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DOI
10.1016/j.inoche.2022.109284

Publication date
2022

Document Version
Final published version

Published in
Inorganic chemistry communications

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Citation for published version (APA):
Short communication

Selective binding of ReO$_4^-$ and PtCl$_4^{2-}$ by a Pd$_2$L$_4$ cage in water

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ARTICLE INFO
Keywords:
Self-assembly cage
Host–guest systems
Molecular recognition
Tetrachloroplatinate
Perhenate

ABSTRACT

Anions such as pertechnetate ($^{99m}$TcO$_4^-$) and tetrachloroplatinate ($^{195m}$PtCl$_4^{2-}$) are important precursors for radioactive substances for medical imaging. Molecules that can sense and bind these small anions in water can be exploited to circumvent lengthy synthesis on radioactive material and improve these applications. The most important property of a host is its selectivity for non-biological anions over common biological anions and/or molecules. Here, we report that a previous published [Pd$_2$L$_4$]$_{16}$ guanidinium cage has higher selectivity for ReO$_4^-$ and particularly for PtCl$_4^{2-}$ (nonradioactive substitutes for $^{99m}$TcO$_4^-$ and $^{195m}$PtCl$_4^{2-}$) over common biological molecules. This selectivity was shown by means of $^{1}$H NMR titrations with the most noticeable affinity for PtCl$_4^{2-}$ in the order of $K_a = 10^7$ M$^{-1}$. A molecular model of PtCl$_4^{2-}$ or ReO$_4^-$ bound inside the cage revealed the best interaction complementary fit with the PtCl$_4^{2-}$ anion, which is held in place by equally short N–H–Cl and C–H–Cl hydrogen bonds. This research shows that a simple coordination cage can already have selective binding for non-biological anions such as ReO$_4^-$ and particularly for PtCl$_4^{2-}$, paving the way to improve coordination cages for use in medical imaging research.

1. Introduction

An important technique within medical imaging is the use of radioactive substances in the diagnosis and treatment of diseases, also called nuclear medicine [1]. Common radioactive compounds incorporate $^{18}$F, $^{99m}$Tc, $^{111}$In, or $^{125}$I isotopes for positron emission tomography (PET) or single photon emission computerized tomography (SPECT) [1b], $^{99m}$Tc (with half-life ($t_{1/2}$) of 6 h) is probably the most multifaceted radionuclide in routine radiopharmacy and molecular imaging applications till date [2]. $^{99m}$Tc bearing structures are synthesized from $^{99m}$TcO$_4^-$, the decay product of $^{99}$MoO$_4^2^-$.

A more recent development has been the incorporation of radioactivity in platinum complexes ($^{195m}$Pt with $t_{1/2}$ of 4 days), allowing not only SPECT imaging to be used on anticancer drugs based on platinum (i.e. cisplatin), but also to utilize the low-energy electrons during decay to kill tumour cells by damaging their DNA [3]. Cisplatin and other platinum complexes are generally synthesized from the tetrachloroplatinate anion (PtCl$_4^{2-}$) [4]. Complexation of PtCl$_4^{2-}$ with rhodamine 123, ethidium or a bisguanidinium also resulted in anticancer activity, with an enhanced effectiveness compared to ‘naked’ PtCl$_4^{2-}$ [5]. However, both 1st generation (i.e. cisplatin) and PtCl$_4^{2-}$ are easily hydrated, limiting their selectivity and/or clinical use [6]. Better selectivity and reduced levels of toxicity were reported for cisplatin analogues by either changing the chloride to bis-carboxylate ligands or using a saline solution during administration [6a]. Unfortunately, these stability enhancements of cisplatin, cannot be translated to the PtCl$_4^{2-}$ anion and other approaches are necessary to enhance its stability and selectivity.

A down-side of the above mentioned $^{99m}$Tc and $^{195m}$Pt isotopes is the degradation of the useful isotope during synthetic modifications (due to their short half-life). Therefore, incorporation of these isotopes is commonly performed at the end of a synthetic route [2b]. Another approach would be to use the radioactive precursors themselves (e.g. $^{99m}$TcO$_4^-$ and $^{195m}$PtCl$_4^{2-}$), eliminating the need for synthesis on radioactive compounds and/or the special equipment necessary and improving the overall yield of the radioactive desired compound. Unfortunately, using the radioactive precursors limits the in vivo targets to the inherent selectivity of these anions. Introducing molecules (hosts) that can recognize these anions (guests) could lead to enhanced stability of the anions. For $^{99m}$TcO$_4^-$ several heterogeneous (Fig. 1a) and homogeneous (Fig. 1b–c) approaches have been developed that rely largely on ionic interactions [7].

The homogeneous approach is most interesting and illustrated by the coordination cages 1 and 2 shown in Fig. 1b and c, respectively [7f,g]. It was shown that 1 can selectively extract ReO$_4^-$ [7e], and that 2 facilitated ReO$_4^-$ to cross the blood–brain barrier [7f]. In these reports ReO$_4^-$ was used as a nonradioactive surrogate for $^{99m}$TcO$_4^-$, as it has similar

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https://doi.org/10.1016/j.inoche.2022.109284
Received 2 December 2021; Received in revised form 8 January 2022; Accepted 7 February 2022
Available online 26 February 2022
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chemical properties [7a,b]. Self-assembled cages like those shown in Fig. 1b and c are attractive supramolecular hosts because they are easily tuned to tweak their molecular recognition properties [7a,b]. Moreover, their flexibility in solution allows them to adapt their structure to accommodate a host, contrary to most heterogeneous systems [7b,9]. Furthermore, coordination cages have been shown to possess selectivity for non-biological anions and their preparation involves less synthetic steps towards macrocycles compared to covalently linked macrocycles [10].

Interestingly, with all these advantages, no coordination cage has been reported as host for PtCl$_2$-4. All in all, creating coordination cages as hosts for the non-radioactive surrogates of $^{99m}$TcO$_4^-$ and $^{195m}$PtCl$_2$-anions could lead to the diversification of in vivo selectivities and can thus broaden the use of the radioactive anions in nuclear medicine. Herein we report that in an aqueous environment guanidinium Pd$_4$L$_4$ cage 3 (Fig. 1c) [11] is capable of selectively binding the non-biological anions ReO$_4^-$ and particularly PtCl$_2^-$, which are the non-radioactive metal analogues of $^{99m}$TcO$_4^-$ and $^{195m}$PtCl$_2^-$ respectively.

2. Results and discussion

The Pd$_4$L$_4$ guanidinium ligand and cage 3 were synthesized according to literature procedures [11] and an overview of the guests studied is provided in Table 1 (see section S2 of the supporting information for details on all binding studies). We have already reported that 3 can bind to anionic carbohydrates such as N-acetyleneuraminic acid 4 with affinities of $K_{a,1}^{1} \leq 24$ M$^{-1}$ [11].

Shown in Fig. 2 are selected $^1$H NMR spectra of titration experiments of 3 with KReO$_4$ (Fig. 2a) and K$_2$PtCl$_4$ (Fig. 2b), together with an assignment of cage resonances. Both titrations reveal significant non-linear peak-shifting of most resonances in the aromatic region, while some remained nearly stationary (notably the outwards pointing b and g). Interestingly, saturation behavior was observed near eight equivalents with KReO$_4$ and around two equivalents with K$_2$PtCl$_4$. To quantify binding, the peak shifts were fitted to a 1:1 model using HypNMR [13] as shown in the middle of Fig. 2. This gave the association constants ($K_{a,1}^{1}$) of 434 M$^{-1}$ for KReO$_4$ and 6900 M$^{-1}$ for K$_2$PtCl$_4$, both with a reasonable correlation of fit ($r^2 > 0.97$). The quality of the fits could be improved when corrections for ion exchange in the binding model were introduced as a 1:3 binding model with weak ($K_a = 10$ M$^{-1}$) 1:2 and 1:3 binding. For KReO$_4$ (Fig. S1), this resulted in a same 1:1 binding constant, but for K$_2$PtCl$_4$ (Fig. S2), this gave $K_{a,1}^{1} = 3.16 \times 10^4$ M$^{-1}$ while improving $r^2$ from 0.974 to 0.996. The 1:1 binding with K$_2$PtCl$_4$ is thus clearly in the order of 10$^5$ M$^{-1}$, which is three orders of magnitude higher than previously reported for anionic carbohydrates [11] and higher than previously reported for PtCl$_2^-$ binding (none are reported in aqueous media) [14].

With the good binding potential of cage 3 for these nonradioactive surrogates of $^{99m}$TcO$_4^-$ and $^{195m}$PtCl$_2^-$ we wondered if 3 would also bind the approved cis-platinum based anticancer drugs cisplatin 5, oxaliplatin 6 and nedaplatin 7 (entries 3–5). Similar titrations were carried out as for PtCl$_2^-$, but in these experiments only very minor and nearly linear shifts of $\Delta \delta_{\text{max}} < 0.04$ ppm were observed. Curve fitting of these data did not provide meaningful binding constants (Figs. S3-S5). These data are rather different from those obtained with PtCl$_2^-$ which showed the non-linear and larger shifts ($\Delta \delta_{\text{max}} = 0.19$ ppm) culminating in clear saturation behavior. These results thus demonstrate the selectivity of 3 for anionic guests such as PtCl$_2^-$. The weaker binding to the mono-anionic ReO$_4^-$ that also consists of five atoms together with the lack of binding to the charge natural cisplatin 5 suggest that the selectivity is at least partially driven by electrostatics. Shape complementarity and solvation/desolation effects are also likely factors and future studies might elucidate the exact origin of the observed selectivity.

Interestingly, titrations with the biologically relevant anions biotin 8 (Fig. S6) chloride (Fig. S7) and acetate (Fig. S8) revealed relatively weak

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Table 1 Overview of binding studies performed with cage 3 and the structures of the titrants.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Guest</th>
<th>Final conc. (mM)</th>
<th>$K_{a,1}^{1}$ (M$^{-1}$)</th>
<th>Correlation of fit ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ReO$_4^-$</td>
<td>5.0</td>
<td>434$^{[4]}$</td>
<td>0.996</td>
</tr>
<tr>
<td>2</td>
<td>PtCl$_2^-$</td>
<td>1.6</td>
<td>6900(31600)$^{[a]}$</td>
<td>0.974(0.996)</td>
</tr>
<tr>
<td>3</td>
<td>Cl$^-$</td>
<td>4.7</td>
<td>n.d.</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>OAc$^-$</td>
<td>5.6</td>
<td>n.d.</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>$^{99m}$TcO$_4^-$</td>
<td>17.3</td>
<td>n.d.</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.974</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.996</td>
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</tr>
<tr>
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</tr>
<tr>
<td>14</td>
<td>$^{195m}$PtCl$_2^-$</td>
<td>140</td>
<td>0.996</td>
<td></td>
</tr>
</tbody>
</table>

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Fig. 1. a) Heterogeneous resins designed for selective $^{99m}$TcO$_4^-$ uptake[7b-d]; b) A Fe$_4$L$_4$ coordination cage for selective anion extraction[7f]; c) Pd$_4$L$_4$ cage for biodistribution studies of the host-guest complex with $^{99m}$TcO$_4^-$, with R = peptidic chain[7g]; d) previous reported [Pd$_4$L$_4$]$^{195m}$ guanidinium cage for selective anionic carbohydrate binding[11].
binding with $K_a^{11} \leq 109 \text{ M}^{-1}$ (see entries 6–8 in Table 1). Similarly, titrations with biomolecules 9–14 gave binding constants of $K_a^{11} \leq 46 \text{ M}^{-1}$ (entries 9–14 in Table 1). In the experiments with cytidine 11, phenylalanine 12, histidine 13 and glutathione 14, there were clear signs of cage degradation (Figs. S9–S14), which is likely caused by competitive coordination to the palladium ions from 3 [12,15]. This decomposability of 3 opens up the possibility to explore modified version of 3 as a drug delivery vehicle where cargo release can be trig.

Molecular models of $[\text{PtCl}_4^{2–}]$ and $[\text{PtCl}_4^{3–}]$ were constructed and subjected to density functional theory (DFT) calculations. The resulting model is shown in Fig. 3a, where the PtCl$_4^{2–}$ guest is not located exactly in the center of both Pd(pyridyl) fragments, as indicated by the different Pd–Pt distances (4.70 and 4.17 Å). The PtCl$_4^{2–}$ anion is held in place by a total of eight H–Cl hydrogen bonds (HBs). Four of these HBs involve N–H of one side of the complex (with longest Pd–Pt distance) and the other four involve C–H d on the opposite side. Interestingly, both the N–H⋯Cl and C–H⋯Cl distances are 2.71 Å on average which amounts to 0.13 Å van der Waals overlap [17].

A similar calculation involving ReO$_4^–$ as guest resulted in the model shown in Fig. 3b, where the anion is primarily held in place by two bifurcated HBs involving NH e (2.08 Å ± 0.06 Å, 0.53 Å van der Waals overlap) and CH d (2.26 Å ± 0.03 Å, 0.35 Å van der Waals overlap) of the same ligand [16]. There are also two additional longer HBs involving CH d of another ligand (2.39 Å ± 0.02 Å, 0.22 Å van der Waals overlap).

While the sort N–H⋯Cl/O distances are typical with amides, the short C–H⋯Cl/O distances are not and are likely a consequence of the proximal charge induced by the Pd ion to polarize the C–H bonds. These models indicate that the square planar PtCl$_4^{2–}$ is a much better and symmetrical spatial fit for the interior of 3 compared to the tetrahedral ReO$_4^–$ (i.e. equally long N/C–H⋯Cl HBs involving all four ligands versus four short HBs with only one ligand). Moreover, the difference between the relative energies of formation ($\Delta\Delta E$) indicates that the ReO$_4^–$ adduct is about 12.1 kcal mol$^{-1}$ less stable, which is in line with the smaller binding constant measured and can be rationalized by the difference in shape-complementarity (square planar versus tetrahedral) and charge (2– vs. 1–). An additional calculation involving the square planar but

Fig. 2. Selected $^1$H NMR spectra of 3 titrated with KReO$_4$ (a) or K$_3$PtCl$_4$ (b) in D$_2$O, together with an assignment of resonances. Also given in the center of the figure are the HypNMR analysis of binding curves fitted to a 1:1 stoichiometry to give $K_a^{11} = 434 \text{ M}^{-1}$ for ReO$_4^–$ and $K_a^{11} = 6900 \text{ M}^{-1}$ for PtCl$_4^{2–}$.

Fig. 3. Molecular models of $[\text{PtCl}_4^{2–}]$ and $[\text{ReO}_4^{3–}]$ where the solubility groups are protonated. Both models are geometry optimized using DFT/ωB97X-D/6-31G* with an explicit solvation model for water as implemented in Spartan 2016. In the $[\text{PtCl}_4^{2–}]$ model, the average N/C–H⋯Cl bonding distances are 2.71 Å (with ± 0.06 Å for NH e and ± 0.03 Å CH d). In the $[\text{ReO}_4^{3–}]$ model, the anion is held in place by two bifurcated hydrogen bonds with N–H⋯O = 2.08 Å ± 0.06 Å (with NH e) and C–H⋯O = 2.26 Å ± 0.03 Å (with CH d). There are also two longer C–H⋯O distances with CH d of 2.39 Å ± 0.02 Å. The ReO$_4^–$ adduct is about 12 kcal mol$^{-1}$ less stable than the PtCl$_4^{2–}$ adduct.
monoanionic AuCl\(_4^-\) gave a nearly identical geometry as with PtCl\(_2^2^-\), but 10.8 kcal mol\(^{-1}\) less stable (see Fig. S15 for details). This suggests that the stability of [PtCl\(_4^2^-\)\(\subset\)C\(_3^\dagger\)]\(^{14+}\) relative to [ReO\(_4^-\)\(\subset\)C\(_3^\dagger\)]\(^{15+}\) is mainly driven by electrostatics.

3. Concluding remarks

This research has revealed a coordination cage for the binding of PtCl\(_2^2^-\) with high affinity in an aqueous medium. Binding studies with other common biological molecules revealed binding with low affinity, which supports the possible use of 3 in biological media. We conclude that this guanidinium type [M\(_2\)Au\(_2\)Cl\(_4^2^-\)]\(^{16+}\) cage paves the way for the exploitation of coordination cages for use in medical imaging research, such as binding to simple radioactive anions.

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.

Acknowledgements

This research was financially supported by the Netherlands Organization for Scientific Research (NWO) with VIDI grant number 723.015.006.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2022.109284.

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