Conformation Analysis

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CH–π and CF–π Interactions Lead to Structural Changes of N-Heterocyclic Carbene Palladium Complexes**

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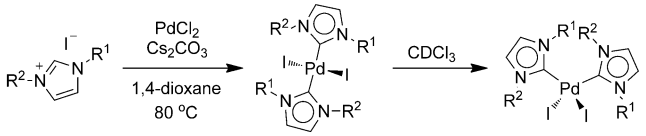
Abstract: *The role of CH–π and CF–π interactions in determining the structure of N-heterocyclic carbene (NHC) palladium complexes were studied using ^{1}H NMR spectroscopy, X-ray crystallography, and DFT calculations. The CH–π interactions led to the formation of the cis-anti isomers in 1-aryl-3-isopropylimidazol-2-ylidene-based [(NHC)$_2$PdX$_2$] complexes, while CF–π interactions led to the exclusive formation of the cis-syn isomer of diiodobis(3-isopropyl-1-pentafluorophenylimidazol-2-ylidene) palladium(II).*

The CH–π interaction, a type of weak hydrogen bonding, plays a significant role in determining or stabilizing structures of a vast variety of chemical and biological molecules.[1] For example, CH–π interactions serve as a driving force for crystal packing or as a stabilizing effect for a particular conformation of a molecule, even in solution. Intramolecular CH–π interactions can also induce optical activity of compounds.[2] In biology, CH–π hydrogen bonds play important roles in the folding mechanisms of proteins and DNA and also in the specific substrate recognition of proteins and enzymes.[3]

Understanding structure and bonding of organometallic complexes is of fundamental importance. Electronic effects such as the *trans* effect, steric effects of ligands, and properties of the metal center, are particularly important in regulating the structures of organometallic complexes.[4] Additionally, weak interactions could alter the conformation and geometry of a catalyst and would thereby exert significant effects on the catalytic activity and selectivity, as is the case with enzymes in nature. For the rational improvement of the catalytic performance of complexes, such structural control should be fully understood.

N-heterocyclic-carbene (NHC)-based palladium complexes have proven to be effective catalysts in many important reactions, especially in cross-coupling reactions.[5] The enhanced catalytic activity has been largely attributed to the electronic and steric properties of NHC ligands. Most well-defined [(NHC)$_2$PdX$_2$]-type complexes reportedly have the *trans* configuration, although *cis* complexes have been reported to show faster catalyst initiation because of their stronger *trans* effect.[6] Some *cis* complexes have been reported, including those with chelating NHC ligands.[7] In spite of the extensive research on catalyst development using NHCs, to the best of our knowledge, there has been no study designed to evaluate the structural effects of these weak interactions in NHC-based transition-metal complexes. Herein, we report the roles of CH–π and CF–π interactions in controlling the structure of [(NHC)$_2$PdX$_2$]-type complexes.

The synthesis of [(NHC)$_2$PdX$_2$]-type complexes, by heating $PdCl_2$, the NHC precursor **1a**, and Cs_2CO_3 in 1,4-dioxane at 80 °C, yielded only the *trans* isomer **2a** after 6 hours (Scheme 1). However, the *trans* isomer was converted into the *cis-anti* isomer **3a** slowly in $CDCl_3$ even at room temperature. The lower solubility of **3a** in $CDCl_3$ caused its crystallization from solution. The structure was readily confirmed by X-ray crystallography (Figure 1).[8] The methyl doublet peaks of the isopropyl group of **2a**, peaks which initially appeared at $\delta =$ 1.40 ppm in the ^{1}H NMR spectra, split into two separate methyl doublet peaks at $\delta = 0.54$ ppm and 1.40 ppm upon



1a–i **2a–g** **3a–g**

1a, 2a, 3a : R^1 = *i*Pr, R^2 = Ph
1b, 2b, 3b : R^1 = *i*Pr, R^2 = *i*Pr
1c, 2c, 3c : R^1 = *i*Pr, R^2 = 4-FC_6H_4
1d, 2d, 3d : R^1 = *i*Pr, R^2 = 4-$MeOC_6H_4$
1e, 2e, 3e : R^1 = *i*Pr, R^2 = C_6F_5
1f, 2f, 3f : R^1 = Ph, R^2 = Ph
1g, 2g, 3g : R^1 = Ph, R^2 = Et
1i, 2i : R^1 = *i*Pr, R^2 = 2,4,6-$Me_3C_6H_2$

Scheme 1. Synthesis of [(NHC)$_2$PdI$_2$] complexes.

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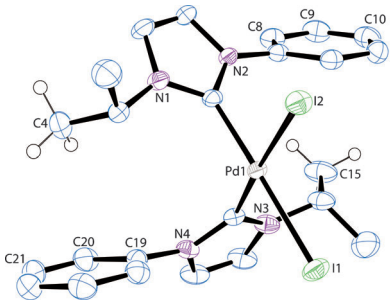

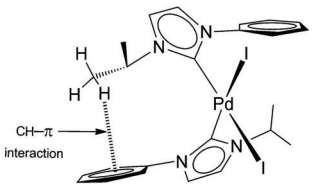

Figure 1. Molecular structure of **3a**.

conversion from **2a** into **3a**. The data suggested that the methyl groups in **3a** are no longer magnetically equivalent because one methyl group experiences a strong shielding effect.[9] With the help of X-ray crystallographic data, we assumed that the close proximity of one of the methyl groups to the isopropyl unit and the phenyl ring in **3a** led to this splitting. The electron density of the phenyl group shields the protons on this methyl group when the methyl group rests above the plane of the phenyl ring.

Nishio and co-workers have done database studies of CH–π interactions since 1970s.[9a,10] They devised a set of methods to prove the existence of CH–π interactions, as shown in Figure S2 in the Supporting Information. Following the Nishio method,[11] we measured the dihedral angles and distances d_a, d_p, d_l, β, and α from the crystal structure of **3a**. Both the dihedral angles and distances of **3a** (Table 1) were consistent with our conjecture. The data showed that C4H and C15H, belonging to the CH_3 of the *i*Pr group, were in *Ra* 1 of the C8,C9 and C19,C20 π-system planes (Figure 1). Thus, we concluded that there exist CH–π interactions between the C4H, C15H, and C19,20, C8,C9 phenyl planes in **3a**.

To further check the stability of the *cis* isomer, compound **2a** was heated in $CDCl_3$ at 55 °C for 12 days (see Figure S1). By monitoring the reaction with ^{1}H NMR spectroscopy, we observed that **2a** was fully converted into the *cis* isomer **3a** with a yield of 90% upon isolation. This result suggested that **3a** is thermodynamically more stable than **2a**. The compound **3a** was stable enough to be re-isolated without any sign of decomposition after being heated in the temperature range of 23–90 °C in various solvents. In contrast, **3b**, bearing only isopropyl groups, did not enjoy this increased stability when converted from **2b**. Unlike **3a**, the isolated **3b** was slowly converted back into **2b** when heated at 30 °C in [D_8]1,4-dioxane or $CDCl_3$. The system eventually reached an equilibrium with a *trans*/*cis* ratio of 3:7. Therefore, it is likely that CH–π interactions play a role in stabilizing the *cis* isomer **3a**.

The convincing proof of the existence of CH–π interactions within NHC-based palladium complexes prompted us to investigate the correlation between the electron density on the phenyl ring and the extent of stabilization caused by CH–π interaction. The compounds **2c**, **2d**, and **2e** were isomerized to form **3c**, **3d** and **3e**, respectively, at room temperature in $CDCl_3$.[8] From the dihedral angle and distance data (Table 1), it can be shown that CH–π interactions occurred in **3c** and **3d**. Notably, **3d** had d_p distances of 2.664 and 2.626 Å, whereas **3c** had d_p distances of 2.750 and 2.687 Å, thus suggesting that the electronic property of the π system influences the strength of the CH–π interaction.[10f,12] The electron-donating methoxy group increases the electron density on the phenyl ring in **3d**, thereby resulting in a stronger CH–π interaction than those brought about by the electron-withdrawing fluoro group in **3c**. We also replaced X ligands with bromides to see whether the CH–π interaction still exists. The initially synthesized *trans* isomer **2h** was successfully transformed into the *cis-anti* isomer **3h**, the CH–π interaction of which was observed in the X-ray crystal structure (Table 1).

An interesting result was achieved in the conversion of **2e** into **3e**. The strong electronegativity of fluorine gives rise to five $C^{\delta+}$–$F^{\delta-}$ bond dipoles in the phenyl ring of **3e**. This feature renders the center of the phenyl ring electropositive, as opposed to the electronegative phenyl ring in **3a**. The $C^{\delta-}$–$H^{\delta+}$ bond dipoles thus disfavor the interaction with the electron-deficient C_6F_5 π system in **3e**. In contrast, the $C^{\delta+}$–$F^{\delta-}$ bond dipoles favorably interact with the C_6F_5 center (see Figure S3).[13] This explains why **3e** adopts the *cis-syn* configuration rather than the *cis-anti* configuration (Figure 2). The compound **3e** had a d_p value of 2.691 Å, which is shorter than the values of 2.757/2.817 Å for **3a**. This CF–π interaction is further supported by ^{19}F NMR spectroscopic data. *Ortho* fluorine substituents, which participate in the CF–π interactions, experience a deshielding anisotropic effect because of the close proximity with an electropositive pentafluorophenyl ring, while *meta*

Table 1: Dihedral angles and distances for *cis*-[$(NHC)_2PdX_2$] complexes.[a]

	Complex	CH/π	d_a [Å]	d_p [Å]	d_l [Å]	β [°]	α [°]
cis-[$(NHC)_2PdI_2$]	**3a**: R^1 = *i*Pr,	CH[15c]/PlC[8,9]	2.812	2.757	2.787	30.36	81.29
	R^2 = Ph	CH[4c]/PlC[19,20]	2.861	2.817	2.845	33.60	81.67
	3c: R^1 = *i*Pr,	CH[18a]/PlC[8,9]	2.920	2.750	2.845	26.97	75.61
	R^2 = 4-FC_6H_4	CH[5a]/PlC[20,21]	2.827	2.687	2.757	23.54	76.99
	3d: R^1 = *i*Pr,	CH[13a]/PlC[20,21]	2.849	2.664	2.799	31.05	72.10
	R^2 = 4-$MeOC_6H_4$	CH[26a]/PlC[7,6]	2.911	2.626	2.829	42.78	68.19
	3e: R^1 = *i*Pr, R^2 = C_6F_5	CF[10]/PlC[8,9]	2.784	2.691	2.756	4.06	77.90
	3f: R^1 = Ph,	CH[15]/PlC[25,26]	2.714	2.613	2.651	22.52	80.34
	R^2 = Ph	CH[18]/PlC[2,3]	2.683	2.527	2.626	16.01	73.97
	3g: R^1 = Ph,	CH[13b]/PlC[8,9]	2.945	2.767	2.883	32.11	73.74
	R^2 = Et	CH[2b]/PlC[19,20]	2.472	2.939	2.694	29.70	71.77
cis-[$(NHC)_2PdBr_2$]	**3h**: R^1 = *i*Pr,	CH[24a]/PlC[7,8]	2.957	2.729	2.899	31.83	70.32
	R^2 = Ph	CH[12a]/PlC[17,18]	3.059	2.831	2.994	30.59	71.05

[a] α: dihedral angle between plane C^1OC^2 and plane HC^1C^2; β: $\measuredangle HC^xC^1$; d_p: distance of H/π plane (H/I); d_l: distance of H/line C^1-C^2 (H/J); d_a: distance of HC^1 (C^1 is the nearest carbon atom to H).

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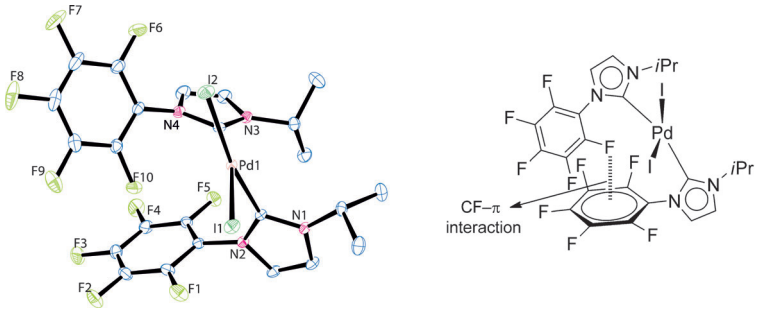

Figure 2. Molecular structure of **3e**.

and *para* fluorine substituents were more shielded in the *cis-syn* isomer **3e** than in the *trans-anti* isomer **2e**.

To make theoretical comparisons of CH–π and CF–π interactions, a series of density functional theory (DFT) calculations were performed on *cis-anti* (Conf-1) and *cis-syn* (Conf-2) geometries of **3a** and **3e** using Gaussian 09.[14] Geometry optimizations were performed with the B3LYP, BP86, M06-2X, and MPW1B95 functionals in conjunction with Lanl2TZ(f) for Pd, Lanl2DZdp for I, and 6-311 + G-(2d,p) for all other atoms.[15–19] The solvent effect of chloroform was taken into account by the IEFPCM method.[20] DFT calculations predicted that **3a** and **3e** prefer Conf-1 and Conf-2, respectively, in accordance with the X-ray structures (see Table S1). This result supports our hypothesis that the configurations of **3a** and **3e** are determined by CH–π and CF–π interactions, respectively. Of all the DFT functionals examined, the MPW1B95 data showed particularly good agreement with experimental geometry and stability (Figure 3 and Tables S1 and S2). In the B3LYP and BP86

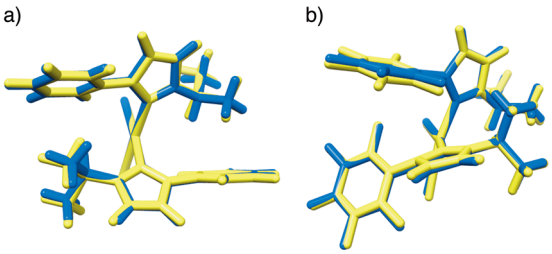

Figure 3. Superposition of the experimental (blue) and MPW1B95-optimized (yellow) geometries: (a) **3a**; (b) **3e**.

optimized geometries, the hydrogen atom of the isopropyl group was hardly within the *Ra* 1 region (see Figure S5), which should be attributable to the inadequate description of dispersion force with these functionals. It should be noted that all these functionals tended to overestimate the stability of the *trans* isomers (Tables S1–S4). This problem of DFT was previously observed for other analogous complexes.[21] Nevertheless, as far as evaluation of the energy gap between the two *cis* conformers is concerned, we believe that the DFT functionals perform reasonably well.

The existence of CH–π and CF–π interactions was further verified by theoretical NMR calculations. The NMR data in Table 2 clearly show that the methyl groups of isopropyl, which are involved in CH–π interaction, have much smaller chemical-shift values than the other methyl group. The two distinct chemical-shift values agreed reasonably well with the experimental values. Furthermore, our atoms-in-molecules (AIM) calculations using AIMALL software[22] yielded bond critical points corresponding to CH–π and CF–π interactions (see Figures S6 and S7).

Having appreciated how significantly CH–π and CF–π interactions could affect the configuration preference of the NHC complexes, we next

Table 2: Comparison of theoretical and experimental chemical-shift values for **3a**.

	δ H_a [ppm][a]	δ H_b [ppm][b]
B3LYP	0.62	1.40
BP86	0.58	1.48
M06-2X	0.21	1.44
MPW1B95	0.18	1.48
experimental	0.54	1.40

[a] Average chemical-shift value for all H_a atoms in the methyl group that is involved in CH–π interaction. [b] Average chemical-shift value for all H_b atoms in the methyl group that is not involved in CH–π interaction.

turned our attention to bulkier and more rigid systems. The compound **3f**, which bears two phenyl groups on each NHC, was found to adopt a twisted shape (Figure 4). Notably, a CH–π interaction occurs between the C_{sp^2}–H of the phenyl ring on the NHC and the π system from the phenyl group on the other NHC. The compound **3f** has d_p values of 2.613 and

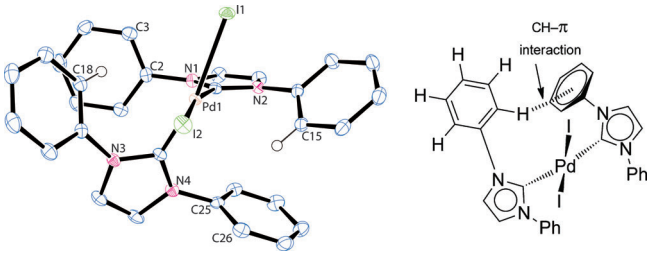

Figure 4. Molecular structure of **3f**.

2.527 Å, which are shorter than those of **3a**, 2.757 and 2.817 Å. It has been reported that the CH–π interaction is stronger when the acidity of the hydrogen atom is greater.[23] The C–H bond that is involved in the CH–π interaction in **3f** is more acidic, because the carbon center is sp^2 hybridized, as compared to the C_{sp^3}–H bond in **3a**. Interestingly, the binding modes of both aryl–aryl interactions in **3f** were in between edge-to-face and face-to-face aryl–aryl interactions with the dihedral angles of 51.9° and 54.6°. In the case of the CF–π-interaction-driven aryl–aryl interactions in **3e**, these interactions were closer to an edge-to-face mode with the dihedral angle of 70.3°.

Another interesting result was obtained when **3g** was synthesized from **2g**. It was expected that the terminal methyl group in the ethyl substituent would point towards the

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aromatic ring, similar to the case of **3a**, because of the CH–π interaction between the C–H group and the phenyl ring. However, the methyl group pointed away in the opposite direction. Analysis of our ^{1}H NMR and X-ray crystallographic data showed that a CH–π interaction occurred between C2H and C19,C20 of the aromatic ring and C13H and C8,C9 of the aromatic ring, instead of C3H and C14H (CH_3) (Figure 5). The H atoms on the CH_2 group are more acidic as they are bonded to a carbon atom which is directly connected to the nitrogen atom of NHC and thus will interact more favorably with the phenyl ring.

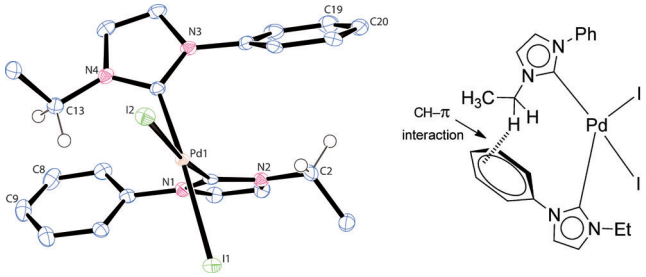

Figure 5. Molecular structure of **3g**.

When the bulkier **1i** was used as a ligand, **2i** was isolated in a mixture of *trans-syn* and *trans-anti* isomers without conversion into the *cis* configuration. This means that the *trans* to *cis* configurational change could be dampened with relatively bulky ligands. Despite the increased steric strain experienced in this conformation, the *trans-syn* isomer was the major isomer (5:1 = *trans-syn*/*trans-anti*). This outcome surprised us because sterically relieved *trans-anti* configurations have been exclusively observed and isolated in the cases of the *trans*-[$(NHC)_2PdX_2$] complexes **2a**, **2c–e**, and **2g**,**h**.[24] Analysis of the ^{1}H NMR spectrum and crystal structure of the *trans-syn* product showed that very weak CH–π interactions might occur between the *ortho* methyl hydrogen atoms of the mesityl group with the other mesityl ring in the *trans-syn* product (Figure 6).

In summary, we investigated the roles of CH–π interactions and CF–π interactions in determining the structure of N-heterocyclic-carbene-based palladium complexes using ^{1}H NMR spectroscopy, X-ray crystallography, and DFT calculations. These weak interactions were found to drive the formation of the *cis-anti* or *cis-syn* isomer of [$(NHC)_2PdX_2$] depending on the type of weak interaction provided by substituent groups of the NHC. Further investigations on the effect of the weak interactions on catalysis are currently ongoing to fully comprehend the roles of weak forces in catalysis with the ultimate goal of developing highly efficient and selective enzymelike transition-metal catalysts which exploit such weak interactions.

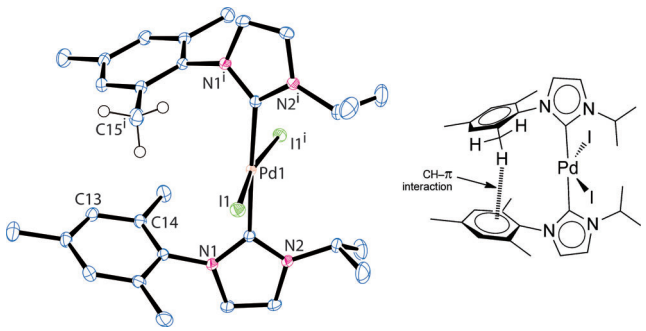

Figure 6. Molecular Structure of **2i**.

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[8] CCDC 753452 (**2a**), CCDC 955845, 955846, 955847, 955848, 955849, 955850, and 955851 (**2b–h**), CCDC 964913 (**2i**) and CCDC 955852, 955853, 955854, 955855, 955856, 955857, 955858, and 955859 (**3a–h**) contain the supplementary crystallographic

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data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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