm0.1)\times10^5\ M^{-1}$ and $K_a(Br^-) = 2.6(\pm0.4)\times10^6\ M^{-1}$ (for details, see the Supporting Information, Figures S39 to S47 and Table S1 to S3). For both anions, the complexation is mainly entropy-driven, with an unfavorable contribution of enthalpy in the case of chloride ($\Delta H_{Cl} = 3.3\ kJ\,mol^{-1}$, $T\Delta S_{Cl} = 33.2\ kJ\,mol^{-1}$; $\Delta H_{Br} = -13.1\ kJ\,mol^{-1}$, $T\Delta S_{Br} = 23.5\ kJ\,mol^{-1}$).

To corroborate that nitrate ions compete with chloride for binding to $[Pd_2(\mathbf{L2})_4]^{4+}$, we have performed ITC measurements in the presence of 0.4 mM $NaNO_3$ ([cage] = 0.1 mM, $[NO_3^-]_{total} = 0.8$ mM). The apparent binding constant for chloride complexation dropped to $K_a(Cl^-) = 1.0(\pm0.1)\times10^5\ M^{-1}$. The reduced affinity in the presence of $NaNO_3$ confirms that nitrate is a competitive guest,[31] and that chloride is captured via an anion exchange mechanism, converting $[Pd_2(\mathbf{L2})_4(NO_3)]^{3+}$ into $[Pd_2(\mathbf{L2})_4Cl]^{3+}$.

Attempts to conduct ITC binding studies with $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ in acetonitrile were impaired by much slower anion exchange. The ^{1}H NMR spectra recorded directly after the addition of one equivalent of NBu_4Cl to a solution of the cage showed limited conversion to the chloride inclusion complex. Complete complexation was observed after equilibration for 5 h at room temperature and time-dependent measurements revealed a half-life of ≈0.2 h (see the Supporting Information, Figures S34 and S35). The faster anion exchange in the highly coordinating solvent water is supportive of a mechanism involving partial or full ligand dissociation of at least one ligand **L2**.

We were interested in exploring if we could alter the host–guest properties of the cage by using substituent effects. Therefore, we synthesized ligand **L3** with fluorine atoms in meta positions relative to the N-donors (Figure 3a). Equilibration of a mixture of **L3** and $Pd(NO_3)_2$ in CD_3CN gave cage $[Pd_2(\mathbf{L3})_4(NO_3)](NO_3)_3$ in nearly quantitative

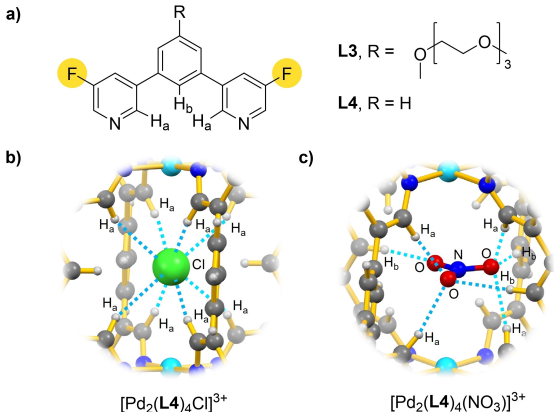


Figure 3. a) Structures of the ligands **L3** and **L4**. b) Close-up view of the chloride anion in $[Pd_2(\mathbf{L4})_4Cl]^{3+}$. c) Close-up view of the nitrate anion in $[Pd_2(\mathbf{L4})_4(NO_3)]^{3+}$. The graphics are based on single-crystal XRD analyses.

yield as shown by NMR and HR-MS analyses (see the Supporting Information, Figures S18 to S22). ITC measurements with NaCl in buffered aqueous solution revealed an apparent association constant of $K_a(Cl^-) = 6.0(\pm 0.4) \times 10^5\ M^{-1}$ ($T = 298$ K). This value is three times superior to the one obtained for the related $[Pd_2(\mathbf{L2})_4(NO_3)](NO_3)_3$ complex. The higher affinity of the fluorinated receptor is mostly due to a favorable change in binding enthalpy (fluorinated cage: $\Delta H_{Cl} = -1.9\ kJ\,mol^{-1}$, $T\Delta S_{Cl} = 31.1\ kJ\,mol^{-1}$; non-fluorinated cage: $\Delta H_{Cl} = 3.3\ kJ\,mol^{-1}$, $T\Delta S_{Cl} = 33.2\ kJ\,mol^{-1}$).

In order to evaluate possible structural effects of the fluorine substituents, we aimed to perform a crystallographic analysis of the fluorinated cage. Unfortunately, we did not succeed in growing suitable single crystals of $[Pd_2(\mathbf{L3})_4(NO_3)](NO_3)_3$ or its chloride adduct. Therefore, we synthesized the structurally related ligand **L4** lacking an ethylene glycol side chain (Figure 3a). With this ligand, we managed to obtain single crystals of $[Pd_2(\mathbf{L4})_4Cl](BF_4)_3$ and $[Pd_2(\mathbf{L4})_4(NO_3)](NO_3)_3$.[19]

XRD analysis of the chloride adduct showed that the overall structure was very similar to what was observed for the non-fluorinated ligand **L1**. The chloride anion is found in the center of the lantern-shaped cage, and one can observe eight C–H···Cl^- hydrogen bonds involving the pyridyl NCH protons "H_a" (Figure 3b).

The encapsulated nitrate in $[Pd_2(\mathbf{L4})_4(NO_3)](NO_3)_3$ is disordered over two equally populated positions. The two anions are bound in the same fashion: two of the three O-atoms are involved in hydrogen bonding to pyridyl H_a-atoms and to H_b-atoms from the central phenylene spacer (Figure 3c). The third O-atom, on the other hand, shows one close C–H_b···ONO_2^- interaction and four longer H-bonds to H_a-atoms (not depicted). The presence of the fluoride atoms in **L4** is expected to strengthen the C–H_a···X^- interaction.[32] The latter appears to be more important for chloride (eight C–H_a···Cl^- bonds) than for nitrate (four close C–H_a···ONO_2^- bonds), providing a rationale for the increased chloride affinity of the fluorinated cage.

To conclude: we have synthesized two Pd-based receptors, which are able to bind chloride in buffered aqueous solution. ITC measurements have revealed apparent binding constants of $1.8(\pm 0.1) \times 10^5\ M^{-1}$ and $6.0(\pm 0.4) \times 10^5\ M^{-1}$. These values exceed what has been reported for other synthetic receptors operating at neutral pH. Crystallographic analyses show that chloride is bound to the Pd receptors via eight C–H···Cl^- hydrogen bonds. The presence of Pd^{2+} promotes anion binding via electrostatic interactions. Furthermore, the coordination of Pd^{2+} to the pyridyl groups is expected to strengthen the hydrogen bonds. In terms of selectivity, the new receptors are very good. Bromide and iodide compete with binding and self-assembly, but common anions such as phosphate, acetate, carbonate, and sulfate do not interfere at all.

Chloride is bound to the receptors via an anion exchange mechanism. Consequently, the observed binding constants represent relative affinities with respect to the nitrate-bound cages. One would expect even higher binding constants for the hypothetical empty cages $[Pd_2(\mathbf{L2})_4]^{4+}$ and $[Pd_2(\mathbf{L3})_4]^{4+}$. However, nitrate seems to be a required template for stabilizing the dinuclear cage structures in water. Future investigations in our lab are directed toward a better understanding of structure-affinity and structure-selectivity relationships of these promising Pd-based receptors.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Anion Receptor · Cage · Chloride · Self-Assembly · Supramolecular Chemistry

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