Inorganic Chemistry

Communication

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Molecular Thioamide ↔ Iminothiolate Switches for Sulfur Mustards

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Supporting Information

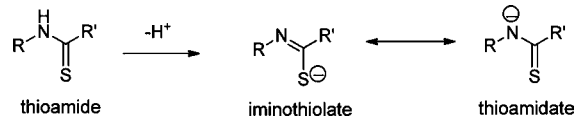
ABSTRACT: SNS platinum(II) pincer complexes reversibly bind and release the surrogate half sulfur mustard, 2-chloroethyl ethyl sulfide (CEES). The switch-like behavior of the pincers is attributed to a reversible transformation between the thioamide and iminothiolate forms of the pincer skeleton under slightly acidic and basic conditions, respectively. An amide-based palladium(II) pincer complex also binds CEES, as confirmed crystallographically and by NMR.

Sulfur mustard, 2,2′-dichlorodiethyl sulfide, and the related nitrogen mustards are cytotoxic chemical vesicants that have been used as chemical warfare agents.[1] An analog of the sulfur mustard, 2-chloroethyl ethyl sulfide (CEES), known as the half sulfur mustard, has frequently been used as a surrogate to study the chemistry of these noxious chemicals. These classes of molecules readily form reactive sulphonium and aziridinium intermediates that can alkylate cellular components of important biomolecules such as DNA, leading to their cytotoxicity.[2] Hence, over the years, various efforts have been made to capture or degrade the mustards in order to achieve chemical detoxification.[3] Interestingly, chemical mustards also have therapeutic applications and have been explored as anticancer drugs.[4] Taken together, these factors have aroused interest both in developing a better understanding of the chemistry of the mustards and in designing artificial receptors for targeting and recognition. Herein, we report platinum and palladium pincer complexes that readily bind to CEES.

Pincer ligands were originally defined as those containing a tridentate ligand composed of a central carbon atom from a cyclometallating group plus two side donor atoms, resulting in an ECE donating chelate.[5] E is usually a nitrogen, phosphorus, or sulfur donor. As the field has developed, the term is now commonly used for similar tridentate chelates containing other heterocycles as the central donor group, for example, pyridine. Pincer and pincer-like complexes are especially of interest because of their varied chemistry that includes an aptitude for both catalysis and luminescence.[5−14] Recently, nickel(II) complexes with a series of simple amide-based NNN pincer ligands, very similar to those reported here, were found to fix CO_2.[7] However, there are not many reports of pincers with thioamide groups,[8−12] and only a few that refer to the acid−base equilibrium of the thioamides described herein.[8−10]

In complexes with palladium(II) and platinum(II), we have found that the SNS pincer ligand *always* binds via the sulfur.[8] However, crystallographic and NMR results indicate that it binds either as the neutral thioamide or the anionic deprotonated iminothiolate form (with the negative charge on the sulfur). It does not appear to have any propensity for binding the other tautomeric form of the deprotonated thioamide, the thioamidate (with the negative charge on the nitrogen; Scheme 1).

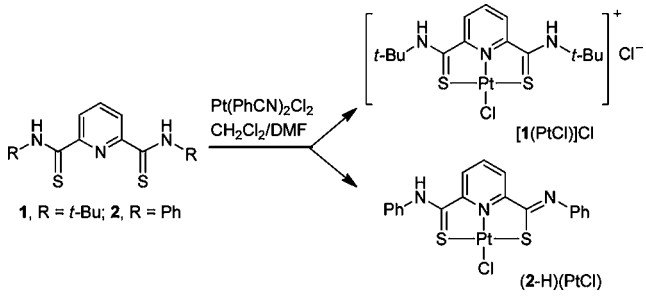
Scheme 1. Thioamide and Its Deprotonated Forms



Earlier, we reported the structure of an S-bonded DMSO platinum(II) complex with the dinegative di-iminothiolate pincer.[8] This, in conjunction with the known affinity of platinum and palladium for sulfur, led to our studies with the half mustard. Not only do the SNS complexes display affinity for CEES but binding can be reversibly turned off and on by the addition of an acid and a base, respectively. Crystallographic confirmation of the sulfur-bound mustard was obtained for the corollary NNN amide pincer palladium complex.

Two simple thioamide-based ligands, **1** and **2**, were chosen for the study. The complexes can be readily synthesized in good yields by reacting the thioamide ligands in DMF with a stoichiometric amount of $PtCl_2(PhCN)_2$ in CH_2Cl_2

Scheme 2. Synthesis of the SNS−Pt Pincer Complexes



(Scheme 2). Crystallographic and NMR analysis of the products of the two reactions showed the anticipated SNS coordination, but different coordination modes. In $[\mathbf{1}(PtCl)]^+$, the *t*-Bu-containing ligand, **1**, is bound as the neutral dithioamide (Figure 1a). However, the phenyl-containing ligand, **2**, is anionic and monodeprotonated, yielding the neutral mixed thioamide−iminothiolate complex, (**2**-H)(PtCl), with both sides of the pincer bound through sulfur (Figure 1b).

Received: September 27, 2011
Published: December 30, 2011

   dx.doi.org/10.1021/ic202087u | *Inorg. Chem.* 2012, 51, 760−762

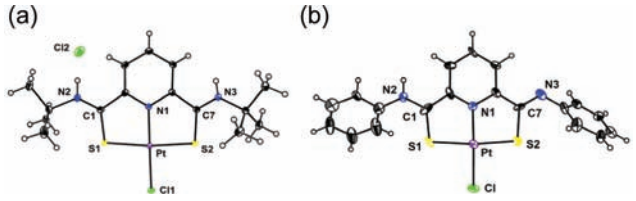
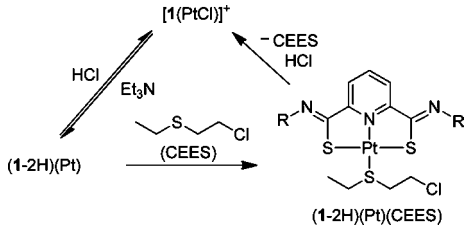


Figure 1. ORTEP views at 30% ellipsoid probability of the SNS–Pt pincer complexes: (a) [**1**(PtCl)]Cl and (b) (**2**-H)(PtCl).

Neither isolated complex showed any reactivity with CEES. However, we decided to test the reactivity of the dideprotonated, platinum complexes of **1** and **2** (Scheme 3). As expected,

Scheme 3. Acid–Base Equilibrium and Binding of CEES with [1(PtCl)]$^+$



upon the addition of Et_3N to [**1**(PtCl)]$^+$, the ^{1}H NMR spectrum changed dramatically, accompanied by the disappearance of the signal due to the NH protons (Figure 2a and b).

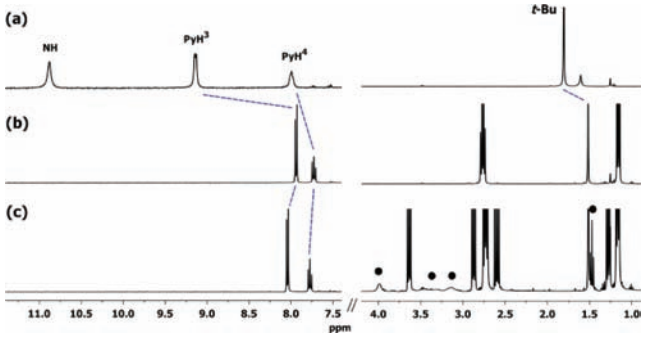


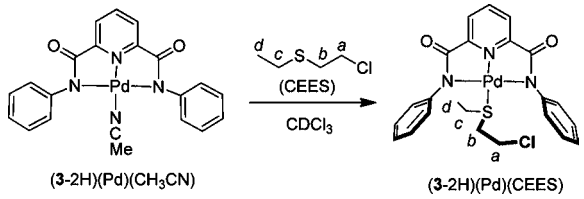
Figure 2. (a) ^{1}H NMR of [**1**(PtCl)]$^+$ in $CDCl_3$ and after addition of (b) Et_3N (5 μL) and (c) CEES (5 μL). Resonance designations "●" correspond to the signals of bound CEES.

Both the pyridine (PyH^3 and PyH^4) and *t*-butyl proton signals showed significant upfield shifts, indicating the formation of the iminothiolate complex, (**1**-2H)Pt. This transformation is reversible, and the original dithioamide complex can be recovered by adding HCl. The transition can be cycled multiple times with iterative additions of base/acid. A similar cycle occurs for **2**.

Both (**1**-2H)Pt and (**2**-2H)Pt were found to react with CEES. By adding excess CEES to (**1**-2H)Pt in $CDCl_3$, the NMR spectrum indicated an immediate transformation, which was complete in 3 h (Figure 2c). The signals due to the initial complex disappeared, and a new set of signals emerged, including downfield shifted CEES signals. Integration is consistent with 1:1 complex formation and was further confirmed by ESI-MS, which shows a predominant peak at m/z = 626.1, corresponding to the complex structure (see Supporting Information). This binding is also reversible and can be recycled upon subsequent sequential additions of HCl and Et_3N. These results demonstrate that the binding and release of CEES can be easily manipulated through simple base/acid control. A similar cycle occurs for (**2**-2H)Pt.

Suitable crystals were not obtained for either of the iminothiolate complexes with CEES. However, a previous report of a palladium(II) NNN pincer complex with ($-CH_2CH_2Ph$)-substituted amides indicated some poorly resolved crystallographic evidence pointing to a coordinated diethyl thioether,[14] although the structure was not of sufficient quality to publish. We therefore synthesized the NNN pincer palladium(II) complex by reacting **3** with $Pd(AcO)_2$ in acetonitrile.[14] Upon coordination, the neutral diamide becomes deprotonated and thus maintains similar negatively charged donor groups as in the successful half mustard-binding platinum(II) iminothiolate complexes. The fourth labile coordination site is occupied by an acetonitrile molecule, which is readily replaced by the addition of CEES (Scheme 4).

Scheme 4. Binding Reaction of CEES with NNN Pd Pincer Showing ^{1}H NMR Assignments for CEES



Crystals of the CEES-bound complex suitable for X-ray crystallography were grown by diffusion of Et_2O into a solution of the CH_3CN complex in neat CEES at room temperature.

The CEES complex, (**3**-2H)(Pd)(CEES), crystallizes in the tetragonal space group, $I4_1/a$, (**3**-2H)(Pd)(CEES)·1.5H_2O. The structure was complicated by disorder, which is best described as two disordered positions (approximately 60:40) in close proximity for each of the atoms. However, by constraining some of the atomic parameters, positions for two very similar coordination spheres were resolved. ORTEP drawings of both of the disordered structures are included in the Supporting Information. The structure of the predominant form is described below. The structure shows the CEES bound within the cleft cavity occupying the fourth palladium coordination site, with a Pd–S bond of 2.302(4) Å (Figure 3). The other

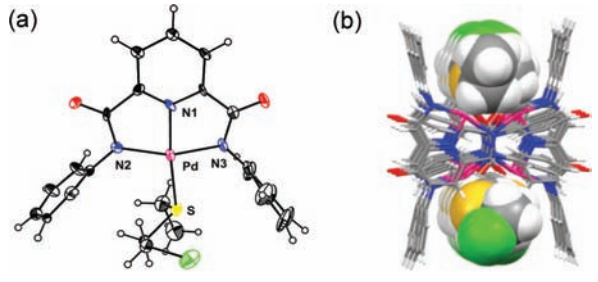


Figure 3. (a) ORTEP drawing of (**3**-2H)(Pd)(CEES) at 30% ellipsoid probability and (b) perspective packing view down the crystallographic *b* axis.

three Pd–N bonds consist of one short bond to the pyridine N1, 1.940(11) Å, and two longer bonds at 2.040(9) and 2.029(9) Å to the outer two nitrogen atoms, as often observed

dx.doi.org/10.1021/ic202087u | *Inorg. Chem.* 2012, 51, 760–762

in structures with heterocyclic central groups.[15] The planes of the two proximal phenyl groups are almost orthogonal to the pincer−Pd−S plane (dihedral angles = 89.8° and 88.3°). The two aromatic groups form a wall "shielding" a chainlike array of the bound CEES molecules along the *b* axis (Figure 3b).

The affinity of the NNN pincer complex (**3**-2H)(Pd)-(CH_3CN) toward CEES was further confirmed by ^{1}H NMR. By adding 5 μL CEES to a solution of the acetonitrile complex in $CDCl_3$, the proton signals of the bound acetonitrile disappeared immediately, and a set of new signals corresponding to the bound CEES arose (Figure 4). On binding, all of the

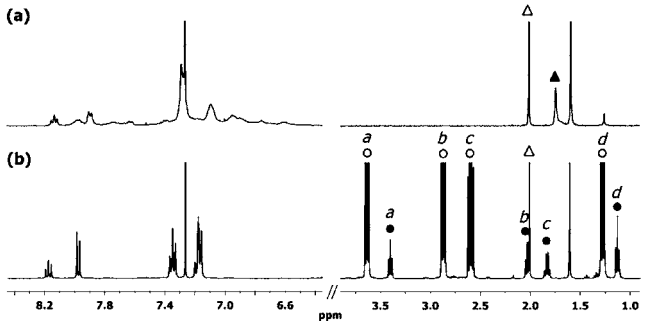


Figure 4. ^{1}H NMR of (a) (**3**-2H)(Pd)(CH_3CN) in $CDCl_3$ (10 mM) and (b) after adding CEES (5 μL). Resonance designations "Δ" and "▲" and "○" and "●" correspond to the signals of free and bound CH_3CN and free and bound CEES, respectively. See Scheme 4 for CEES H-atom assignments.

CEES proton signals shifted upfield (compared to the downfield shifts observed in the di-iminothiolate complexes). The apparent reversal in direction is probably a result of the shielding effect of the two adjacent phenyl rings, as indicated by the crystal structure.

In conclusion, SNS platinum pincer complexes are capable of controlled base/acid binding/release of the half sulfur mustard CEES. The presence of the base allows for the conversion of the dithioamide complex to the di-iminothiolate form and thus activates the binding. The subsequent addition of acid reverses the reaction, resulting in the release of the mustard. Binding and release of the mustard can be readily followed by ^{1}H NMR spectroscopy. Crystallographic insight into the structure was obtained with a corollary amide complex. These findings illustrate an early glimpse of the potential chemical implications of these systems. Ultimately, extended studies may afford more sophisticated molecular switches that, if serving as molecular and ion transport vehicles, could lead to applications in a variety of areas including separations chemistry and drug delivery.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data in CIF format. Synthetic details, NMR and ESI-MS spectra, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

This project received support from the Defense Threat Reduction Agency—Joint Science and Technology Office for Chemical and Biological Defense (B104283I). The authors also thank the National Science Foundation, CHE-0923449, for purchase of the X-ray diffractometer.

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