

Conformational Switching on Platinum(II) Coordination Plane Triggered by Oxalate Anion

Ki-Hyun Kim, Rira Ju, Hae-Jo Kim,[†] Moo-Jin Jun,[‡] and Kwan Mook Kim*

Department of Nano-Chemistry, Ewha Womans University, Seoul 120-750, Korea. *E-mail: kkmook@ewha.ac.kr

[†]Department of Chemistry, Hankuk University of Foreign Studies, Yongin 449-791, Korea

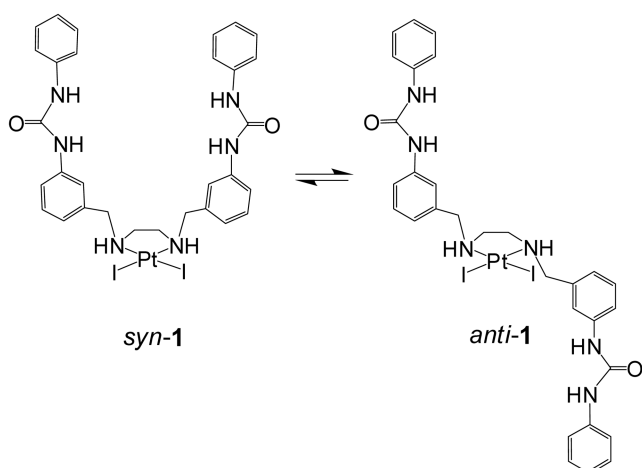
[‡]KISTI ReSEAT program senior fellow, Korea Institute of Science and Technology Information, Seoul 130-742, Korea

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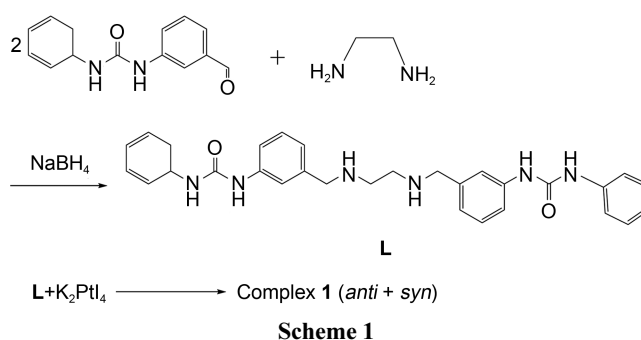
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A molecular conformational switching has been of growing interest in association with molecular electronics,¹ machines² and sensors.³ External stimuli such as a transition metal,⁴ light,⁵ a redox reaction,⁶ pH variation⁷ and guest molecules⁸ were used to control the thermodynamic equilibrium between the conformers. For example, complexation with Lewis acid, TiCl₄, changes the conformation of arene-dicarboxamide from *syn* to *anti* atropisomer.⁴ The specially designed ligand is programmed to have *syn* conformer by the application of the transition metal complex PdCl₂(PhCN)₂.⁹

N-Alkyl-substituted-ethylenediamine complexes of platinum(II) are well known to adopt *syn* and *anti* conformers which are inter-converted fast in aqueous solutions.¹⁰ We have been interested in developing a conformational switching system by exploiting this behavior, thus designed complex **1** with two uryl groups which are well known to bind carboxylates.¹¹ We speculated that the thermodynamic ratio of *syn* to *anti* conformer of **1** would be influenced by a suitable dicarboxylate anion such as oxalate which is a biologically important anion.¹²



Ligand *N,N'*-bis(3-phenyluranyl-benzyl)-ethylenediamine (**L**), was synthesized by the reductive amination of 3-phenyluranyl-benzaldehyde by ethylenediamine and NaBH₄ (Scheme 1). The compound, 3-phenyluranyl-benzaldehyde, was prepared by the PCC oxidation of 3-phenyluranyl-benzylalcohol. Platinum complex **1** was obtained as a crude



precipitate by the treatment of **L** with K₂PtI₄ in water/methanol cosolvent. The platinum complex was further purified by recrystallization in DMF/water.

Complex **1** is insoluble in water, only marginally soluble in acetone, acetonitrile and methanol, freely soluble in DMF, and decomposes in DMSO probably due to the coordination of the solvent to the metal complex. The analysis of ¹H NMR spectrum for the crude product revealed that the *syn* conformer exists in less amount than the *anti* conformer with the initial *syn/anti* ratio of 0.47/1 in DMF-*d*₇. We obtained similar results with the crude products from several experimental batches. At equilibrium, however, the *syn/anti* ratio of the crude complex changed to 1.55/1 in DMF-*d*₇. The *anti-syn* conversion rate of **1** in DMF-*d*₇ was so slow that more than 14 days were required to reach the equilibrium, which was much slower compared to the known inversion rates¹⁰ of other platinum(II) complexes in aqueous solution.

Figure 1 shows time-dependent partial ¹H NMR spectra in the region of uryl NH and ethylene CH signals when 1.0 equivalent oxalic acid was added to **1** in the presence of excess base triethylamine in DMF-*d*₇. The concentration of **1** was kept to be 20 mM. The experiment started with the crude complex **1** which has more *anti* conformer than *syn* conformer. The two uryl NH signals of the *syn* conformer shift to more downfield region than those of the *anti* conformer with the addition of oxalate anions. The more downfield signals imply the stronger hydrogen bonding between the oxalate and the uryl group. The ethylene CH signals around 5.0 ppm change to 5.1 ppm, which certainly reflect the conformational changes from *anti* to *syn* of **1**. The

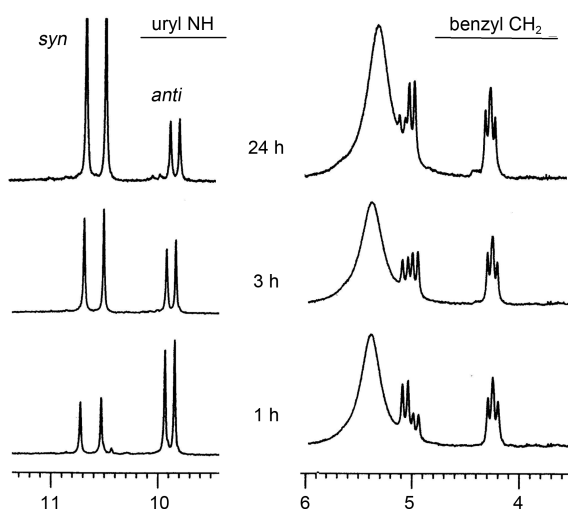


Figure 1. Time-dependent ^1H NMR spectra showing the conformational switching of **1** from *anti*-excess to *syn*-excess in the presence of 1 equiv. oxalate.

time dependent spectra in Figure 1 demonstrates that the *syn/anti* ratio increases notably with the addition of 1.0 equiv oxalate. At final equilibrium, the amount of *syn* conformer exceeds that of *anti* one by the ratio of $\sim 4:1$. This equilibrium ratio in the presence of oxalate is significantly greater than the ratio of the solution without oxalate.

The same ^1H NMR studies demonstrated as in Figure 1 were applied to other dicarboxylates, malonate and succinate. *Syn/anti* ratios at final equilibrium were 2.22/1 and 2.13/1 for malonate and succinate, respectively. The *syn/anti* ratio (4/1) of the oxalate solution at equilibrium is apparently larger than those of malonate and succinate.

Figure 2 shows the dependence of the chemical shifts of an NH proton peak in ^1H NMR on the change of the concentrations of oxalate, malonate and succinate. The concentration of the base TEA has been kept to be 4 equivalents of the diacids in this study, while the concentration of **1** was kept to be 20 mM. The chemical shift of NH uryl proton appears at 9.08 ppm in the solution without any substrate,

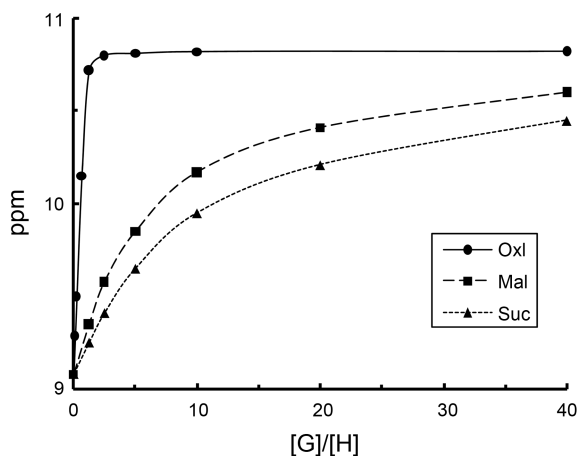


Figure 2. The dependence of ^1H NMR chemical shift of one NH upon the addition of dicarboxylate anions. ●: oxalate, ■: malonate, ▲: succinate.

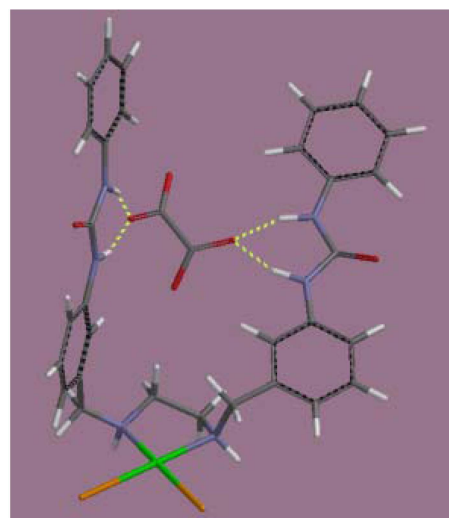
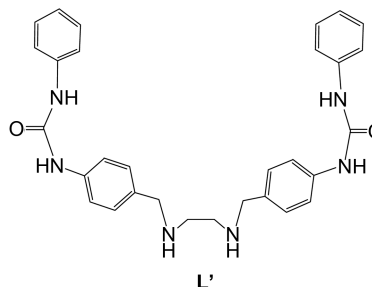


Figure 3. Predicted structure of *syn-1* binding oxalate calculated by Molecular Mechanics.

and saturates to 10.81 ppm with the addition of oxalate. Based on the 1:1 binding model between **1** and dicarboxylate, the dissociation constant of oxalate for the platinum complex, *syn-1*, was calculated to be $(3.95 \pm 0.20) \times 10^{-4}$ M, whose binding affinity is much stronger than $(1.12 \pm 0.04) \times 10^{-1}$ M of malonate and $(1.81 \pm 0.08) \times 10^{-1}$ M of succinate. Oxalate exhibits a prominent *syn* selectivity of complex **1** with more than 280-fold binding affinity over other structurally similar dicarboxylates.

The 1:1 binding of oxalate to *syn-1* can be explicable by the energy minimum structure in Figure 3, which suggests the optimum interaction between oxalate and two uryl groups.¹³ Two uryl groups fix ideally the oxalate anion between them. This binding mode is considered to induce complex **1** to take the *syn* conformation for the optimal hydrogen bonds.

For comparison, we also prepared the ligand, *N,N'*-bis-(4-phenyluryl-benzyl)-ethylenediamine (**L'**), which has the uryl group at para position.



The platinum complex, (**L'**)PtI₂ (**2**), was prepared by the same method as **1** using **L'** and K₂PtI₄. The *syn/anti* ratio of the crude compound **2** was 0.5/1 in DMF-*d*₇, and the ratio in the equilibrium was 1.5/1, which are very similar to those of compound **1**. However, the two uryl groups in complex **2** might be located in unfavorable positions, so that its binding affinity toward oxalate anion is expected to be less than that

Table 1. The *syn/anti* ratios of **1** and **2** at different conditions in DMF-*d*₇

Solutions	<i>syn/anti</i> ratio
1 in initial	0.47/1
1 at equilibrium	1.55/1
1 + 4 TEA + 1.0 Oxal	4.00/1
1 + 4 TEA + 1.0 Mal	2.22/1
1 + 4 TEA + 1.0 Succ	2.13/1
2 in initial	0.5/1
2 at equilibrium	1.5/1
2 + 4 TEA + 1.0 Oxal	1.6/1

of **1**. Indeed, the *syn/anti* ratio of compound **2** in the presence of oxalate was ~1.6/1, which is almost same with that in the absence of oxalate. The comparison of complexes **1** and **2** demonstrates certainly that the binding mode in Figure 3 is a key factor driving **1** into the *syn* conformation.

Table 1 summarizes the *syn/anti* ratios obtained in this work in different conditions.

In conclusion, we have developed molecular switching system triggered by oxalate anion operating on platinum square planar coordination plane by controlling well-known alkyl inversion process on nitrogens. This work shows that oxalate anion disturbs the thermodynamic equilibrium between *syn* and *anti* conformer and induces the *syn* conformer to be produced in excess. Thus oxalate may be regarded as a trigger that bring about the conformational change of complex **1**. This behavior might be exploited to develop sensors for the kidney stone disease-related oxalate anions.³

Experimental Section

(*N,N'*)-Bis(3-phenylurlyl-benzyl)-ethylenediamine (**L**).

A mixture of 3-phenylurlyl-benzaldehyde (2.0 g, 8.3 mmol) and ethylenediamine (0.25 g, 4.1 mmol) in ethanol (30 ml) was refluxed for 18 h. The solvent was then evaporated. The residue was reacted with NaBH₄ (0.38 g, 10.0 mmol) in THF (50 mL) at room temperature for 4 h. The solvent was evaporated and the product was extracted with chloroform. The crude product was purified by recrystallization in CHCl₄ and hexane to obtain 1.8 g of **L** (yield: 83%). ¹H NMR (250 MHz, DMSO-*d*₆): δ (TMS) 6.8-7.5 (m, 18H, aromatic), 3.75 (s, 4H, benzyl), 2.73 (s, 4H, ethylene). HRMS (FAB) calcd for C₃₀H₃₂N₆O₂: 508.6285; found: 508.6208.

(*N,N'*)-Bis(4-phenylurlyl-benzyl)-ethylenediamine (**L'**).

The compound **L'** was obtained by the same procedures as **L** starting from 4-phenylurlyl-benzaldehyde and ethylenediamine. ¹H NMR (250 MHz, DMSO-*d*₆): δ (TMS) 6.8-7.5 (m, 18H, aromatic), 3.56 (s, 4H, benzyl), 2.52 (s, 4H, ethylene). HRMS (FAB) calcd for C₃₀H₃₂N₆O₂: 508.6285; found: 508.6252.

(**L**)PtI₂ (**1**). K₂PtCl₄ (1.0 g, 2.5 mmol) and KI (7.0 g, 42 mmol) was stirred in water (20 mL) for 1 h. **L** (1.4 g, 2.7 mmol) in 20 mL acetone was added dropwise to the solution, and the resulting solution was refluxed for 24 h. Fine yellow precipitate, (**L**)PtI₂ (**1**), was formed in the

reaction solution, which was separated by filtration and washed with ethanol, diethylether and dried under vacuum. The product was a mixture of *anti*-**1** and *syn*-**1** with total yield of 85%. ¹H NMR (250 MHz, DMF-*d*₇) for *anti*-**1**: δ (TMS) 9.84 (s, 2H, uryl NH), 9.76 (s, 2H, uryl NH), 8.03 (s, 2H, aromatic), 6.9-7.8 (m, 16H, aromatic), 4.78 (d, 2H, benzyl), 3.99 (d, 2H, benzyl), 3.05 (dd, 2H, ethylene), 2.41 (dd, 2H, ethylene). ¹H NMR (250 MHz, DMF-*d*₇) for *syn*-**1**: δ (TMS) 9.85 (s, 2H, uryl NH), 9.77 (s, 2H, uryl NH), 8.03 (s, 2H, aromatic), 6.9-7.8 (m, 16H, aromatic), 4.90 (d, 2H, benzyl), 4.02 (d, 2H, benzyl), 2.72 (dd, 2H, ethylene), 2.61 (dd, 2H, ethylene).

(**L'**)PtI₂ (**2**). This was obtained by the same procedures as **1** starting with **L'**. The ¹H NMR was same with **1** except in the aromatic region.

Determination of Binding Constant by NMR Titration Method.¹⁴ Our analysis is based on a simple 1:1 binding equilibrium model. A host (**H**) and a guest (**G**) are assumed be in equilibrium with the complex (**HG**). The observed chemical shift (*d*_{obs}) of a selected proton on the host is a weighted average of that proton's chemical shift in two possible environments - the chemical shifts in the unbound host environment (δ_H) and the chemical shift in the bound host environment (δ_{HG}). If the initial host concentration is defined to be [H]₀, then Equation (1) applies.

$$\delta_{\text{obs}} = \frac{[\text{H}]_0 - [\text{HG}]}{[\text{H}]_0} \delta_{\text{H}} + \frac{[\text{HG}]}{[\text{H}]_0} \delta_{\text{HG}} \quad (1)$$

Defining Δδ_{max} to be the difference in chemical shift for the two environments between complex and free host, the observed chemical shift can be expressed as a function of [H]₀, [G]₀, K_d and δ_H.

$$\delta_{\text{obs}} = \delta_{\text{H}} \frac{([\text{H}]_0 + [\text{G}]_0 + K_d) - \sqrt{([\text{H}]_0 + [\text{G}]_0 + K_d)^2 - 4[\text{H}]_0[\text{G}]_0}}{2[\text{H}]_0} \Delta\delta_{\text{max}} \quad (2)$$

Equation (2) was used for the binding affinity determination by applying a linear regression method implemented in the program Sigma plot.

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