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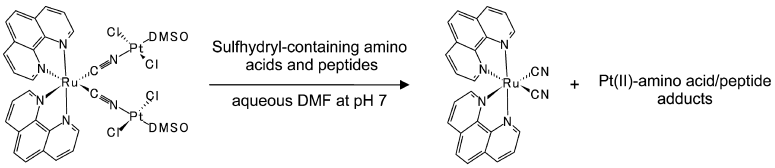

Complex **1**
Weakly emits at 590 nm

Strongly emits at 621 nm

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A Trinuclear Heterobimetallic Ru(II)/Pt(II) Complex as a Chemodosimeter Selective for Sulfhydryl-Containing Amino Acids and Peptides

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Chemosensing of amino acids, peptides, and proteins in aqueous media of physiologically relevant conditions is a rapidly developing field.[1] We are particularly interested in sulfhydryl-containing amino acids and peptides as they play many crucial roles in biological systems.[2] Some of them are also important parameters in clinical diagnostics. For example, plasma levels of glutathione (GSH), cysteine (Cys), and homocysteine (Hcys) have been linked to various human diseases such as AIDS,[3] Alzheimer's and Parkinson's diseases,[4] as well as cardiovascular diseases and stroke.[5] The tendency of proteins to bind with labile platinum(II) complexes via sulfhydryl and methionine functionalities[6] suggests that the platinum(II) metal center is a suitable candidate for molecular recognition and binding of sulfhydryl-containing amino acids and peptides. Low-energy metal-to-ligand charge transfer (MLCT) luminescence of coordination and organometallic complexes has been very useful in the transduction of chemosensing signals through biological fluids as it is not masked by the ubiquitous high-energy background fluorescence from sample matrixes.[7] Here, we report the synthesis and characterization of a neutral trinuclear heterobimetallic cyano-bridged Ru(II)/Pt(II) complex, *cis*-Ru(phen)$_2$[CN−Pt(DMSO)Cl$_2$]$_2$ (phen = 1,10-phenanthroline) (**1**), as a chemodosimetric ensemble[8] for sulfhydryl-containing amino acids and peptides. ^{3}MLCT emission of *cis*-[Ru(phen)$_2$(CN)$_2$] is quenched upon coordination of the cyano moieties by the electron-accepting Pt(DMSO)Cl$_2$ moieties. Selective coordination of the Pt(II) centers with Cys, Hcys, methionine (Met), and GSH in aqueous DMF at pH 7 causes the cleavage of the cyano bridge and the restoration of the characteristic orange-red ^{3}MLCT luminescence of the Ru(II)-diimine chromophore.

Complex **1** is formed by stirring 2 equiv of [Pt(DMSO)$_2$Cl$_2$][9] with 1 equiv of *cis*-[Ru(phen)$_2$(CN)$_2$][10] in chloroform at room temperature.[11] A perspective view of the crystal structure of **1**, with atom labeling, is shown in Figure 1. The three metal centers adopt a V-shaped configuration with two Pt(DMSO)Cl$_2$ moieties bridged to a Ru(II) center via cyano bridges. Such molecular configuration has already been proposed by Bignozzi and Scandola in an analogous complex {Ru(bpy)$_2$[CN−Pt(dien)]$_2$}(ClO$_4$)$_4$ (dien = diethylenetriamine).[12] The coordination geometry of the two Pt(II) centers is square planar with two chloro ligands trans to each other and a coordinated DMSO trans to the cyano bridge. The averaged bond distance between Ru and the cyano-C is 1.961 Å, and that between Pt and cyano-N is 2.001 Å. The two Ru−C≡N−Pt bridges are slightly bent from linearity with the mean bond angles of 176.2° at Ru−C≡N and 171.4° at C≡N−Pt. The mean Pt−S bond distance is 2.208 Å. Integrity of the cyano-bridges of **1** in aqueous DMF (pH 7) is demonstrated by its electrospray-MS showing peaks at *m*/*z* 1166 corresponding to [M − Cl]$^+$.

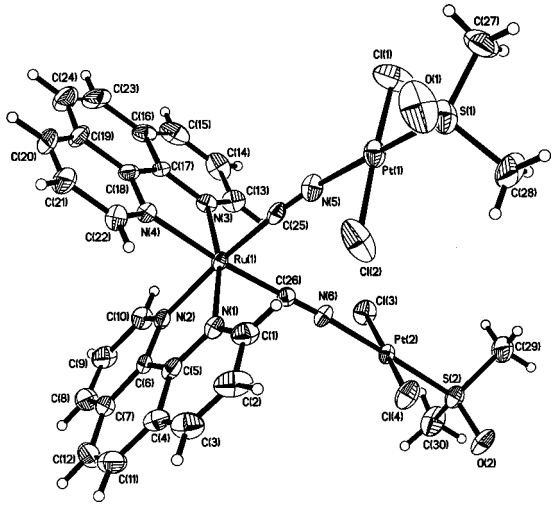

Figure 1. Perspective view of *cis*-{Ru(phen)$_2$[CN−Pt(DMSO)Cl$_2$]$_2$} (**1**). Selected bond lengths (Å) and angles (deg): Ru(1)−N(1) 2.082 (8), Ru(1)−N(2) 2.107 (8), Ru(1)−N(3) 2.073 (7), Ru(1)−N(4) 2.124 (8), Ru(1)−C(25) 1.954 (12), Ru(1)−C(26) 1.966 (11), Pt(1)−N(5) 2.013 (10), Pt(2)−N(6) 1.987 (9), Pt(1)−Cl(1) 2.275 (4), Pt(1)−Cl(2) 2.284 (4), Pt(2)−Cl(3) 2.295 (3), Pt(2)−Cl(4) 2.287 (3), Pt(1)−S(1) 2.206 (3), Pt(2)−S(2) 2.210 (3). C(25)−Ru(1)−C(26) 86.7 (4), N(5)−C(25)−Ru(1) 173.9 (10), N(6)−C(26)−Ru(1) 178.4 (9), C(25)−N(5)−Pt(1) 169.5 (10), C(26)−N(6)−Pt(2) 173.3 (9), N(5)−Pt(1)−Cl(1) 89.2 (3), N(5)−Pt(1)−Cl(2) 89.2 (3), N(6)−Pt(2)−Cl(3) 89.5 (3), N(6)−Pt(2)−Cl(4) 86.6 (3), Cl(1)−Pt(1)−Cl(2) 175.14 (18), Cl(3)−Pt(2)−Cl(4) 175.76 (12), N(5)−Pt(1)−S(1) 175.0 (3), N(6)−Pt(2)−S(2) 178.7 (3)

Upon coordination of the Pt(DMSO)Cl$_2$ acceptors, the Ru(dπ) → phen(π*) MLCT transition[13] of the Ru(II)-diimine chromophore shifts from 452 to 384 nm, and the ^{3}MLCT emission[12] shifts from 621 to 595 nm with a drastic reduction in luminescent intensity. The concomitant blue-shift of the MLCT transitions and the decrease of the ^{3}MLCT emission intensity are consistent with the coordination of good electron acceptors to the cyano donors of [Ru(phen)$_2$(CN)$_2$].[12,14] Solventochromic studies of *cis*-[Ru(phen)$_2$(CN)$_2$] have demonstrated the reduction of emission quantum yield, ϕ_{em}, in solvents with a large Gutmann's solvent acceptor number, that is, good electron-accepting ability.[14]

Figure 2a shows typical luminescent responses of **1** to Cys in aqueous DMF at pH 7. Addition of the thiol amino acid shifts the ^{3}MLCT emission of the complex from 595 to 621 nm with a significant enhancement in intensity. Figure 2b and 2c summarizes spectrofluorimetric titrations of **1** with common amino acids and GSH. For amino acids, only those with sulfhydryl functionality (Cys, Hcys, and Met) are able to induce the spectrofluorometric responses. GSH, a cysteine-containing small peptide, is also found to be able to produce similar results. It is envisioned that **1** can also respond to other sulfhydryl-containing peptides.

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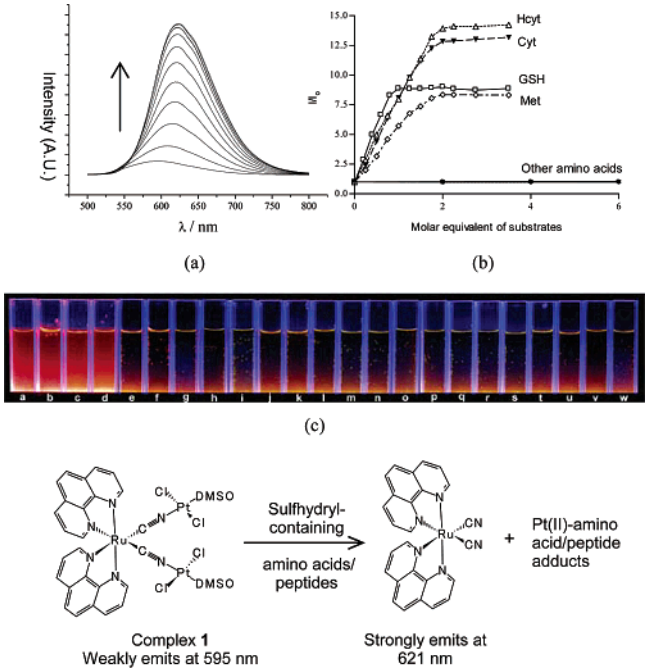

Figure 2. Luminescent responses of **1** toward amino acids and peptides: (a) enhancement of luminescent intensity at 621 nm in a typical spectrofluorimetric titration of **1** by cysteine. (b) Results of spectrofluorimetric titrations of **1** by common amino acids/GSH monitored as a function of the increase in emission intensity (I/I_O) at 621 nm. (c) Photographs of the chemosensing responses: (a) **1** + Cys; (b) **1** + Met; (c) **1** + Hcys; (d) **1** + GSH; (e−v) **1** + L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine, respectively; (w) complex **1** alone. All titrations were carried out in aqueous DMF (1:1 v/v) at pH 7. Excitation λ was 467 nm.

The close resemblance of the luminescent responses of **1** to those of *cis*-[Ru(phen)$_2$(CN)$_2$] and the subsequent observation of [Ru(phen)$_2$(CN)$_2$] in the electrospray-MS of **1**−amino acid mixtures (*m*/*z* 553 [M + K]$^+$; *m*/*z* 537 [M + Na]$^+$; *m*/*z* 515 [M + H]$^+$)[11] suggest that the cyano-bridges between Ru(II) and Pt(II) of the trinuclear complex are cleaved after the binding of sulfhydryl-containing amino acids/peptides to the Pt(II) centers of **1**. The substrate selectivity of the binding-induced dissociation is attributable to the preferential coordination of thiol-amino functionalities to Pt(II).[15] For the small thiol amino acids (Cys, Hcys, and Met), the complex:substrate binding stoichiometry is 1:2. For GSH, a 1:1 binding stoichiometry is revealed. Murdoch et al. have recently reported the formation of di-platinum(II) adduct between GSH and [Pt(en)Cl$_2$] (en = ethylenediamine).[6c] It is likely that, in the present case of GSH binding, two Pt(II) centers are required to bind each GSH.

The substrate binding process can be analyzed assuming that each Pt(II) center binds the amino acid/peptide substrates in a 1:1 ratio.[16] In the case of GSH, a 1:1 binding between the complex and the substrate is assumed. Affinity of the chemodosiometer toward the thiol amino acids and peptide, in descending order of the binding constant K_B, is found to be 1.74 ± 0.19 × 10^5 M^{-1} (GSH), 8.40 ± 0.23 × 10^4 M^{-1} (Cys), 4.99 ± 0.81 × 10^4 M^{-1} (Hcys), and 2.92 ± 0.25 × 10^4 M^{-1} (Met).

To the best of our knowledge, complex **1** is the first luminescent chemodosimeter selective for sulfhydryl-containing amino acids and peptides. The heterobimetallic chemodosimetric ensemble approach, where one metal center which acts as a functional-specific binding site is bridged to another metal center responsible for signal transduction, seems to be a versatile way of designing new chemodosimeters and chemosensors.

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Supporting Information Available: Synthetic procedures, spectroscopic properties, and crystallographic data of **1**; details of the spectrofluorimetric titrations and electrospray mass spectra of selected **1**−amino acid mixtures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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