Metal salen complexes incorporating triphenoxymethanes: efficient, size selective anion binding by phenolic donors with a visual report†

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A metal salen complex has been designed to orientate four phenol groups into a tetrahedral array that tightly binds fluoride ion though four OH···F hydrogen bonding interactions.

For the design of anion receptors, Lewis acidic metals[1] or organic ligands that employ hydrogen bonding and/or electrostatic interactions are often used.[2] In the case of hydrogen bond donors, virtually all of the attention has focused on ligands incorporating N–H groups such as amides, amines, pyrroles, and ureas,[3] and in some instances, metals help orient these groups.[4] Surprisingly, despite the wide participation of serine and tyrosine hydroxides in anion binding sites in biological systems including ClC chloride channels[5] and halorhodopsin[6] among numerous others,[7] the use of O–H donors in the design of anion receptors has been limited to only a handful of examples that are not particularly well defined systems.[8]

The addition of hydroxides has been noted to induce an increase in the affinity of N–H containing ligands for anions,[9] but we envisioned that a tetrahedral pocket of phenolic donors templated by a metal could provide an ideal environment for the selective binding of anions, particularly since the size of the cavity could be modulated by the choice of metal. Metals also offer convenient pathways to report the binding event *via* spectral changes. Salens have been engineered to orient two sets of N–H donors by several groups,[10] and herein, we report the synthesis and attributes of an anion receptor incorporating four phenols at the periphery of salen. It represents the first example of a selective, efficient, and well-defined system for halide binding containing purely O–H donors.

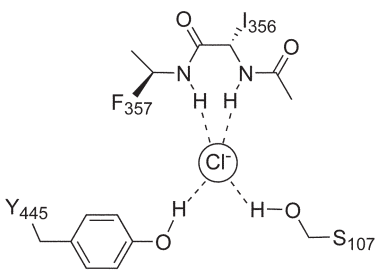

Fig. 1 Schematic diagram of the binding site of ClC chloride channel from *Salmonella typhimurium* (ref. 5). Chloride is held in place by two OH–Cl hydrogen bonds from Y_{445} and S_{107}.

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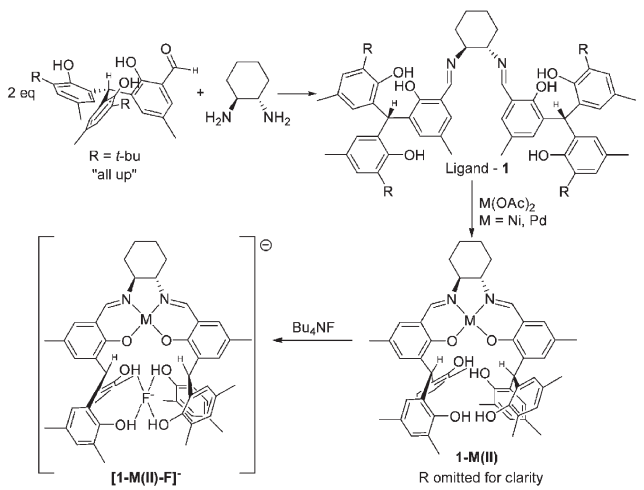
In our previous work with triphenoxymethanes, a preference has been noted for the molecule to adopt an "all-up" orientation wherein all three phenols align with respect to the central methine hydrogen (Scheme 1),[11] and a derivative incorporating an aldehyde group on a single phenol can be readily isolated.[12] The molecule reacts with 1,2-diaminocyclohexane to form **1-H$_2$**.

A range of metals including Mn(II), Ni(II), Zn(II), and Pd(II) can be incorporated into the salen binding sites without affecting the four remaining phenols. The phenols still prefer to remain aligned, and since the metal coordinates to one of them, a pocket is created which is lined by four hydrogen bond donor groups in a pseudo tetrahedral arrangement.

Initial work on the development of an anion sensor has focused on the diamagnetic, square planar Ni(II) and Pd(II) metals since their radii differ by approximately $\sim$ 0.15 Å, providing the opportunity to adjust the size of the binding cavity. Salen complexes with these metals also exhibit intense MLCT absorptions ($\varepsilon \sim 7400$) in the visible region.[13] Both Pd(II) and Ni(II) metal complexes with **1-H$_2$** were structurally characterized, and in each, two symmetry independent molecules crystallized in the asymmetric unit.‡ In both cases, the molecules were nearly indistinguishable, but the orientation of the unbound phenols with respect to the chiral centers on the cyclohexyl rings differed. The chiral *R*,*R*-cyclohexyl backbone was used to isolate single crystals of **1-Ni(II)** and the structure of one of the two symmetry independent molecules is presented in Fig. 2.

As expected, the average distance of the four Ni–oxygen bonds in the two complexes (1.842(8) Å) is typical for a Ni(II) salen



Scheme 1 Procedure used for the synthesis of **1-H$_2$**, macrocycle metalation to form **1-M(II)**, and fluoride binding of **1-M(II)**.

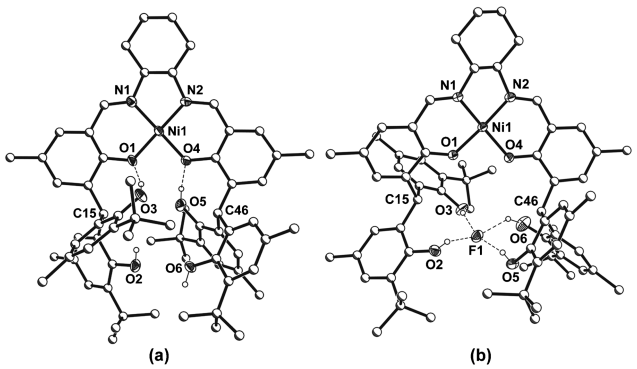


Fig. 2 Depiction of the solid-state structures (30% probability ellipsoids, carbons drawn with arbitrary radii) of (a) **1-Ni(II)** (b) $[$**1-Ni(II)-F**$]^{1-}$ with fluoride bound in the phenolic pocket. The tetrabutylammonium cation, solvates, and hydrogens have been omitted for clarity. Selected distances: (a) C(15)···C(46) 5.28 Å; O(1)···O(3) 2.697(7) Å; O(4)···O(5) 2.784(8) Å; (b) C(15)···C(46) 5.73 Å; O(2)···F(1) 2.539(2) Å; O(3)···F(1) 2.509(2) Å; O(5)···F(1) 3.098(3) Å; O(6)···F(1) 2.573(2) Å.

complex[14] but significantly shorter than the corresponding average Pd–oxygen distance (2.009(4) Å). The subtle size difference between the two metals produces a profound increase in the separation between the two sets of phenolic donors attached to the salen backbone. The distance between the two methine carbons, C(15) and C(46), increases from 5.28 Å in **1-Ni(II)** complex to 6.03 Å in the **1-Pd(II)**, and this increase manifests other changes. In both symmetry independent Ni(II) complexes, a phenolic group from each side of the cavity maintains short hydrogen bonding interactions with the salen phenolates (O–O separations vary from 2.697(7) Å to 2.885(9) Å) and the two remaining phenolic oxygens are situated 2.762(7) Å or 2.784(8) Å from each other, creating a cavity held together by several intramolecular hydrogen bonds. In contrast, only a single phenol hydrogen bonds to the salen phenolate in the cavity formed in **1-Pd(II)** with an O–O separation of 2.824(4) Å, and this oxygen also maintains a close contact of 2.804(4) Å with a phenol oxygen on the opposite side of the cavity. The remaining two phenols are more than 3.989 Å from the nearest oxygen.

Anion binding properties of the two metal complexes were tested with n-Bu_4N^+ halide salts in a variety of solvents including chloroform, acetone, and DMSO, and both **1-Pd(II)** and **1-Ni(II)** complexes only reacted with fluoride at low anion concentrations. The binding cavity appears to be too small to accommodate the larger anions and even after the addition of a large excess of Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, or HSO_4^- no changes could be detected in the ^{1}H NMR or UV/Vis spectra. Treatment of **1-Pd(II)** and **1-Ni(II)** with one equivalent of more basic anions such as $H_2PO_4^-$ and OAc^- produced no discernable change in the UV/Vis or ^{1}H NMR spectrum other than the disappearance of the OH resonances in the ^{1}H NMR spectrum, but at very high concentrations (> 30 eq), the anions induced precipitation in the NMR experiment and a small (< 8 nm) shift of the absorption maxima in the UV/Vis spectra of the complexes. In contrast, the addition of fluoride to **1-Ni(II)** results in dramatic change in the ^{1}H NMR spectrum, and with any amount less than a full equivalent of fluoride, the spectrum is quite broad, suggesting a rapid equilibrium of fluoride between open binding sites since the complex remains diamagnetic. Unfortunately, cooling of the sample initiated crystallization and variable temperature NMR experiments could not be performed. Addition of fluoride to **1-Pd(II)** has a much less dramatic effect on the ^{1}H NMR spectrum of the complex (Fig. 3), and the only significant change involves the two resonances associated with the phenolic protons that shift from 6.83 and 6.44 ppm in d^6-DMSO and appear as a doublet at 9.93 ppm (J_{HF} = 46 Hz). Similar magnitudes for H–F coupling constants have been noted in halide receptors incorporating amides[15] and pyrroles.[16] The phenolic resonances for $[$**1-Ni(II)-F**$]^{1-}$ also occur as a doublet downfield at 9.69 ppm (J_{HF} = 42 Hz) in d^6-DMSO, but in solvents such as $CDCl_3$ and $(CD_3)_2CO$, the resonances for the phenolic protons on both the **1-Ni(II)** and **1-Pd(II)** are absent, presumably due to deuterium exchange with solvent. Fluoride is known to facilitate deuterium exchange on amides in halide receptors.[17] In the ^{19}F NMR spectrum, a quintet resonance (J_{HF} = 46 Hz) slowly grows in at −117.2 ppm (referenced against trifluorotoluene at −63.7 ppm) as fluoride is added to a d^6-DMSO solution of **1-Pd(II)**, intimating that the four phenolic O–H···F interactions are equivalent and produce the $2nI$ + 1 quintet resonance. After addition of more than one equivalent of anion, a new resonance arises at −145.7 ppm, the normal position of the resonance of free fluoride ion. The ^{19}F NMR spectrum of **1-Ni(II)** species after addition of fluoride exhibited a broad resonance at −116.2 ppm, and the value for the H–F coupling constant could not be accurately determined. Once again, solvents such as chloroform and acetone favor deuterium exchange, and all H–F coupling in the ^{19}F NMR disappears in these solvents.

Addition of fluoride to **1-Ni(II)** and **1-Pd(II)** disrupts the hydrogen bonds to the salen phenolates and induces a red shift in the MLCT absorption with two distinct isosbestic points (Fig. 4), intimating a single species forms in solution. In the case of **1-Ni(II)**, the absorption shifts from 411 nm to 431 nm with a small decrease in the molar absorptivity while the **1-Pd(II)** exhibits a slightly larger shift from 407 nm to 440 nm. Job plots indicated that a single equivalent of fluoride binds in the phenolic cavity and from the

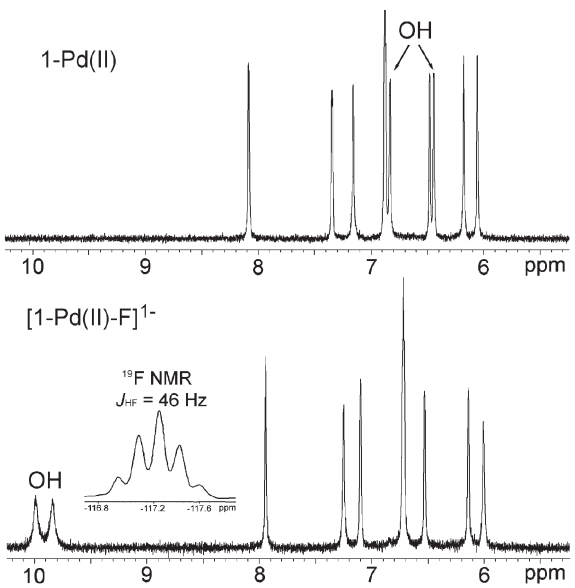


Fig. 3 ^{1}H NMR spectrum of **1-Pd(II)** (top) and $[$**1-Pd(II)-F**$]^{1-}$ (bottom) taken in d^6-DMSO with an inset of the ^{19}F NMR spectrum of $[$**1-Pd(II)-F**$]^{1-}$ in the region of bound fluoride.

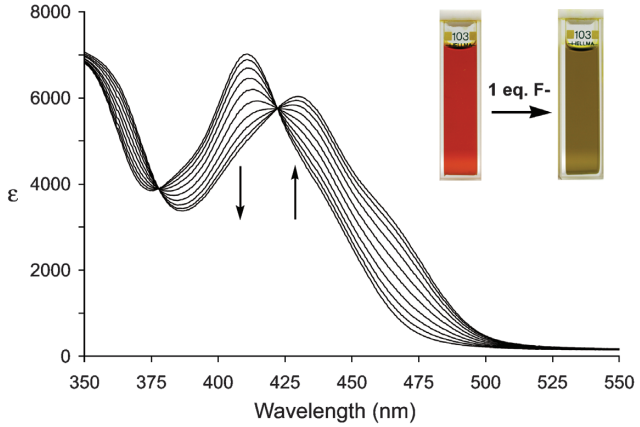


Fig. 4 UV-Vis titration of **1-Ni(II)** salen (4.61×10^{-5} M) with tetrabutylammonium fluoride in acetone. Titration was complete after the addition of a single equivalent of fluoride.

titration data, the log K_s values (errors $\pm 10\%$) were determined to be 5.6 for **1-Ni(II)** complex and 5.8 for **1-Pd(II)** in acetone (log K_s = 5.8 for both complexes in DMSO).

Single crystals of the **1-Ni(II)** complex with fluoride were obtained, and in the solid state (Fig. 2), the fluoride is held in the phenolic cavity by three short and one long hydrogen bond to form $[\mathbf{1\text{-}Ni(II)\text{-}F}]^{1-}$ (fluorine–oxygen separations of 2.539(2) Å, 2.509(2) Å, 2.573(2) Å, and 3.098(3) Å). Although the resonances are a bit broader than the data presented in Fig. 3 for $[\mathbf{1\text{-}Pd(II)\text{-}F}]^{1-}$, the solution NMR spectra for $[\mathbf{1\text{-}Ni(II)\text{-}F}]^{1-}$ suggest the fluoride is held in a symmetric environment by the four phenols, and the lone, long OH···F interaction may be an artifact of crystal packing. In order to fit the anion, the phenolic pocket has had to open up, and the separation between the methine carbons, C(15) and C(46), has increased by almost 0.5 Å to 5.73 Å. Ni(II) appears to be resisting the increase in size of the cavity, and the metal distorts from planarity with an angle of 15.8° between the two N–Ni–O planes in the salen. The cavity created by the Pd(II) center should be able to accommodate the fluoride anion with much less distortion, since the separation between C(15) and C(46) is already 6.03 Å in **1-Pd(II)**.

In conclusion, a salen ligand has been designed to orient four phenolic groups into a tetrahedral array. The Ni(II) and Pd(II) complexes tightly bind fluoride, and the ion is held by three short and one long O–H···F interactions, representing a rare example of efficient anion binding by purely OH hydrogen bonding in a well-defined sensor. Addition of fluoride induces a red-shift in the MLCT transition, offering a visual report of the binding event. Efforts to increase the size and number of phenols that create the cavity by using different metals and amine linkers are underway.

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Notes and references

‡ *Crystal data (173 K, Mo-Kα) for* **1-H$_2$·CH$_3$CN**: $C_{70}H_{89}N_3O_6$; M = 1068.44; triclinic; *P*-1; a = 13.8245(12), b = 14.1393(12), c = 17.9268(15), α = 70.554(2), β = 89.380(2), γ = 71.177(2); V = 3109.2(5); Z = 2; μ = 0.072; D_c = 1.141; $R1$ = 0.0860 for 3349 reflections ($I > 2\sigma(I)$), and $R1$ = 0.2843 $wR2$ = 0.2043. ***R,R*-1-Ni·CH$_3$CN**: $C_{72}H_{90}N_4O_6Ni$; M = 1166.19; triclinic; *P*1; a = 13.1800(9), b = 13.7606(10), c = 20.2871(14), α = 83.267(1), β = 77.170(1), γ = 66.100(1); V = 3278.4(4); Z = 4; μ = 0.349; D_c = 1.181; $R1$ = 0.0522 for 9890 reflections ($I > 2\sigma(I)$), and $R1$ = 0.0851 $wR2$ = 0.1404. **1-Pd·Et$_2$O**: $C_{72}H_{94}N_2O_7Pd$; M = 1205.89; triclinic; *P*-1; a = 16.6011(11), b = 21.7001(15), c = 23.4994(16), α = 71.380(1), β = 86.289(1), γ = 71.152(1); V = 7585.3(9); Z = 4; μ = 0.291; D_c = 1.056; $R1$ = 0.0570 for 13733 reflections ($I > 2\sigma(I)$), and $R1$ = 0.1089 $wR2$ = 0.1302. **(Bu$_4$N)[1-Ni(II)-F]·Et$_2$O** $C_{88}H_{130}N_3O_7NiF$; M = 1419.66; triclinic; *P*-1; a = 13.7248(9), b = 17.0299(11), c = 22.1543(14), α = 71.408(1), β = 89.085(1), γ = 72.851(1); V = 4672.3(5); Z = 2; μ = 0.257; D_c = 1.009; $R1$ = 0.0589 for 12735 reflections ($I > 2\sigma(I)$), and $R1$ = 0.0871 $wR2$ = 0.1731. CCDC 296133–296136. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517944k

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