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Indole Rings in Palladium(II) Complexes. Dual Mode of Metal Binding and Aromatic Ring Stacking Causing syn–anti Isomerism

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In view of the interesting metal-binding properties of lichen substances and the indole ring as a potential ligand, we studied the Pd(II) complexes of indole-containing ligands, *N*-(indole-3-ethyl)-$\Delta^{2,11}$-enaminousnic acid (IEU) and 4-[2-(indol-3-yl)-ethylamino]pent-3-en-2-one (IEP) obtained by condensation of tryptamine with usnic acid and its model acetylacetone, respectively. Reactions of Pd(II) with IEU and IEP gave isomeric complexes resulting from coordination of the C(3) atom of the indole ring in the 3*H*-indole form, $Pd_2(IEUH_{-2})_2$ (**1** and **2**) and $Pd_2(IEPH_{-2})_2$ (**3** and **4**) ($IEUH_{-2}$ and $IEPH_{-2}$ denote doubly deprotonated forms of IEU and IEP, respectively). Complexes **1**–**4** were determined, from the NMR and MS spectra, to have dimeric structures doubly bridged by the indole rings, which were stacked in different orientations. X-ray crystal structure analysis of **3** and **4** established that they are indole-bridged dimers of the [C,N,O]-donor palladacycles with the Pd(II) centers in a square-planar geometry formed by a CN_2O donor set and are anti and syn isomers with respect to the bridging indole rings, respectively. On the basis of the spectral similarity with **4**, **1** and **2** were concluded to be stereoisomers assuming the syn form with the same donor set. The results demonstrate the metal binding and stacking abilities of the indole ring and the stereoisomerism from the sp^3 C(3) atom formed upon coordination.

Introduction

Tryptophan (Trp) is an essential amino acid with the highest hydrophobicity among the amino acids from protein sources.[1] The indole ring of Trp is known to undergo noncovalent interactions such as aromatic−aromatic stacking interactions and cation−π interactions.[2] It is often found near catalytic or substrate-recognition sites, forming a hydrophobic environment. For example, the active site of wild-type *Trypansoma vivax* nucleoside hydrolase with a bound competitive inhibitor, 3-deaza-adenosine, was shown to have the inhibitor sandwiched between the aromatic side chains of Trp83 and Trp260, and the face-to-face stacking was inferred to promote the protonation of nucleobases, providing an explanation for the catalytic role of Trp260.[3] Aromatic ring stacking in ternary copper(II) complexes with an aromatic amino acid and an aromatic ligand such as 1,10-phenanthroline (phen) stabilizes the complexes relative to those without stacking, Trp exhibiting the largest stability enhancement because of the indole ring, compared with the aromatic ring of phenylalanine and tyrosine.[4,5] Attention has recently been focused on the reactivities of the indole ring in biological systems. It is known to give the indole π-cation radical in the catalytic cycle of cytochrome *c* peroxidase,[6] and recent studies on cellular prion proteins revealed that, as a result of Cu(II) binding by the octapeptide repeat region, the Trp residue of the octapeptide is located close to the Cu(II) center and is involved in the reduction of Cu(II) to Cu(I).[7−9]

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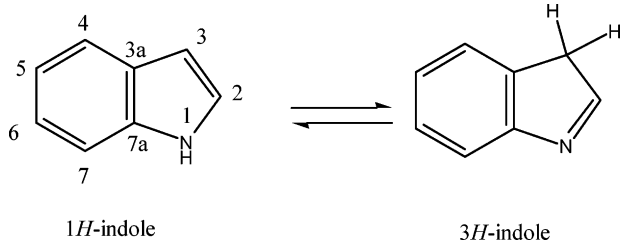

Figure 1. Structures of the tautomeric forms of indole.

In addition to the weak interactions and redox activities, the indole ring has further interesting properties. Although it is not known to coordinate to a metal ion in biological systems, it has been shown to have a versatile metal binding ability in chemical systems. Indole derivatives can bind with a metal ion both at the nitrogen and carbon atoms. We reported earlier that Pd(II) binds with the imine nitrogen of the indole ring in the tautomeric 3*H*-indole form (Figure 1),[10] where the NH proton is bound to the C(3) atom to convert it to an sp^3 carbon, and that Pd(II) reacts with indole-3-acetate to form a dimeric structure having a unique *spiro*-ring as a result of the binding at the carboxylate oxygen atom and cyclopalladation at the C(3) atom of the 3*H*-indole ring.[11] A pendent indole ring in a Cu(I) complex of a 3N-donor ligand was found to bind with Cu(I) at the C(2)−C(3) moiety through η^2-bonding,[12] and in the Pd(II) complexes of 2N1O-donor ligands it replaced the coordinated phenolate oxygen to be bound at the C(2) atom by cyclopalladation when their solutions were refluxed.[13] Metal binding at the C(2), C(3), or C(4) positions by cyclometalation with Pd(II) and Pt(II) have been reported for various systems,[14−19] and Kostić et al. developed Pd(II) and Pt(II) complexes functioning as artificial peptidases, which bind with the indole ring of Trp residues by cyclometalation and cleave the adjacent peptide bond.[20−22] These observations indicate that an indole ring attached to the side chain of ligands may provide metal binding and other reaction sites under suitable conditions

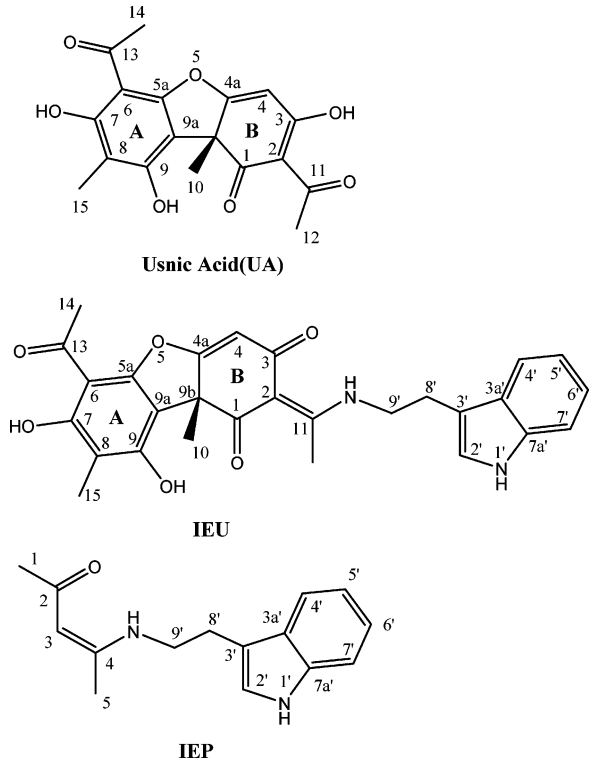

Figure 2. Structures of *d*-usnic acid, IEU, and IEP.

and at the same time serve as an excellent partner of aromatic−aromatic interactions. To explore these possibilities, we selected 2,4-pentanedione (acetylacetone) and a natural β-diketone-like ligand usnic acid (UA) (Figure 2), which is one of the most common lichen substances and is widely known for its antibiotic,[23,24] antiviral,[25] and other activities,[26−30] as ligands. UA which is an optically active compound with an asymmetric carbon (C(9b)) has been used as a biomonitor of the environment together with the other lichen substances,[31−36] and from our previous synthetic and

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structural studies on the Pd(II) and Cu(II) complexes,[37] a UA derivative with an indole ring in its side chain is expected to exhibit interesting metal binding abilities.

With these points in mind, we synthesized *N*-(1*H*-indole-3-ethyl)-$\Delta^{2,11}$-enaminousnic acid (IEU) and its model 4-[2-(1*H*-indol-3-yl)ethylamino]-pent-3-en-2-one (IEP) as ligands (Figure 2) by condensation of tryptamine with UA and acetylacetone, respectively, and isolated the isomers of the Pd(II) complexes, $Pd_2(IEUH_{-2})_2$ and $Pd_2(IEPH_{-2})_2$ ($IEUH_{-2}$ and $IEPH_{-2}$ denote doubly deprotonated forms of IEU and IEP, respectively), which have been characterized by spectroscopic and X-ray diffraction methods. We present here the metal binding and stacking properties of the indole ring in the UA analogues and its function as a structure-determining factor.

Experimental Section

Materials and Spectroscopic Measurements. Disodium tetrachloropalladate(II), *d*-usnic acid (UA), tryptamine, potassium *tert*-butoxide (*t*-BuOK), and 2,4-pentanedione were purchased from Kanto Chemicals, Wako Chemicals, Merck, Nacalai Tesque, and Sigma-Aldrich Chemicals, respectively. All UV−vis spectra were recorded on a Hitachi U-3010 spectrophotometer, and infrared (IR) spectra were measured on a Shimadzu FTIR-8400 spectrophotometer in a KBr disk. Nuclear magnetic resonance (NMR) spectra were obtained with JEOL JNM-EX-270 and JNM-GSX-500 NMR spectrometers with tetramethylsilane (TMS) as an internal reference. ^{1}H and ^{13}C spectra were assigned by two-dimensional correlation spectroscopy (^{1}H−^{1}H and ^{1}H−^{13}C COSY). Circular dichroism (CD) spectra were measured with a JASCO J-820 spectropolarimeter. Unless otherwise noted, $CHCl_3$ and $CDCl_3$ were used as solvents for the spectroscopic measurements. Mass spectra (MS) were measured on JEOL JMS-AX5 and JMS-SX102A mass spectrometers. TLC and column chromatography were carried out on Merck F_{254} and Merck 70−230 mesh silica gels, respectively.

***N*-(Indole-3-ethyl)-$\Delta^{2,11}$-enaminousnic Acid (IEU).** A solution of tryptamine (2.32 g, 14.5 mmol) and *d*-usnic acid (4.94 g, 14.5 mmol) in absolute ethanol (100 mL) was refluxed for 50 min. The precipitate was filtered and recrystallized from benzene−methanol to give IEU as yellow needles (6.52 g, 92.5%). mp: 230 °C. Anal. Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.02; H, 5.46; N, 5.61. MS: *m*/*z* (relative intensity) 486 (M^+, 80), 471 (8), 260 (50), 232 (11), 227 (100), 217 (16), 144 (26), 130 (19). IR (KBr disk) ν (cm^{-1}): 1695 (C(1)═O), 1624 (C(13)═O), 1553 (ketoenamine system). ^{1}H NMR ($CDCl_3$): δ 1.67 (s, 9b-Me), 2.10 (s, 8-Me), 2.67 (s, 6-Ac), 5.76 (s, 4-H), 11.94 (s, 9-OH), 13.36 (s, 7-OH; br, 9′-NH).^{13}C NMR: δ 174.0 (4a−C), 155.9 (5a−C), 101.4 (6-C), 163.5 (7-C), 107.9 (8-C), 158.3 (9-C), 102.4 (9a-C), 57.0 (9b-C), 32.0 (10-C), 31.3 (14-C), 7.5 (15-C), 118.2 (4′-C), 119.7 (5′-C), 122.4 (6′-C), 111.6 (7′-C).

4-[2-(Indol-3-yl)-ethylamino]pent-3-en-2-one (IEP). A solution of tryptamine (3.20 g, 20.0 mmol) and acetylacetone (2.00 g, 20.0 mmol) in absolute ethanol (50 mL) was refluxed for 1.5 h. The precipitate was recrystallized from ethanol to give IEP as white needles (4.36 g, 90.0%). mp: 124 °C. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.32; H, 7.79; N, 11.54. MS: *m*/*z* (relative intensity) 242 (M^+, 13), 144 (19), 143 (100), 131 (16), 130 (71), 113 (15), 112 (96), 98 (15), 94 (10), 77 (11), 43 (17). IR (KBr disk) ν (cm^{-1}): 1605 (C(2)═O), 1555 (ketoenamine system).

Pd(II)−IEU Complexes, $Pd_2(IEUH_{-2})_2$ (1 and 2). Na_2PdCl_4 (118 mg, 0.400 mol) was added to a solution of IEU (584 mg, 1.20 mmol) and *t*-BuOK (91 mg, 0.80 mmol) in dimethyl sulfoxide (3 mL), and the mixture was stirred for 11 h at room temperature. The reaction mixture was poured into water, and the precipitate was column chromatographed on silica gel with benzene−ethyl acetate (3:1), when 356 mg of IEU was recovered. The fraction with R_f = 0.90 (TLC, benzene−ethyl acetate (3:1)) was column chromatographed repeatedly on silica gel with benzene−*n*-hexane−ethyl acetate (2:2:1) to afford Pd−IEU complexes **1** and **2** (recrystallized from chloroform−ethanol) with the same composition $Pd_2(IEUH_{-2})_2$ ($IEUH_{-2}$ = doubly deprotonated form of IEU). Complex **1**: orange prisms (46 mg, 19% based on Na_2PdCl_4 used), R_f = 0.47 (TLC, benzene−*n*-hexane−ethyl acetate (2:2:1)). Anal. Calcd for $C_{56}H_{48}N_4O_{12}Pd_2 \cdot 0.5H_2O$: C, 56.48; H, 4.15; N, 4.70. Found: C, 56.43; H, 4.07; N, 4.47. MS: *m*/*z* (relative intensity) 1182 (0.5), 1181 (0.5), 1180 (0.5), etc. IR (KBr disk) ν (cm^{-1}): 1701 (C(1)═O), 1624 (C(13)═O), 1545 (ketoenamine system). ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 9b-Me), 2.11 (s, 8-Me), 2.60 (s, 6-Ac), 5.78 (s, 4-H), 11.98 (s, 9-OH), 13.34 (s, 7-OH). ^{13}C NMR: δ 173.6 (4a−C), 156.4 (5a−C), 101.5 (6-C), 163.6 (7-C), 108.0 (8-C), 158.4 (9-C), 109.1 (9a−C), 57.6 (9b-C), 30.8 (10-C), 31.2 (14-C), 7.5 (15-C), 120.2 (4′-C), 123.3 (5′-C), 125.1 (6′-C), 118.2 (7′-C). Complex **2**: orange prisms (14 mg, 5.9%), R_f = 0.34 (TLC, benzene−*n*-hexane−ethyl acetate (2:2:1)). Anal. Calcd for $C_{56}H_{48}N_4O_{12}Pd_2 \cdot H_2O$: C, 56.06; H, 4.20; N, 4.67. Found: C, 55.96; H, 4.03; N, 4.49. MS: *m*/*z* (relative intensity) 1186 (1.2), 1185 (2.1), 1184 (2.3), 1183 (3.0), 1182 (3.1), 1181 (3.0), etc. IR (KBr disk) ν (cm^{-1}): 1699 (C(1)═O), 1628 (C(13)═O), 1545 (ketoenamine system). ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 9b-Me), 2.12 (s, 8-Me), 2.61 (s, 6-Ac), 5.79 (s, 4-H), 12.27 (s, 9-OH), 13.35 (s, 7-OH). ^{13}C NMR: δ 174.2 (4a-C), 156.2 (5a-C), 101.4 (6-C), 163.5 (7-C), 108.0 (8-C), 158.5 (9-C), 109.1 (9a-C), 57.4 (9b-C), 32.3 (10-C), 31.2 (14-C), 7.5 (15-C), 120.5 (4′-C), 123.4 (5′-C), 125.2 (6′-C), 118.2 (7′-C).

Pd(II)−IEP Complexes, $Pd_2(IEPH_{-2})_2$ (3 and 4). Na_2PdCl_4 (118 mg 0.400 mmol) was added to a solution of IEP (291 mg, 1.20 mmol) and *t*-BuOK (91 mg, 0.80 mmol) in dimethyl sulfoxide (3 mL), and the mixture was stirred for 12 h at room temperature. The reaction mixture was column chromatographed on silica gel with benzene−acetone (30:1) to yield Pd−IEP complexes **3** and **4**. Complex **3**: red prisms recrystallized from chloroform−methanol (31 mg, 23%), R_f = 0.50 (TLC, benzene-acetone (30:1)). Anal. Calcd for $C_{30}H_{32}N_4O_2Pd_2 \cdot 0.5H_2O$: C, 51.29; H, 4.74; N, 7.98. Found: C, 51.52; H, 4.60; N, 8.00. MS: *m*/*z* (relative intensity) 695 (1.1), 694 (1.3), 693 (1.3), 692 (1.2), 691 (1.1), etc. IR (KBr disk) ν (cm^{-1}): 1580, 1508. Complex **4**: red plates recrystallized from chloroform−methanol (59 mg, 43%), R_f = 0.28 (TLC, benzene-acetone (30:1)). Anal. Calcd for $C_{30}H_{32}N_4O_2Pd_2 \cdot 0.5H_2O$: C, 51.29; H, 4.74; N, 7.98. Found: C, 51.47; H, 4.74; N, 8.02. MS: *m*/*z* (relative intensity) 696 (3.3), 695 (4.1), 694 (4.6), 693 (4.6), 692 (3.9), 691 (3.4), etc. IR (KBr disk) ν (cm^{-1}): 1578, 1508.

X-ray Crystal Structure Analysis. The X-ray measurements were carried out on a Rigaku Saturn CCD area detector with graphite-monochromated Mo Kα radiation (λ = 0.71070 Å). The crystals were mounted in loops. To determine the cell constants and orientation matrix, 6 oscillation photographs were taken for each frame with the oscillation angle of 0.5° and an exposure time of 3 s. Intensity data were collected at −100 ± 1 °C by taking 720 oscillation photographs using ω scans from −110.0 to 70.0° in 0.5° step at χ = 45.0° and ϕ = 0.0 and 90.0°. Refraction data were

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Table 1. Crystallographic Data for Pd(II) Complexes

	3	**4**
formula	$C_{30}H_{32}N_4O_2Pd_2 \cdot CHCl_3$	$C_{30}H_{32}N_4O_2Pd_2$
fw	812.79	693.40
cryst color, habit	orange, plate	orange, block
cryst dimensions (mm)	$0.19 \times 0.05 \times 0.01$	$0.19 \times 0.12 \times 0.10$
cryst syst	triclinic	triclinic
lattice params		
a (Å)	11.449(2)	8.502(2)
b (Å)	11.755(2)	11.609(2)
c (Å)	12.184(2)	15.377(3)
α (deg)	77.928(5)	69.250(9)
β (deg)	76.406(5)	74.329(9)
γ (deg)	83.020(6)	70.879(9)
V (Å^3)	1554.2(4)	1320.3(4)
space group	$P\bar{1}$	$P\bar{1}$
Z	2	2
D_{calcd} (g/cm^3)	1.737	1.744
F(000)	812	696
μ(Mo Kα) (cm^{-1})	14.514	13.990
$2\theta_{max}$ (deg)	55.0	55.0
range of transm factors	0.617−0.748	0.841−0.869
observed reflns	6839	5772
measured reflns	2697	2268
no. variables	412	376
GOF	0.936	1.044
reflns/params ratio	16.60	15.35
Final R indices $[I > 2\sigma(I)]$[a]	R1 = 0.0415	R1 = 0.0390
R indices (all data)[b]	R = 0.0618 wR2 = 0.0640	R = 0.0700 wR2 = 0.0780

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$ for $I > 2\sigma(I)$. [b] $R = \sum||F_o| - |F_c||/\sum|F_o|$, $wR2 = \{\sum(w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{1/2}$; $w = 1/\sigma^2(F_o^2) = 1/\sigma^2(F_o)/(4 \cdot F_o^2)$.

corrected for Lorentz and polarization effects. Crystal data and experimental details of the data collection for all the complexes are shown in Table 1. The structures were solved by the direct method and expanded by Fourier techniques using the DIRDIF-99 program.[38] The non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculations on F^2. Atomic scattering factors and anomalous dispersion terms were taken from the literature.[39] Hydrogen atoms for all the structures were assigned a fixed displacement with d(C−H) = 0.95 Å and refined using the riding model. All the calculations were performed by using Crystal Structure software package.[40]

Results and Discussion

Synthesis of IEU and IEP. The ligands IEU and IEP used in this work (Figure 2) were prepared by condensation of tryptamine with UA and acetylacetone, respectively. UA has potentially reactive groups such as the β-triketone moiety (C(1) carbonyl, C(2)-acetyl, and C(3) carbonyl groups) and C(6)-acetyl group, which are capable of imine formation with tryptamine. When UA was treated with primary amines as methylamine and benzylamine, it gave *N*-substituted $\Delta^{2,11}$-enaminousnic acids.[37,41] The mass spectrometric fragmentation in the usnic acid series proved invariable as a structural basis in this investigation. The benzofuranylketene (*m*/*z* 260.071) and fragment *m*/*z* 227.119 $[M - 260 + H]^+$ are the characteristic fragment ions resulting from a retro Diels−Alder reaction of ring B (Scheme 1). The data clearly indicate that the reaction of tryptamine with usnic acid took place at the C(1) or C(11) carbonyl group of ring B rather than at the aromatic methyl ketone of ring A. Table 2 shows that the characteristic ^{1}H NMR signal for the enolic hydroxyl group of ring B is absent in IEU and that the signals for the indole protons are observed at 7.1−7.6 ppm. The ^{13}C NMR spectral data (Table 3) reveal that the C(11) signal is shifted upfield by 27.0 ppm relative to that of UA, indicating the change from the C(11) carbonyl carbon of UA to the imine carbon of IEU. From these data, we conclude that IEU has the structure shown in Figure 2. On the other hand, IEP may be regarded as a simplified model of IEU, which bears the structural feature of the B ring moiety of IEU and is thus expected to show similar metal-binding properties.

Synthesis and Spectroscopic Characterization of Palladium(II) Complexes. (a) $Pd_2(IEUH_{-2})_2$ (1 and 2). The reaction of IEU with Na_2PdCl_4 gave two isomeric Pd(II) complexes, **1** and **2**, with the same formula $Pd_2(IEUH_{-2})_2$. Complex **1** has a marked similarity to **2** in the ^{1}H and ^{13}C NMR spectra (Tables 2 and 3) and IR spectra, suggesting that their metal binding sites are the same. The ^{1}H NMR data in Table 2 show that the C(8)-CH_3 signal is not shifted (i.e., the complex shift $\Delta\delta = \delta_{complex} - \delta_{ligand} \leq 0.02$ ppm) and that the C(7)- and C(9)-OH signals are present. In contrast, the NH proton signal of the B ring side chain is absent, and the ^{13}C NMR signals for the C(3) and C(11) atoms (Table 3) are significantly shifted upfield ($\Delta\delta = -5.3$ to -7.2 ppm), which indicates that Pd(II) is bound at the β-ketoenamine moiety through the C(2) substituent and the C(1) or C(3) oxygen atom. On the basis of the structures established for the Pd(II) complexes of UA derivatives,[37] we conclude that Pd(II) is bound to the enamine nitrogen atom and the C(3) carbonyl oxygen atom. Interestingly, the ^{1}H NMR spectra of **1** and **2** showed no NH signal expected for the indole ring observed at 8.16 ppm for IEU. We reported earlier that the indole ring coordinates to Pd(II) through the nitrogen atom, the C(3′) atom in the 3*H*-indole form (Figure 1),[10,11] or both, exhibiting a ^{1}H NMR signal of the C(3′) moiety,[10] which is absent in the spectra of **1** and **2**. The absence of the C(3′)-H signal together with the NH signal in the ^{1}H NMR spectra (Table 2) indicates that deprotonation occurred from the indole ring to form the Pd(II)−indole bond.[10,11,20] The ^{13}C NMR spectra of the Pd(II) complexes have some characteristic signals as shown in Table 3, from which we see that C(3′) is an sp^3 carbon exhibiting a signal at a higher field (δ = 71.9 and 72.1 ppm for **1** and **2**, respectively) and that C(2′) (δ = 165.4 and 164.8 ppm for **1** and **2**, respectively) is more like an imine carbon[10,11,41,42] rather than an aromatic carbon.[43,44] This substantiates that Pd(II) binds with the indole nitrogen and C(3′) atoms, and

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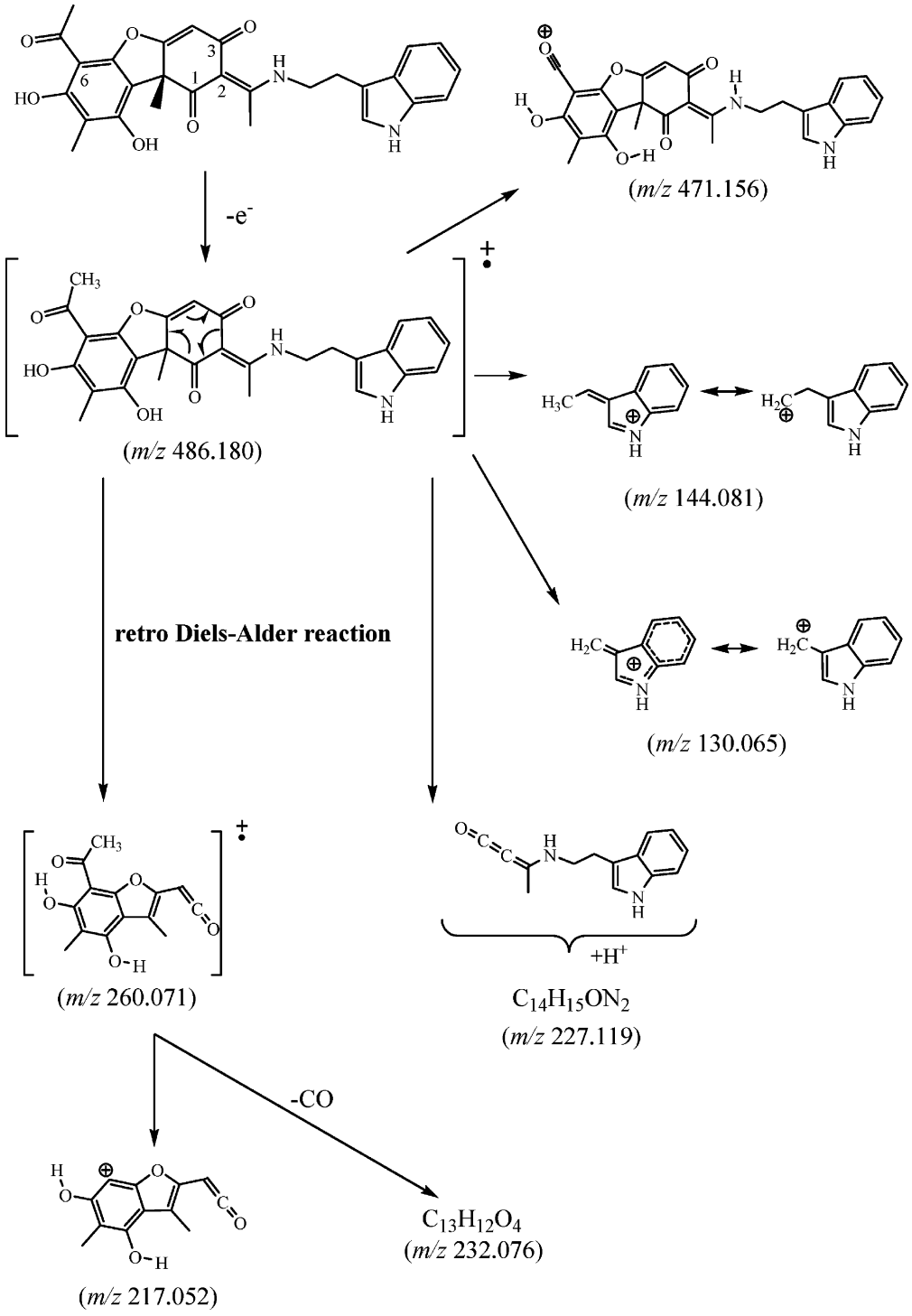
Scheme 1. Fragmentations of IEU in MS Spectra



from the MS spectra with the main feature of Pd(II) complexes at *m*/*z* 1181, corresponding to the pseudo-molecular ion of $[Pd_2(IEUH_{-2})_2 + H]^+$, the Pd(II) complexes are concluded to have a dimeric structure bridged by the imine nitrogen of the 3*H*-indole ring, which is in accordance with our previous observation.[11]

From the above considerations, the coordination site for each Pd(II) in the dimeric unit is occupied by the enamine nitrogen, the deprotonated C(3′) carbon of the indole ring, the C(3) carbonyl oxygen,[37] and the indole nitrogen (N(1′)) of the other complex unit in a square-planar geometry. Interestingly, the indole protons exhibit characteristic complex shifts; the C(2′) protons are shifted downfield ($\Delta\delta$ = 0.96 and 1.03 ppm for **1** and **2**, respectively), and the C(5′)−C(7′) protons are shifted upfield ($\Delta\delta$ = −0.15 to −0.66 ppm). These results most probably reflect the stacking interaction between the benzene moieties of the bridging indole rings, the C(2′) proton being out of the stacked rings.

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Table 2. ^{1}H NMR Spectral Data for UA, IEU, **1**, and **2** in $CDCl_3$ (ppm)[a]

	UA	IEU	**1**	**2**
3-OH	18.85 s			
11-Me	2.67 s	2.52 s	2.52 s	2.58 s
1′-NH		8.16 s	deprotonated	deprotonated
2′-H		7.19 d	8.15 s	8.22 s
4′-H		7.58 d	7.69 d	7.68 d
5′-H		7.15 t	7.00 t	6.99 t
6′-H		7.23 t	6.70 t	6.70 t
7′-H		7.40 d	6.76 d	6.74 d
8′-CH_2		3.20 t	2.06 m	2.08 m
9′-CH_2		3.81 q	4.25 m	4.22 m
9′-NH		13.36 br	deprotonated	deprotonated

[a] The rest of the data except those for UA are shown in the Experimental Section.

Table 3. ^{13}C NMR Spectral Data for UA, IEU, **1**, and **2** in $CDCl_3$ (ppm)[a]

	UA	IEU	**1**	**2**
1-C	198.1	198.2	200.1	198.1
2-C	105.2	105.1	105.2	105.2
3-C	191.7	190.2	183.0	184.7
4-C	98.3	102.2	101.3	101.0
11-C	201.8	174.8	168.6	169.5
12-C	27.9	18.4	21.8	22.4
13-C	200.3	200.7	200.6	200.6
2′-C		123.0	165.4	164.8
3′-C		111.0	71.9	72.1
3a′-C		126.7	140.5	140.4
7a′-C		136.5	148.6	148.6
8′-C		25.1	30.9	31.0
9′-C		44.6	62.9	62.5

[a] The rest of the data except those for UA are shown in the Experimental Section.

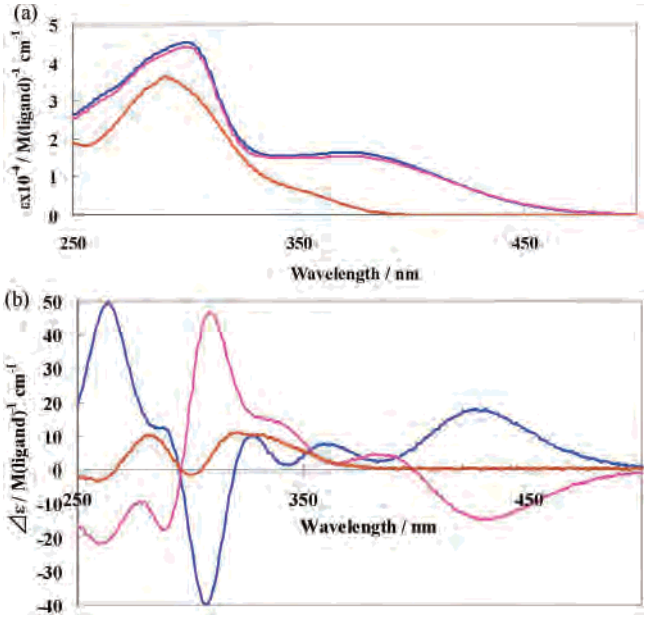

Figure 3. UV (a) and CD (b) spectra of IEU (orange), **1** (blue), and **2** (pink).

Complexes **1** and **2** exhibited essentially the same absorption spectra, but remarkable differences have been observed for the CD spectra (Figure 3 and Table 4). The peaks with opposite signs were observed at around 427−432 nm ($\Delta\epsilon$ = +18.1 and −14.8 for **1** and **2**, respectively) and 307−309 nm ($\Delta\epsilon$ = −39.9 and +46.6 for **1** and **2**, respectively). The nearly symmetrical CD spectra with opposite signs in the d−d region are mainly due to the vicinal effect of the asymmetric carbon (C(9b)) of the UA moiety. The CD spectra and the very similar NMR and absorption spectra indicate that **1** and **2** are stereoisomers resulting from the sp^3 carbon at the C(3′) position by stacking of the bridging indole rings.

Table 4. Absorption and CD Spectral Data of **1** and **2** in $CHCl_3$

	absorption		CD	
	λ_{max} (nm)	ϵ (M(ligand)$^-$ cm^{-1})	λ_{ext} (nm)	$\Delta\epsilon$ (M(ligand)$^{-1}$ cm^{-1})
1	239	29300	264	49.3
	300	45300	307	−39.9
	372	16400	329	10.1
			343	1.5
			359	7.8
			382	2.8
			427	18.1
2	238	28500	260	−22.0
	301	44200	277	−9.6
	372	15400	289	−17.9
			309	46.6
			365	1.6
			382	4.8
			432	−14.8

Table 5. ^{1}H NMR Spectral Data for IEP, **3**, and **4** in $CDCl_3$ (ppm)

	IEP	**3**	**4**
1-Me	1.99 s	2.10 s	2.10 s
5-Me	1.83 s	1.91 s	1.92 s
3-CH	4.93 s	4.97 s	4.98 s
1′-NH	8.27 br	deprotonated	deprotonated
2′-H	7.14 d	6.58 s	8.18 s
4′-H	7.57 d	7.65 d	7.55 d
5′-H	7.12 t	7.23 t	6.90 t
6′-H	7.19 t	7.36 t	6.60 t
7′-H	7.36 d	8.49 d	6.83 d
8′-CH_2	3.05 t	2.14 m	2.05 m
9′-CH_2	3.55 t,d	4.04 m	4.03 m
4-NH	10.89 br	deprotonated	deprotonated

(b) [Pd_2(IEPH_{-2})$_2$] (3 and 4). IEP, which has the essential metal-binding groups of IEU, is expected to form a Pd(II) complex with the same coordination structure. By the reaction of IEP and Na_2PdCl_4, two isomeric Pd(II) complexes **3** and **4** with the same formula, [Pd_2(IEPH_{-2})$_2$], were obtained as crystals. The MS spectra revealed that **3** and **4** gave the same pseudo-molecular ion at *m*/*z* 693 corresponding to [Pd_2(IEPH_{-2})$_2$+H]$^+$ (IEPH_{-2} = doubly deprotonated form of IEP), which corresponds well with the observation with **1** and **2**, showing that **3** and **4** also have similar dimeric structures. The ^{1}H and ^{13}C NMR spectra (Tables 5 and 6) correspond well with those of **1** and **2** except for the signals from the aromatic protons. From the complex shifts, $\Delta\delta$, and in analogy with **1** and **2**, we conclude that the Pd(II) ions in **3** and **4** are in a square-planar geometry formed by the deprotonated enamine nitrogen, the C(3′) carbon, the C(2) carbonyl oxygen, and the nitrogen from the neighboring indole ring.

Interestingly, an upfield shift ($\Delta\delta$ = −0.56 ppm) was observed for the C(2′) proton of **3** upon complex formation. This is attributed to the ring current effect of the nearby aromatic ring, indicating that the C(2′) proton of **3** is located close to the other indole ring because of aromatic ring stacking. A large downfield shift ($\Delta\delta$ = 1.13 ppm) of the

Table 6. ^{13}C NMR Spectral Data for IEP, **3**, and **4** in $CDCl_3$ (ppm)

	IEP	**3**	**4**
1-Me	28.6	21.4	21.4
2-C	194.6	175.8	176.4
3-CH	95.2	99.1	99.1
4-C	163.2	163.0	162.7
5-Me	18.9	25.5	25.5
2′-CH	122.9	163.8	168.2
3′-C	111.7	72.3	71.8
3a′-C	126.9	138.3	140.8
4′-CH	118.2	121.5	119.8
5′-CH	119.2	123.9	122.5
6′-CH	121.8	123.8	123.7
7′-CH	111.4	121.2	118.4
7a′-C	136.5	152.0	149.0
8′-CH_2	26.0	32.3	31.7
9′-CH_2	43.5	60.7	61.8

C(7′) proton of **3** suggests that the proton is deshielded in the close proximity of Pd(II) because of the rigid dimeric structure. The indole C(5′), C(6′), and C(7′) proton signals of **4** (Table 5) were shifted upfield relative to IEP ($\Delta\delta$ = −0.22, −0.59, and −0.53 ppm, respectively) while the C(2′) signal was shifted downfield ($\Delta\delta$ = 1.04 ppm), which coincides well with the spectral behavior of the IEU complexes **1** and **2**. The results indicate that the indole rings of **4** are stacked with each other in a manner different from that in **3**, and the large differences in the shifts suggest that the indole rings in **3** undergo off-set stacking. The upfield shifts for **4**, following the order C(7′)-H, C(6′)-H > C(5′)-H > C(4′)-H, are considered to reflect the distances from the center of the other indole ring, C(6′)-H and C(7′)-H being closest. Formation of the isomers **3** and **4** is the result of the stereochemistry of the C(3′) atom of the bridging indole rings in the dimeric structure.

Molecular Structures of 3 and 4. The structures of the Pd(II) complexes **3** (with one $CHCl_3$ molecule of crystallization) and **4** were determined by the X-ray diffraction method and are shown in Figures 4 and 5, respectively, the selected bond lengths and angles being summarized in Table 7. Both complexes have a dimeric structure doubly bridged by the indole rings, where each Pd(II) ion coordinates an oxygen, an enamine nitrogen, an indole carbon (C(3′)), and a 3*H*-indole nitrogen to form a square-planar coordination structure. The Pd−N distances for **3** and **4** are 1.989−2.048

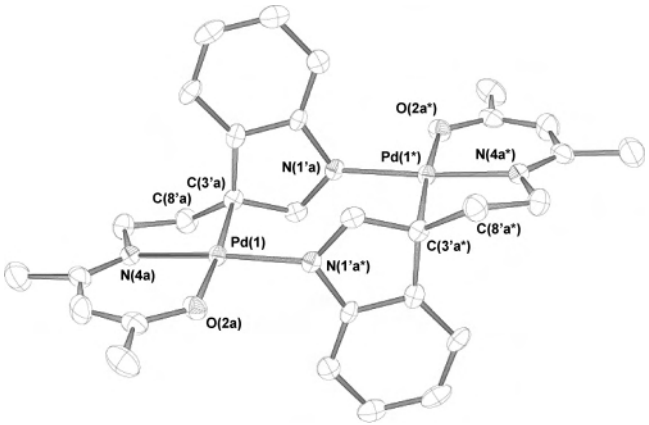

Figure 4. ORTEP view of $[Pd_2(IEPH_{-2})_2]$ (anti form) (**3**) drawn with the thermal ellipsoids at the 50% probability level, showing atomic labeling scheme.

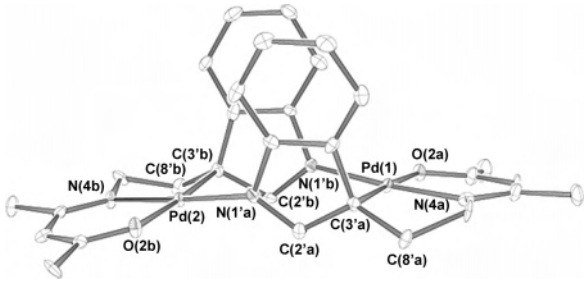

Figure 5. ORTEP view of $[Pd_2(IEPH_{-2})_2]$ (syn form) (**4**) drawn with the thermal ellipsoids at the 50% probability level, showing atomic labeling scheme.

Table 7. Selected Bond Lengths (Å) and Angles (deg) for **3** and **4**

		complex **3**	
Pd(1)−O(2a)	2.044(3)	Pd(1)−N(1′a*)	2.048(3)
Pd(1)−N(4a)	1.989(3)	Pd(1)−C(3′a)	2.133(4)
Pd(2)−O(2b)	2.038(3)	Pd(2)−N(1′b*)	2.047(3)
Pd(2)−N(4b)	2.001(3)	Pd(2)−C(3′b)	2.122(4)
C(2′a)−C(3′a)	1.448(5)	C(2′b)−C(3′b)	1.426(7)
C(3′a)−C(3a′a)	1.459(7)	C(3′b)−C(3a′b)	1.475(6)
O(2a)−Pd(1)−N(1′a*)	87.86(13)	O(2a)−Pd(1)−N(4a)	94.15(14)
O(2a)−Pd(1)−C(3′a)	176.11(13)	N(1′a*)−Pd(1)−N(4a)	174.85(18)
N(1′a*)−Pd(1)−C(3′a)	95.37(15)	N(4a)−Pd(1)−C(3′a)	82.81(16)
Pd(1)−C(3′a)−C(2′a)	100.6(2)	Pd(1)−C(3′a)−C(3a′a)	104.3(3)
Pd(1)−C(3′a)−C(8′a)	102.3(2)	C(2′a)−C(3′a)−C(3a′a)	104.3(3)
C(2′a)−C(3′a)−C(8′a)	118.6(4)	C(3a′a)−C(3′a)−C(8a′a)	123.3(3)
		complex **4**	
Pd(1)−O(2a)	2.029(3)	Pd(1)−N(1′b)	2.050(5)
Pd(1)−N(4a)	2.007(5)	Pd(1)−C(3′a)	2.143(4)
Pd(2)−O(2b)	2.044(3)	Pd(2)−N(1′a)	2.044(5)
Pd(2)−N(4b)	2.001(5)	Pd(2)−C(3′b)	2.157(4)
C(2′a)−C(3′a)	1.437(8)	C(2′b)−C(3′b)	1.443(8)
C(3′a)−C(3a′a)	1.492(6)	C(3′b)−C(3a′b)	1.485(6)
O(2a)−Pd(1)−N(1′b)	85.43(16)	O(2a)−Pd(1)−N(4a)	94.30(17)
O(2a)−Pd(1)−C(3′a)	176.88(19)	N(1′b)−Pd(1)−N(4a)	175.51(13)
N(1′b)−Pd(1)−C(3′a)	97.3(2)	N(4a)−Pd(1)−C(3′a)	83.1(2)
Pd(1)−C(3′a)−C(2′a)	97.2(3)	Pd(1)−C(3′a)−C(3a′a)	103.8(2)
Pd(1)−C(3′a)−C(8′a)	103.7(3)	C(2′a)−C(3′a)−C(3a′a)	102.0(4)
C(2′a)−C(3′a)−C(8′a)	122.7(3)	C(3a′a)−C(3′a)−C(8′a)	122.9(4)

Å and are comparable with those of the Pd(II)−indole[11] and Pd(II)−enaminousnic acid complexes[37] (Table 7). The Pd−C distances (2.122−2.157 Å) are close to the values observed for the Pd(II)−indole-3-acetate complex having the same coordination mode.[11] The bond lengths and angles involving the C(3′) atom suggest that this atom may have an intermediate character between the sp^2 and sp^3 carbons along the line of the $\sigma-\pi$ continuum.[45] The electrons in the β-ketoenamine moiety forming the chelate ring is considered to be more or less delocalized (see Supporting Information).

The coordination structures are exactly the same as those expected from the spectral data, and the molecular structures reveal the structural details of the coordinating indole rings. The unique double bridge between the Pd(II) centers is formed by the indole rings, each of which is coordinated to two Pd(II) ions through the N(1′) and C(3′) atoms with deprotonation as a result of cyclopalladation. This mode of coordination has been detected for the Pd(II) complex of indole-3-acetate[11] and therefore may be regarded as a

(45) Reed, C. A.; Kim, K.-C.; Stoyanov, E. S.; Stasko, D.; Tham, F. S.; Mueller, L. J.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2003**, *125*, 1796−1804.

common binding mode for indole derivatives with a metal-binding side chain at the C(3′) atom. This atom is at the center of the *spiro*-ring, composed of an indole and a chelate ring; while the two C(3′) atoms in **4** have the same chirality, they are enantiomeric in **3**, so that complexes **3** and **4** have a C_i and a pseudo-C_2 symmetry, respectively. Another interesting feature of the double bridge is the indole−indole stacking interaction. Different orientations of the stacked indole rings, giving rise to the anti and syn isomers, have been revealed for **3** and **4**, respectively, the former being in a meso form and centrosymmetric and the latter in an active form. In the crystal structure of **4**, however, there are the same number of enantiomers of the active form, so that complex **4** as isolated is optically inactive. As seen from Figure 4, only the five-membered pyrrole rings are involved in the stacking in **3**, and the C(2′) proton of one pyrrole moiety is located close above the other with a C(2′)−N(1′a or 1′a*) distance of 2.757(6) Å. In complex **4** (Figure 5), on the other hand, the two indole rings are juxtaposed to be in stacking interaction with a C(2′)−N(1′a or 1′a*) distance of 2.821(6) Å. The structural difference between **3** and **4** is in line with the conclusion from the ^{1}H NMR spectra (Table 5), which show a large upfield shift of the C(2′) proton and a downfield shift of the C(7′) proton for **3** and a large downfield shift of the C(2′) proton and upfield shifts of C(5′), C(6′), and C(7′) protons for **4**.

Structures of 1 and 2. The $\Delta\delta$ values showing upfield shifts for C(5′)-H−C(7′)-H in **1** and **2** (−0.15 to −0.66 ppm) and the large downfield shifts for C(2′)-H (ca. 1 ppm) (Table 2) are very similar to those observed for **4**, indicating that the indole rings in **1** and **2** are stacked with each other in the syn form in the way shown in Figure 5**.** The tetrahedral C(3′) atom of the indole moiety of **1** and **2** becomes a new chiral center as a result of coordination, in addition to the asymmetric C(9b) atom, and would result in three structural isomers, **A**, **B**, and **C** (Figure 6), but we could isolate only two of them as **1** and **2**, the spectral properties of which are very similar except the CD spectra, indicating that they are diastereomers **A** and **B**. Complex **C**, which has the same bridging mode as revealed for the anti isomer **3**, was not isolated as crystals. However, a scrutiny of the ^{1}H NMR spectrum of the reaction mixture revealed signals at 6.63 and 6.62 ppm and at 8.48 and 8.39 ppm, which correspond well with the characteristic signals of 2′-H and 7′-H of **3** (Table 5), respectively, and therefore strongly support the formation of complex **C**. The presence of two similar species may be attributed to the two diastereomeric ligands in **C** which is a meso complex. If we assume that the reaction between IEU and Pd(II) takes place statistically, the amount of the meso complex **C** should be equal to the sum of **1** and **2**, but actually the species showing the above signals was estimated to be ca. 22% of the total amount of **1** and **2** from the NMR signal intensity. These results suggest that the stacking between the indole rings favors the formation of **1** and **2** over **C**.

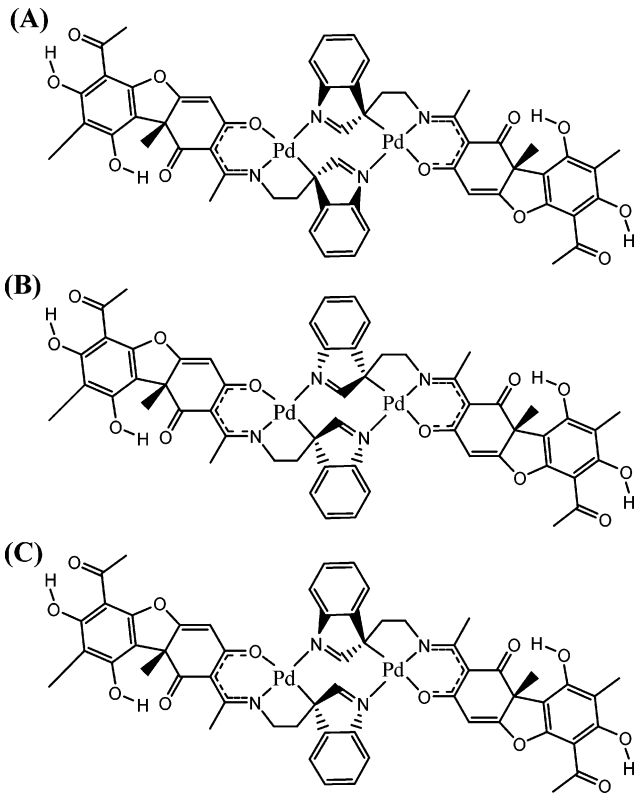

Figure 6. Structures of three possible isomers of $[Pd_2(IEUH_{-2})_2]$.

Concluding Remarks

We studied the Pd(II) complexes of the ligands incorporating the metal-binding groups of a lichen substance UA and an indole ring with a potential metal-binding ability. Reactions of Pd(II) with IEU, which is a condensation product of tryptamine with UA, and IEP, containing the essential coordinating groups of IEU, gave dimeric complexes in two isomeric forms, $[Pd_2(IEUH_{-2})_2]$ (**1** and **2**) and $[Pd_2(IEPH_{-2})_2]$ (**3** and **4**), respectively. The ^{1}H and ^{13}C NMR and MS spectra indicated that both ligands coordinate to Pd(II) through the amine nitrogen and the carbonyl oxygen and the C(3′) atom of the pendent indole ring by cyclopalladation. The indole nitrogen in the 3*H*-indole form then coordinates to the Pd(II) ion of a neighboring complex molecule to form a bridge, giving the dimeric complexes. Since the NMR spectra of **1** and **2** agree well with those of **4** (Tables 2 and 5), we conclude that **1** and **2** have essentially the same coordination structure as that revealed for **4**. The upfield shifts of the indole C(5′), C(6′), and C(7′) protons observed for **1**, **2**, and **4** are most probably induced by the ring current effect of the other indole ring because of stacking in the syn form. The X-ray crystal structure analyses of **3** and **4** revealed their molecular structures, according to which **4** (syn form) exhibits intramolecular stacking interactions between the bridging indole rings, while **3** (anti form) has only a limited interaction. The structures are in agreement with those determined from the ^{1}H NMR spectra and further substantiate the structures of **1** and **2**, which are diastereomers described as **A** and **B** in Figure 6. A small amount of the third diastereomer was detected in the reaction mixture and was

assigned structure **C** (Figure 6) from the ^{1}H NMR spectrum which exhibited signals very similar to those of **3**.

Coordination of the indole ring of IEU and IEP may affect its stacking interactions; metal binding at C(3′) and N(1′) should have an electron-withdrawing effect,[46,47] and the decrease in the electron density may weaken the electrostatic repulsion between aromatic rings and hence enhance the aromatic−aromatic interaction, although the effect of such repulsion may be small because the two indole rings are only partly stacked or tilted. Preferred formation and isolation of **1** and **2** having the stacked indole rings may reflect the effect of stacking.

The present study has established the metal-binding properties of the indole ring and suggests that the $\pi-\pi$ stacking interaction can be a complex-stabilizing factor in the formation of certain diastereomers. Cyclometalated compounds, palladacycles, have recently attracted wide attention because of their potential importance in organic and organometallic syntheses and homogeneous catalysis, and attempts to prepare Pd(II) complexes of CNO-donor ligands have been intensively made.[48] Metal−indole complexes have not been detected in biological systems yet, but they may be interesting possibilities in both chemical and biological reactions.

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Supporting Information Available: X-ray crystallographic data (CIF) for complexes **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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