Unusual Fluorenylidene-philic Interactions for Effective Conformational Induction**

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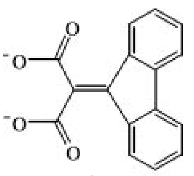
The observation and modulation of unusual noncovalent interactions is of central importance in the field of functional molecules since the interactions play critical roles in the determination of structural motifs and reaction pathways.[1–5] Conformational equilibria have often been studied to deduce general structure–stability relationships, and the results can be extended beyond the initial goal to such diverse areas as quantum-mechanical calculations, spectroscopic studies, molecular biology, chiral catalysts, and tunable receptors.[6–10] Switchable conformation through such specific interactions may serve in the development of sensing or recognition materials. Herein we report a systematic study of conformational induction by intramolecular fluorenylidene-philic interactions during the oxidative addition of $[Pt^{II}(fm)]$ to $[Pt^{IV}(fm)]$ complexes (fm = 9-fluorenylidenemalonate). The coordination chemistry of platinum(II) compounds is subtly dependent upon the electronic and steric effects of ligands and coligands.[11, 12] Moreover, the oxidation of Pt^{II} to Pt^{IV} compounds has been utilized in various aspects of platinum chemistry, such as mixed-valence chain compounds, oral antitumor (pro)drugs, and reaction mechanisms.[13–16]



fm

Reaction of $[Pt^{II}(NO_3)_2(dpda)]$ (dpda = 2,2-dimethyl-1,3-propanediamine) with fm afforded $[Pt^{II}(fm)(dpda)]$ (**1**). The oxidative addition of **1** with a 30 % aqueous solution of H_2O_2 in methanol produced the mixed-axial hydroxo/methoxoplatinum(IV) complex *trans,cis,cis*-$[Pt^{IV}(OH)(OCH_3)(fm)(dpda)]$ (**2**) in 81.3 % yield. When ethanol was used as solvent instead of methanol, the oxidative addition gave an ethoxo analogue. The structure of **2** was confirmed by an X-ray crystallography[17] (Figure 1), and the relevant bond lengths and angles are not exceptional. The local geometry around the platinum atom approximates to a typical octahedral arrangement with the added hydroxo/methoxo ligands in *trans* coordination sites. The 9-fluorenylidene (flu) moiety is bent towards the methoxo group instead of the smaller hydroxo group, and snugly interacts with the methoxo group. The distances C22 ··· C9 (C22–H ··· C9) and O5 ··· C9 are 3.45 Å (2.75 Å) and 3. 47 Å, respectively, which are comparable to usual values for a C–H ··· π interaction.[4, 18] The substitution reaction of **2** with acetic anhydride gives *trans,cis,cis*-$[Pt^{IV}(OOCCH_3)(OCH_3)(fm)(dpda)]$ (**3**) in 80.3 % yield. The crystal structure analysis of **3** (Figure 1)[17] shows that the molecular configuration is retained during the reaction of **2** to **3**. Interestingly, in **3** the flu moiety is directed towards the $OOCCH_3$ group. Thus, the axial acetato group lies parallel to the flu moiety at distances usual for C(H) ··· π interactions (O6 ··· C9, 3.33 Å), indicating that the flu moiety prefers an acetato to a methoxo group.

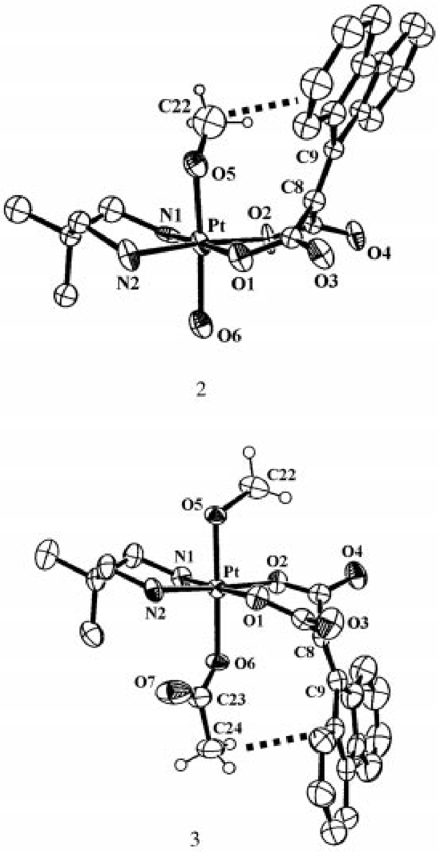


Figure 1. Crystal structures of **2** and **3**. The solvate molecules are omitted for clarity. The dashed line designates the flu-philic interaction.

The aliphatic region of ^1H NMR spectra of **1** and **3** in *N,N*-dimethylformamide are depicted in Figure 2. Resonances were assigned by $^1H/^{13}C$ COSY NMR spectroscopy (see Supporting information). The proton resonances of **1** exhibit a marked temperature dependence in the range −10–40 °C. The NH_2, NCH_2, and CH_3 groups each display a pair of resonances at −10 °C. Warming the sample results in broadening of the peaks; by 40 °C the pairs have coalesced to singlets at $\delta = 5.68$ (NH_2), 2.27 (NCH_2), and 0.91 (CH_3). The fluxional process indicates interconversion between the "bent-up" and "bent-down" positions of the flu moiety at elevated temperature ($T_c = 20\,^\circ C$; $\Delta G^{\neq} = 58.8\,kJ\,mol^{-1}$). In contrast, ^1H NMR spectra of **3** did not change significantly over the same temperature range except for the sharpness of the signals. This fact indicates that the flu conformation in **3** is rigid (in contrast to that in **1**) on the ^1H NMR time scale even in solution. In addition, the chemical shift of $OOCCH_3$ ($\delta = 0.99$) is apparently shielded relative to that ($\delta \approx 2.0$) usually observed for (acetato)platinum(IV) compounds.[19] The high-field shift is explained in terms of a π-shielding effect: in the

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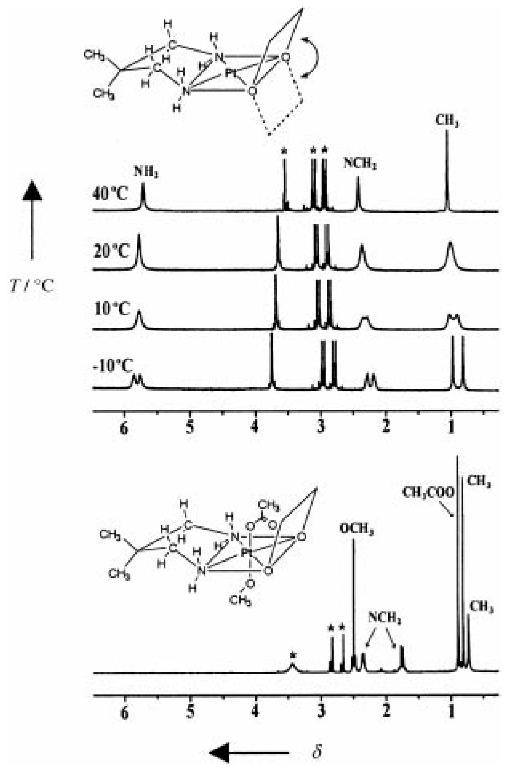


Figure 2. Variable-temperature ^1H NMR spectra of **1** (top) and ^1H NMR spectrum of **3** (bottom) (500 MHz, [D$_7$]DMF, TMS, aliphatic region). Asterisk indicates the solvent.

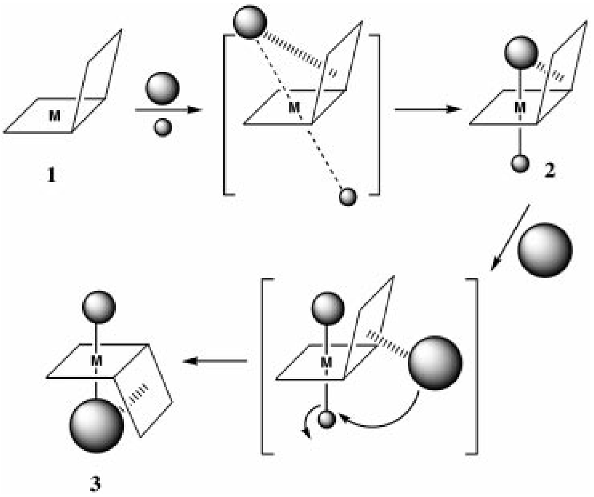
conformation depicted by the X-ray structure analysis, the acetato protons lie above the flu plane. The rigid structure of **3** may be attribued to both the flu interaction and the crowded coordination of the octahedral platinum(IV) compound. The behavior of **2** in solution is very similar to that of **3**, and the flu-axial interaction is not merely the result of crystal packing.

The electron-donor ability[10, 20] of the anionic fm ligand may contribute to a critical driving force for the conformational induction through the interaction with the flu moiety. Even though the fm ligand is an α,β-unsaturated carboxylato ligand, the bending conformation prevents delocalization of π electrons. Thus, the fm ligand is an effective electron-rich plane for π interactions. Evidence in support of the localization is found in the C8–C9 bond lengths (1.32(4) Å for **2** and 1.34(1) Å for **3**) which correspond to that (1.34 Å) of a normal ethylene group.[21] The angle between the platinum square and the flu plane is clearly dependent on the strength of the flu interaction, which in turn is dependent on the axial substituent X in the *trans,cis,cis*-[Pt^{IV}(X)(Y)(fm)(dpda)] compounds (Table 1). The plane angle suggests the pronounced order of flu-philicity decreases $OOCCH_3 > OCH_3 > OH$, that is, inversely proportional to the bulkiness of the axial ligand. For the oxidative addition of **1** to **2**, the OCH_3 group competes with the OH group for the flu interaction. The successive substitution of **2** to **3**, in which $OOCCH_3$ replaces OH, effectively induces the conversion of the flu conformation, resulting in the formation of $OOCCH_3\cdots$flu interactions (Scheme 1). We attribute the order of flu-philicity to the felicitous "shape-confluence" rather than the "acidic" character of the axial ligand.

Table 1. The plane angle between the platinum(IV) square and the flu plane in *trans,cis,cis*-[Pt^{IV}(X)(Y)(fm)(dpda)] compounds.

trans,cis,cis-[Pt^{IV}(X)(Y)(fm)(dpda)] compounds	Plane angle[a]
X = OH, Y = OH[b]	113.0(4)
X = OCH_3, Y = OH (**2**)	112.2(7)
X = OAc, Y = OCH_3 (**3**)	105.1(2)

[a] The plane angle between the platinum plane (Pt, O1, O2, N1, and N2) and the flu plane (C6, C7, C8, C9, C10, C11, C16, and C17). [b] The compound for comparison was prepared by the reaction of **1** with a 30% aqueous solution of H_2O_2 in acetone. Crystal data for *trans,cis,cis*-[Pt(IV)(OH)$_2$(fm)(dpda)] · 3 C_2H_5OH: $P2_1/a$, $a = 10.312(2)$, $b = 22.044(5)$, $c = 14.225(3)$ Å, $\beta = 110.25(2)°$, $V = 3034(1)$ Å^3, $R = 0.0572$.



Scheme 1. Procedures of oxidative addition and substitution in reactions to give **2** and **3**.

Although the example of flu-induced conformation described is probably unique to fm complexes, we believe it represents an important conceptual advance. It demonstrates that noncovalent interactions critically influence conformational structure. Our observation should allow us to employ the "noncovalent interaction assistance" concept as an effective strategy in the design and reaction of structural components. The flu–axial ligand interaction is the first noncovalent interaction existing in solution that has been demonstrated for noncage compounds.

Experimental Section

1: K_2(fm) · 2 H_2O (0.76 g, 2.0 mmol) in water (50 mL) was added to a suspension of [Pt^{II}(NO$_3$)$_2$(dpda)] · 2 H_2O (0.91 g, 2.0 mmol) in water (50 mL). The reaction mixture was stirred for 3 h, and the resulting yellow precipitate was washed with water. Recrystallization from a mixture of DMF and diethyl ether gave yellow crystals of **1** in 85.2% yield. M.p. 212 °C (decomp); ^1H NMR (500 MHz, [D$_7$]DMF, TMS): $\delta = 0.91$ (br, 6H). 2.27 (br, 4H), 5.68 (br, 4H), 7.26 (t, 2H, $J = 7.5$ Hz), 7.43 (t, 2H, $J = 7.7$ Hz), 7.92 (d, 2H, $J = 7.3$ Hz), 8.14 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125.76 MHz, [D$_7$]DMF, TMS): $\delta = 23.8$, 36.0, 53.6, 120.0, 125.9, 126.5 (C=C), 127.5, 128.8, 138.0, 140.1 (C=C), 140.5, 172.8 (C=O); IR (KBr): $\tilde{\nu} = 1648$, 1620 ($\nu(COO)_{asym}$); 1338 ($\nu(COO)_{sym}$) cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{22}N_2O_3Pt \cdot 2\,C_3H_7NO$: C 45.82, H 5.13, N 7.92; found: C 45.70, H 5.10, N 7.87.

2: A 30% aqueous solution of H_2O_2 (1 mL) was added to a solution of [Pt^{II}(fm)(dpda)] · 2 DMF (0.71 g, 1.0 mmol) in methanol (100 mL). The reaction mixture was stirred for 6 h. After the solid material had been filtered off, the filtrate was condensed to 5 mL, to which excess diethyl ether was added to obtain the solid product. Slow evaporation of the methanol solution gave crystals of **2** in 81.3 % yield. M.p. 147 °C (decomp). ^{1}H NMR (500 MHz, [D$_7$]DMF, TMS): $\delta = 0.95$ (s, 3H), 1.02 (s, 3H), 2.19 (br, 4H), 2.96 (s, 3H), 6.84–7.18 (m, 4H), 7.30 (t, 2H, $J = 7.3$ Hz), 7.45 (t, 2H, $J = 7.4$ Hz), 7.91 (d, 2H, $J = 7.5$ Hz), 8.19 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (125.76 MHz, [D$_7$]DMF, TMS): $\delta = 23.4$, 23.6, 35.7, 50.3, 55.8 (OCH$_3$), 120.1, 126.2, 127.8, 129.9, 132.8 (C=C), 136.0 (C=C), 137.0, 141.1, 170.9 (C=O); IR (KBr): $\tilde{\nu} = 1666$, 1652, 1634 (ν(COO)$_{\mathrm{asym}}$); 1324 (ν(COO)$_{\mathrm{sym}}$) cm^{-1}; elemental analysis (C, H, N) gave erratic results presumably due to the easy evaporation of solvate methanol molecules.

3: Compound **2** (1.0 mmol) was dissolved in acetic anhydride (20 mL), and the resulting solution was then stirred for 3 h. After the solid residue had been filtered off, the filtrate was evaporated to dryness. Slow evaporation of the DMF solution gave crystals of **3** in 80.3 % yield. M.p. 168 °C (decomp). ^{1}H NMR (500 MHz, [D$_7$]DMF, TMS): $\delta = 0.84$ (s, 3H), 0.92 (s, 3H), 0.99 (s, 3H), 1.77–1.93 (m, 2H), 2.39–2.52 (m, 2H), 2.58 (s, 3H, $^3J_{\mathrm{Pt,H}} = 27.10$ Hz), 7.16–7.38 (br, 2H), 7.25 (t, 2H, $J = 7.6$ Hz), 7.39 (t, 2H, $J = 7.6$ Hz), 7.84 (d, 2H, $J = 7.5$ Hz), 7.98–8.22 (br, 2H), 8.15 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (125.76 MHz, [D$_7$]DMF, TMS): $\delta = 22.2$, 23.0, 24.8 (OOC*CH$_3$*), 35.8, 50.2, 57.3 (OCH$_3$), 120.0, 126.5, 127.7, 129.9, 133.9 (C=C), 134.6 (C=C), 137.2, 141.2, 170.6 (C=O), 180.2 (C=O); IR (KBr): $\tilde{\nu} = 1666$, 1601 (ν(COO)$_{\mathrm{asym}}$); 1302 (ν(COO)$_{\mathrm{sym}}$) cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{28}N_2O_7Pt \cdot C_3H_7NO$: C 44.75, H 4.87, N 5.80; found: C 44.60, H 4.85, N 5.88.

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[17] Crystal data for **2**: $C_{22}H_{26}N_2O_6Pt \cdot 2CH_3OH$: monoclinic, $P2_1/n$, $a = 10.371(3)$, $b = 10.857(5)$, $c = 23.417(8)$ Å, $\beta = 100.71(3)°$, $V = 2591(2)$ Å^3, $\rho_{\mathrm{calcd}} = 1.727$ Mg m^{-3}, $F(000) = 1336$, $\lambda = 0.71073$ Å, $\mu = 5.465$ mm^{-1}, crystal size $0.15 \times 0.20 \times 0.30$ mm, $Z = 4$, $R(wR2) = 0.0787$ (0.1932) on 2313 unique reflections with $I > 2\sigma(I)$, GOF = 1.102, 316 parameters refined. Crystal data for **3**: $C_{24}H_{24}N_2O_7Pt \cdot C_3H_7NO$: triclinic, $P\bar{1}$, $a = 9.982(1)$, $b = 10.267(2)$, $c = 14.633(2)$ Å, $\alpha = 76.69(1)$, $\beta = 77.179(9)$, $\gamma = 76.411(1)°$, $V = 1396.1(3)$ Å^3, $\rho_{\mathrm{calcd}} = 1.724$ Mg m^{-3}, $F(000) = 720$, $\lambda = 0.71073$ Å, $\mu = 5.079$ mm^{-1}, crystal size $0.30 \times 0.45 \times 0.30$ mm, $Z = 2$, $R(wR2) = 0.0426$ (0.1040) on 4508 unique reflections with $I > 2\sigma(I)$, GOF = 1.109, 352 parameters refined. Programs used: SHELXS-97 and SHELXL-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163484 (**2**) and CCDC-163485 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Design, Synthesis, and Biological Evaluation of $\alpha_4\beta_1$ Integrin Antagonists Based on β-D-Mannose as Rigid Scaffold

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The tuning of protein–protein interactions by small nonpeptidic molecules remains one of the great challenges in medicinal chemistry. Although already proposed in 1980 by Farmer,[1] only a few successful examples on the synthesis of peptidomimetics based on rigid scaffolds such as cyclohexane and pyranose sugars have been reported so far.[2] Starting from the β-D-mannose scaffold we developed peptidomimetics in a rational combinatorial approach focusing on the interaction of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins with their ligands. The basis of this research were cyclic hexapeptides as potent and selective $\alpha_4\beta_7$ integrin antagonists recently developed by our group using the "spatial screening" procedure.[3]

$\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins play an important role in numerous inflammatory and autoimmune disorders.[4] The most important biological ligands for these α_4 integrins are fibronectin

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