Articles

Spectroscopic, Kinetic, and Mechanistic Study of a New Mode of Coordination of Indole Derivatives to Platinum(II) and Palladium(II) Ions in Complexes

Natalia V. Kaminskaia,[†] G. Matthias Ullmann,[‡] D. Bruce Fulton,[§] and Nenad M. Kostić*,[||]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, Department of Chemistry, Iowa State University, Ames, Iowa 50011, Department of Chemistry and Molecular Biology and Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California 92037, and NMR Facility, Department of Biochemistry, Biophysics, and Molecular Biology, Iowa State University, Ames, Iowa 50011

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Binding of tryptophan residue to intrinsic metal ions in proteins is unknown, and very little is known about the coordinating abilities of indole. Indole-3-acetamide displaces the solvent ligands from *cis*-$[Pt(en)(sol)_2]^{2+}$, in which sol is acetone or H_2O, in acetone solution and forms the complex *cis*-[Pt(en)(indole-3-acetamide)]$^{2+}$ (**3**) of spiro structure, in which the new bidentate ligand coordinates to the Pt(II) atom via the C(3) atom of the indolyl group and the amide oxygen atom. This structure is supported by ^{1}H, ^{13}C, ^{15}N, and ^{195}Pt NMR spectra and by UV, IR, and mass spectra. Molecular mechanical simulations by Hyperchem and CHARMM methods give consistent structural models; the latter is optimized by density-functional quantum chemical calculations. Dipeptide-like molecules *N*-(3-indolylacetyl)-L-amino acid in which amino acid is alanine, leucine, isoleucine, valine, aspartic acid, or phenylalanine also displace the solvent ligands in acetone solution and form complexes *cis*-[Pt(en) *N*-(3-indolylacetyl)-L-amino acid)]$^{2+}$ (**6**), which structurally resemble **3** but exist as two diastereomers, detected by ^{1}H NMR spectroscopy. The bulkier the amino acid moiety, the slower the coordination of these dipeptide-like ligands to the Pt(II) atom. The indolyl group does not coordinate as a unidentate ligand; a second donor atom is necessary for bidentate coordination of this atom and the indolyl C(3) atom. The solvent-displacement reaction is of first and zeroth orders with respect to indole-3-acetamide and *cis*-$[Pt(en)(sol)_2]^{2+}$, respectively. A mechanism consisting of initial unidentate coordination of the ligand via the amide oxygen atom followed by closing of the spiro ring is supported by ^{1}H NMR data, the kinetic effects of acid and water, and the activation parameters for the displacement reaction. In the case of *N*-(3-indolylacetyl)-L-phenylalanine, the bulkiest of the entering ligands, the reaction is of first order with respect to both reactants. The bidentate indole-3-acetamide ligand in **3** is readily displaced by $(CH_3)_2SO$ and 2-methylimidazole, but not by CNO^-, CH_3COO^-, and CH_3CN. Complexes *cis*-$[Pd(en)(sol)_2]^{2+}$ and *cis*-$[Pd(dtco)(sol)_2]^{2+}$ react with indole-3-acetamide more rapidly than their Pt(II) analogues do and yield complexes similar to **3**. This study augments our recent discovery of selective, hydrolytic cleavage of tryptophan-containing peptides by Pd(II) and Pt(II) complexes.

Introduction

Because of its unique properties, tryptophan plays important roles in proteins and in experiments by which they are studied.[1−3] As the most hydrophobic amino acid, tryptophan is often found at or near catalytic active sites and sites for molecular recognition.[4] Luminescence makes tryptophan a useful fluorophore, a reporter of dynamic processes in proteins.[1]

All of these interesting and useful properties are consequences of the aromaticity of the 3-indolyl group in the side chain, designated **1**. This group sometimes forms stacks with side chains of tyrosine and phenylalanine, and there are claims of the indolyl group's involvement in efficient electron-tunneling paths in electron carriers and redox enzymes.[5,6] The aromatic system, of course, reacts with oxidants and electrophiles, and some of these reactions are useful in chemical modification and cross-linking of proteins. In substitution reactions, electrophiles initially attack at the C(3) atom and usually then migrate to the C(2) atom.[1]

[†] Department of Chemistry, Massachusetts Institute of Technology.
[‡] Department of Chemistry and Molecular Biology and Skaggs Institute for Chemical Biology, The Scripps Research Institute.
[§] Department of Biochemistry, Biophysics, and Molecular Biology, Iowa State University.
[||] Department of Chemistry, Iowa State University.

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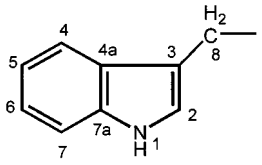


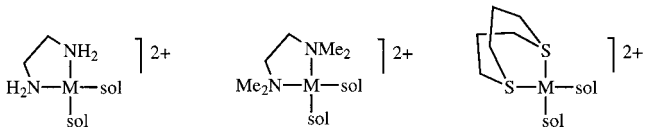
1

Several amino acids contain nucleophilic side chains that coordinate to transition-metal ions. These ions may be intrinsic parts of the proteins and may be required for the protein's structure or function. Recently, transition-metal complexes attached to protein surfaces have become useful as agents for cleavage of proteins.[7−17] In particular, attachment of suitable palladium(II) and platinum(II) complexes to the side chains of methionine and histidine in peptides and proteins can cause selective, hydrolytic cleavage of proximate amide bonds.[8−17] Very recently, we discovered that these complexes (Chart 1), when attached to tryptophan residues, can rapidly cleave peptides.[18] This discovery raised the question of the coordinating abilities of the indolyl group as investigated in the present study.

The pair of electrons on the nitrogen atom in indole is an integral part of the π-electron system and is not readily available for binding to metal ions.[19] The N(1)H group is very weakly acidic (pK_a is 16.82) and can be deprotonated only by strong bases.[20] Alkali metals and Grignard reagents can form ionic metal−nitrogen bonds.[21,22] Methylmercury can displace the hydrogen atom from nitrogen under mild conditions in aqueous ethanol as the solvent.[23] The kinetics and mechanism of this reaction have not been studied.

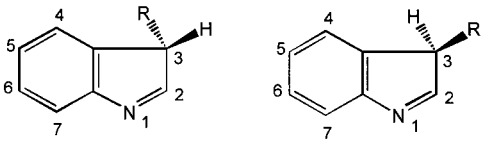
Transition-metal ions, such as copper(II), readily form familiar chelates with amino and carboxylate groups of tryptophan.[24,25] The indole tautomer in which a hydrogen has moved from the nitrogen to C(3) is named 3*H*-indolenine or simply indolenine. Its 3-substituted derivatives exist in two enantiomeric forms (*R* and *S*), shown in **2**. Palladium(II) complexes of ligands **2** coordinated via the nitrogen atom have been characterized by

Chart 1. Structures of the Complexes



M = Pt or Pd sol = H_2O or acetone

X-ray crystallography and spectroscopic methods.[26] Binuclear dimeric complexes between palladium(II) and indole-3-acetate involve cyclopalladation.[27] Bidentate coordination to palladium(II) through the N(1) and the C(2) atoms occurs in binuclear complexes.[28] Hydrogen migration from N(1) to C(3) creates a double bond between N(1) and C(2), as shown in **2**.



2

We present here a spectroscopic, kinetic, and mechanistic study of a reversible coordination of various indole derivatives to platinum(II) and palladium(II) and the formation of new complexes **3** and **6**. Our findings show that indole, as a part of tryptophan, can serve as an anchor for platinum(II) and palladium(II) binding to peptides and proteins. Such labeling by transition-metal complexes is important because it makes possible selective cleavage of amide bonds and opens new possibilities for the study of protein structure and function by methods of inorganic chemistry.

Experimental Procedures

Chemicals. The deuterium-containing compounds D_2O and $DClO_4$ and the salts $K_2[PdCl_4]$, $PdCl_2$, and $AgClO_4 \cdot H_2O$ were obtained from Sigma Chemical Co. and Aldrich Chemical Co. Indole-3-acetamide, indole-3-acetic acid, indole-3-propionic acid, indole-3-acetic acid ethyl ester, tryptophol, 3-indolemethanol, *N*-acetyl-5-hydroxy-tryptamine, *N*-(3-indolylacetyl)-L-phenylalanine, *N*-(3-indolylacetyl)-L-isoleucine, *N*-(3-indolylacetyl)-L-alanine, *N*-(3-indolylacetyl)-L-valine, *N*-(3-indolylacetyl)-DL-aspartic acid, *N*-(3-indolylacetyl)-L-leucine, and *N*-(3-indolylacetyl)-glycine were obtained from Sigma and Aldrich. The complexes *cis*-[Pd(Me_4en)Cl_2], [Pt(bpy)Cl_2], and *cis*-[Pt(en)Cl_2] were obtained from Aldrich. Anhydrous $AgBF_4$, $Ag(CF_3SO_3)$, and $AgClO_4$ (caution, strong oxidant!) were obtained from Aldrich. The ligands ethane-1,2-diamine (en), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Me_4-en), and 1,5-dithiacyclooctane (dtco) were obtained from Aldrich. Acetone-d_6, methanol-d_4, and dimethylformamide-d_7 were obtained from Cambridge Isotope Laboratories. These and all other chemicals were of reagent grade.

Palladium(II) and Platinum(II) Complexes. The palladium(II) complexes *cis*-[Pd(en)Cl_2], *cis*-[Pd(dtco)Cl_2], and [Pd(dien)I]I were prepared by the published procedures.[29−31] The chloro and iodo ligands were displaced by the solvent ligands (sol) in solutions of these complexes and of purchased dichloro complexes and 2 equiv of $AgBF_4$, $Ag(CF_3SO_3)$, $AgClO_4$, or $AgClO_4 \cdot H_2O$ in acetone-d_6. The solutions were stirred in the dark at 25 °C for 1 and 8 h for palladium(II) and

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platinum(II) complexes, respectively. The precipitates of AgCl and AgI were filtered off in the dark, and a fresh solution of the complex was used in further experiments. The coordinated solvent (sol) is acetone-d_6 or H_2O. The salts *cis*-$[Pd(en)(sol)_2](ClO_4)_2$ and *cis*-$[Pt(en)(sol)_2](ClO_4)_2$ had absorption maxima at 360 and 327 nm, respectively, as reported before.[29] The complex *trans*-$[Pd(PhCN)_2Cl_2]$ was prepared by the published procedure.[32]

One-Dimensional Proton, Carbon-13, and Nitrogen-15 NMR Spectra. These spectra were recorded with Varian VXR-300, Bruker DRX-400, Bruker DRX-500, and AC-200 spectrometers. The chemical shifts (δ) in the proton and carbon-13 spectra are given in ppm downfield from the methyl resonance of the solvent, which was acetone-d_6. The chemical shifts in nitrogen-15 spectra are given in ppm downfield and upfield from the resonance (at 0.00 ppm) of the external standard, which was a saturated solution of $^{15}NH_4NO_3$ in D_2O. The internal reference in ^{1}H NMR kinetic experiments was tetramethylsilane. The quality of the ^{13}C and ^{15}N spectra was improved by their acquisition in narrow windows. Usually 3000−20000 scans were taken. Carbon-13 spectra were recorded with and without proton decoupling. In quantitative experiments, in which accurate relative intensities were needed, decoupling was not used, and 0.050 M $[Cr(acac)_3]$ was added, to shorten T_1. The proton and carbon-13 resonances were integrated with estimated errors of ±5 and ±10%, respectively. Concentrations of the compounds were determined on the basis of these integrals and the known initial concentrations of reagents. Rates and rate constants were calculated from the known concentrations of the reactants and products, with estimated errors of 10−20%.

Platinum-195 NMR Spectra. These spectra were recorded with an AC-200 spectrometer at 43 MHz, using 5-mm NMR tubes. The chemical shifts are given in ppm upfield from the resonance (at −1628 ppm) of the external standard, which was a saturated solution of $K_2[PtCl]_4$ in a 1.0 M solution of NaCl in D_2O at 296 K. The following parameters were chosen: 90° pulse, P1 = 8.7 μs, and delay D1 = 1.0 s.

Two-Dimensional NMR Spectra. These spectra were recorded with Bruker DRX-400 and DRX-500 spectrometers. Two-dimensional heteronuclear shift correlation spectroscopy (HETCOR) was performed using standard Bruker pulse programs. The ^{1}H−^{13}C HETCOR spectra were obtained with the pulse sequence inv4gs and the following parameters: 90° pulses; P1 = 12.2 μs and P3 = 10.0 μs; delays, D1 = 1.80 s and D2 = 3.57 s. The ^{1}H−^{15}N HETCOR spectra were obtained using the following parameters: 90° pulses; P1 = 9 μs and P3 = 38 μs; delays, D1 = 1.75 s and D2 = 3.45 ms. The ^{1}H−^{13}C experiments optimized on long-range couplings were performed with the pulse program inv4gslplrnd. The decoupling was not used during acquisition. There were 128 free-induction decays of 1024 data points, with 4 scans for each point. NOESY spectra were obtained with the standard pulse sequence noesyst. There were 512 free-induction decays of 2048 data points, with 8 scans for each point. The repetition time was 8.3 s, and the spectral width was 4500 Hz in both dimensions. ROESY spectra were obtained with the standard pulse sequence roesyst. There were 256 free-induction decays of 2048 data points, with 16 scans for each point. The repetition time was 8.3 s, and the spectral width was 4500 Hz in both dimensions.

Diffusion Coefficients. The self-diffusion constants D_s were measured by use of pulsed-field gradient NMR spectroscopy with a Bruker DRX-500 spectrometer. The variable-temperature controller was calibrated over the range 265−305 K using a standard methanol sample.[33] All diffusion measurements were made using a stimulated-echo pulse sequence[34] modified by the inclusion of bipolar gradient pulses and a longitudinal delay to minimize eddy-current effects.[35] A series of 1D ^{1}H spectra were acquired with this pulse sequence, successively increasing the gradient strength. The delays δ = 2 ms and Δ = 50 ms were used for all experiments. The gradient strengths were calibrated by measuring the decay of the integral of the NMR signal of residual HOD in 99.98% D_2O at 298 K. By use of the published value of D_s = 2.272×10^{-5} cm^2 s^{-1},[36] the maximum gradient strength was determined by a nonlinear least-squares fitting of the data to eq 1; the result was $G_{max} = 78.9 \pm 2.0$ G cm^{-1}.[37] In eq 1, G is the gradient strength (in G/cm), I is the observed NMR signal intensity, I_0 is the signal intensity for $G = 0$, γ is the gyromagnetic ratio of the ^{1}H nucleus, δ is the gradient duration, and Δ is time between the encode and decode gradient pulses.

$$I = I_0 \exp[-(\gamma\delta G)^2(\Delta - \delta/3)D_s] \quad (1)$$

A 0.10 M solution of **3** was prepared in acetone-d_6 and 1 equiv of indole-3-acetamide was added, so the solution contained equal concentrations of the free ligand and **3**. Because many of the resonances in the ^{1}H NMR spectra of indole-3-acetamide and **3** are well resolved, this sample was used to measure the self-diffusion coefficients for both species, under identical conditions. A series of stimulated-echo NMR spectra with increasing G values was obtained at 271 K. Several well-resolved lines for indole-3-acetamide and **3** were integrated, and the resulting decay data were fitted by nonlinear least-squares to eq 1 to determine values of D_s, as shown in Figure S1. An average value of D_s, obtained from the integration of several resonances, is reported for both the free ligand and the complex.

Other Spectra. UV−visible spectra were recorded with a Perkin-Elmer Lambda 18 spectrophotometer at 296 K. Infrared spectra of solutions were recorded with a Nicolet Magna-IR 560 spectrometer, using sodium chloride cells with 0.1-mm spacers. Electrospray ionization mass spectra were obtained with a Finnigan TSQ700 triple quadrupole spectrometer fitted with a Finnigan ESI interface. Samples were introduced directly into the electrospray interface through an untreated fused-silica capillary with a 50-μm i.d. and a 190-μm o.d.

Formation of Complexes 3 and 6. Complex **3** was prepared in situ from the solvento complex, *cis*-$[Pt(en)(sol)_2]^{2+}$, and indole-3-acetamide. To 5 mL of a 0.10 M solution of *cis*-$[Pt(en)(sol)_2]^{2+}$ (5×10^{-4} mol) in acetone-d_6 was added 0.087 g (5×10^{-4} mol) of solid indole-3-acetamide, and the reaction mixture was stirred at room temperature. The formation of the product, complex **3**, was usually completed within 30 min and was monitored by ^{1}H NMR spectroscopy. The product was not isolated. Yield was 99%, according to ^{1}H NMR spectra. In another series of ^{1}H NMR experiments, the concentration of *cis*-$[Pt(en)(sol)_2]^{2+}$ was varied between 0.0059 and 0.094 M, and the concentration of indole-3-acetamide was 0.0094 M. The concentration of **3** was determined by integrating the respective ^{1}H NMR resonances. Complexes **6** were synthesized in situ from *cis*-$[Pt(en)(sol)_2]^{2+}$ and amino acid derivatives of indole-3-acetamide by a similar procedure with a longer incubation time, up to 6 h; yields were 95−99%, according to ^{1}H NMR spectra.

Kinetics of Reactions. The solvent in all the reactions was acetone-d_6. The temperature was always 296 ± 0.5 K, except in the experiments concerning the effects of temperature. The initial concentrations of the solvento complex of palladium(II) or platinum(II) and the derivative of indole were 0.094 and 0.0094 M, respectively, unless stated otherwise. The coordination of the indole derivatives to various metal complexes was followed by ^{1}H NMR spectroscopy. In a typical experiment, to a solution of a freshly prepared complex was added an optional chemical, such as H_2O or trifluoroacetic acid, and then a solution of the indole derivative was added to start the reaction. The acquisition began within less than a minute.

Rate constants for relatively fast reactions were determined in experiments lasting for at least 7 half-lives by fitting the experimental data to eq 2 obtained under pseudo-first-order conditions when *cis*-

$$[\text{ligand}] = [\text{ligand}]_0 \exp(-k_{obs}t) \quad (2)$$

$[Pt(en)(sol)_2]^{2+}$ was present in large excess over the incoming, indole-containing ligand. Rate constants for relatively slow reactions were determined from the initial rates, in experiments in which only 3−5% of the reaction was followed. The reported values are the average of at least three experiments; the error margins include 2 standard deviations.

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They are obtained from repeated experiments, not from the fitting of data. The microscopic rate constants were determined from fitting the experimental data to the respective equations shown in Results and Discussion.

The temperature was varied between 263 and 323 K. Activation parameters were determined by fitting the experimental data to the Eyring equation. Fitting to a linearized form of the Eyring equation proved less accurate.

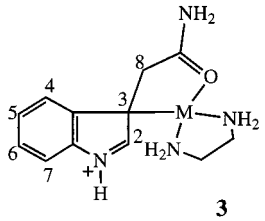
NMR Spectra of Indole Derivatives. The following derivatives of indole were tested as ligands: indole-3-acetamide, indole-3-acetic acid, indole-3-propionic acid, indole-3-acetic acid ethyl ester, tryptophol, 3-indolemethanol, *N*-acetyl-5-hydroxy-tryptamine, *N*-(3-indolylacetyl)-L-phenylalanine, *N*-(3-indolylacetyl)-L-isoleucine, *N*-(3-indolylacetyl)-L-alanine, *N*-(3-indolylacetyl)-L-valine, *N*-(3-indolylacetyl)-DL-aspartic acid, *N*-(3-indolylacetyl)-L-leucine, and *N*-(3-indolylacetyl)-glycine. All of these compounds were monitored by ^{1}H and ^{13}C NMR spectroscopy. For their spectral properties, see the Supporting Information. For those indole derivatives that coordinate to the platinum(II) atom as bidentate ligands, ^{1}H and ^{13}C NMR chemical shifts of the resulting complexes are shown in Tables S1, S2, S6, and S7. The chemical shifts could deviate from the stated values by 0.20 ppm or less, depending on the composition of the reaction mixture and other conditions.

Molecular Mechanics Simulations. Structures of the complexes **3** and **6** were simulated with CHARMM.[38] The spiro-carbon atom was set to be tetrahedral. Different improper angles were set at the spiro-carbon atom to account for the diastereomers **6a** and **6b**. Planarity and bond angles of 90° were imposed on platinum(II) and palladium(II) atoms. The atoms of the coordinated amide bond and the metal atom were kept in one plane, which was not necessarily the same as the coordination plane. The energies were minimized by a simulated annealing procedure. The structures of complexes **3** and **6** were also built with the program Hyperchem[39] and optimized with both steepest-descent and Fletcher−Reeves algorithms.

Quantum Chemical Calculations. The geometries obtained from the CHARMM calculations were further optimized with the Amsterdam Density Functional (ADF) package version 2.3[40] with the basis set IV. The local density approximation for exchange and correlation is based on the standard parametrization.[41] For the nonlocal corrections, the exchange part[42] and the correlation part[43] were used. The geometry optimization was considered to be converged if the energy change was <0.001 hartree and the bond length changes were <0.005 Å. Solvation effects were not included. The structures were visualized with the molecular graphics program RasMol2.[44]

Results and Discussion

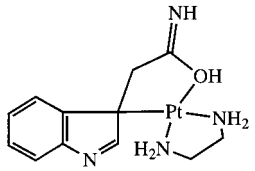
Coordination of Indole-3-acetamide to *cis*-[Pt(en)(sol)$_2$]$^{2+}$. When indole-3-acetamide and *cis*-[Pt(en)(sol)$_2$]$^{2+}$ are mixed in acetone solution, a new complex of composition [Pt(en)($C_{10}H_{10}N_2O$)] is formed. Structure **3**, in which platinum(II) is coordinated to both the carbonyl oxygen and the indole carbon, is shown below.



M is Pt(II) or Pd(II)

3

Proton and Carbon-13 NMR Spectra. As Table S1 shows, ^{1}H resonances of the amide group at 6.63 and 6.30 ppm in the free ligand move downfield to 8.90 and 9.15 ppm, respectively, upon binding. The ^{13}C resonance of the carbonyl carbon moves downfield from 174.0 ppm in the free indole to 192.0 ppm in the product, as data in the supporting information and Table S2 show. These findings are consistent only with the direct binding of the carbonyl oxygen to the platinum(II) atom, as in structure **3**.[45−47] Proton and ^{13}C NMR spectra were assigned by two-dimensional correlation (^{1}H−^{1}H COSY and ^{1}H−^{13}C HETCOR) and NOESY spectroscopy. Two-dimensional ^{1}H−^{15}N HETCOR experiments ruled out formation of the iminol species **4** and the deprotonation of the amide nitrogen atom, because two protons attached to that nitrogen atom were clearly seen.



4

Upon coordination, the proton resonance of N(1)H does not disappear but is shifted from 10.32 ppm in the free indole to 10.80 ppm in the product. Two-dimensional ^{1}H−^{15}N HETCOR experiments confirmed that the second resonance belongs to the indole N(1)H and not to the hydroxide proton in iminol, as in **4**.

Two previous reports[26,27] on complexes containing the 3*H*-indolenine tautomer (**2**) noted the characteristic ^{1}H resonance of C(3)−H, which is absent in the spectrum of the indole tautomer (**1**). Absence of this resonance in the ^{1}H NMR spectrum of **3** supports our proposal of direct coordination of the C(3) atom to the metal atom. Consistent heteronuclear ^{1}H−^{13}C correlation spectra (Figure S2) do not show a proton attached to the C(3) atom in **3**. Because the absence of the hydrogen atom bonded to the C(3) atom is an important feature of structure **3**, we checked even the improbable case that it is undetectable because it is replaced by the deuterium atom from acetone-d_6. If so, upon addition of H_2O, the protium atom would reappear at the C(3) atom. Neither one-dimensional nor two-dimensional ^{1}H NMR spectra showed it, however. We conclude that the C(3) atom does not bear a hydrogen atom. This fact is consistent with structure **3**.

The singlet resonance of C(8)H_2 at 3.60 ppm in the free indole is split into a pattern like an AB quartet in the product. Evidently, the two methylene protons have different environments in the complex, owing to the neighboring groups. One of these protons in the complex is shifted by 1.10 ppm downfield

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relative to the free indole, probably because of its proximity to a phenyl ring.[48] The resonances of C(2)H at 7.28 ppm and C(4)H at 7.59 ppm shift downfield upon coordination to 8.55 and 8.12 ppm, respectively. All the other indole resonances also move downfield upon coordination, but these changes are much smaller, as Table S1 shows.

The ^{13}C NMR resonance of C(3) at 110.0 ppm in free indole-3-acetamide moves to 72.0 ppm upon coordination. This change is diagnostic of a conversion of an aromatic to a tetrahedral carbon atom. Downfield movement of the methylene C(8) and aromatic C(7a) resonances upon coordination are consistent with the published values.[27,46,47] The presence of the N(1) proton and extended conjugation in **3** result in an upfield movement of the imine C(2) resonance from the position of this resonance in similar complexes.[26,27,49−51]

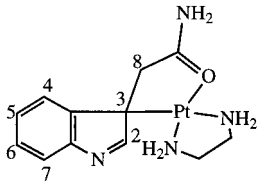
Platinum-195 NMR Spectra and Platinum-195 Satellites. Because the ^{195}Pt NMR chemical shift depends greatly on the type (donor ability) and number of ligating atoms, this shift is very informative about the composition of the complex, provided its dependence on solvent and temperature is taken into consideration (Table S3).[52−54] Our finding for $K_2[PtCl_4]$ agrees with that reported earlier.[54] Dependence of the ^{195}Pt chemical shift on temperature is greater for *cis*-$[Pt(en)(sol)_2]^{2+}$ (1.2 ± 0.2 ppm/K) than for **3** (0.29 ± 0.10 ppm/K), presumably because the former complex contains solvent molecules as ligands and the latter does not.[52]

The resonances for all the complexes containing ethylenediamine ligands are relatively broad (~20 ppm at half-maximum) because of the unresolved coupling to ^{14}N nuclei and fast quadrupolar relaxation.[55] As Table S4 shows, upon addition of indole-3-acetamide the ^{195}Pt resonance of *cis*-$[Pt(en)(sol)_2]^{2+}$ shifts upfield by 442 ppm. This finding suggests the presence of donors much stronger than acetone and water and is consistent with the coordination of the indolyl carbanion and the amide oxygen, as in structure **3**.[56] The reported ^{195}Pt chemical shifts for ascorbic acid complexes are higher than those for **3** because the anionic oxygen is a stronger electron donor than the amide oxygen in **3**.[57] We did not detect platinum-195 satellites in ^{13}C and ^{15}N NMR spectra even for nuclei directly bound to platinum, such as the nitrogen in the ethylenediamine ligand in *cis*-$[Pt(en)(sol)_2]^{2+}$ and the C(3) carbon in **3**, presumably because of the broadening caused by ^{14}N-induced relaxation. This is a known phenomenon.[58] There are, however, broad ^{195}Pt satellites for C(2)H in ^{1}H NMR spectra. The coupling constant $^3J = 55.8$ Hz agrees with the reported values.[59]

Ultraviolet Absorption Spectra. These spectra of indole derivatives are sensitive to substituents and coordination to metals. When indole-3-acetamide binds to *cis*-$[Pt(en)(sol)_2]^{2+}$, the relatively narrow absorption maxima near 272 nm change to a very broad band centered near 260 nm. The peaks at 220 nm decrease in intensity upon coordination. These findings are consistent with structure **3**.[19,26,60] The platinum(II) d−d absorption band at 330 nm for *cis*-$[Pt(en)(sol)_2]^{2+}$ shifts to 327 nm for complex **3**, consistent with the relative strength of the ligand fields of acetone and water on one hand and indole on the other.[61]

Infrared Spectra. Substitution in the indole nucleus markedly affects the N(1)−H stretching frequency.[19] We confirmed[19,62] that this value in indole-3-acetamide is 3365 cm^{-1} ($\epsilon = 160$). Upon coordination, this band is split into two bands, at 3252 and 3160 cm^{-1}; a new band, corresponding to the protonated imine group, C=$^+$NH−, appears at 1650 cm^{-1}.[19] These findings also support structure **3**.

Mass Spectra. The main feature at $m/z = 429.0$ (Table S5) corresponds to the molecular formula $[Pt(en)(C_{10}H_9N_2O)]$ and overall charge +1. This finding argues for the deprotonated complex **3** that incorporated deuterium from the solvent in the course of the sample preparation. According to the NMR spectra, however, complex **3** is not deprotonated in solution; all the protons in fresh samples were clearly assigned to NMR resonances. Deprotonation in the course of electrospray ionization is a recognized phenomenon. The most probable site of this deprotonation is the indole nitrogen in **3**, because it has the lowest pK_a value, ca. 8−9. The product is the 3*H*-indolenine complex designated **5**.[63]



5

Molecular Size. The diffusion coefficients D_s for indole-3-acetamide and its complex **3** are $(4.50 \pm 0.13) \times 10^{-5}$ and $(4.38 \pm 0.10) \times 10^{-5}$ cm^2 s^{-1}, respectively (Figure S1). Because these values are equal, we conclude that the hydrodynamic volumes of the two compounds are similar. Clearly, complex **3** does not contain two molecules of indole-3-acetamide. Formation of the dimeric species containing two platinum atoms bridged by two indole molecules can also be ruled out.[64]

Structural Model for Complex 3. The evidence presented so far consistently supports structure **3**, for which there is a recent precedent.[27] Because suitable crystals could not be obtained despite much effort, this conclusion could not be verified crystallographically. Therefore, we undertook a comprehensive theoretical simulation of this structure. Two widely used molecular mechanics programs, CHARMM[38] and Hyperchem,[39] yielded structures that are qualitatively the same. The CHARMM output was optimized in calculations based on density-functional theory. The result is shown in Figure 1. Because the C(3) atom in indole-3-acetamide is prochiral, its

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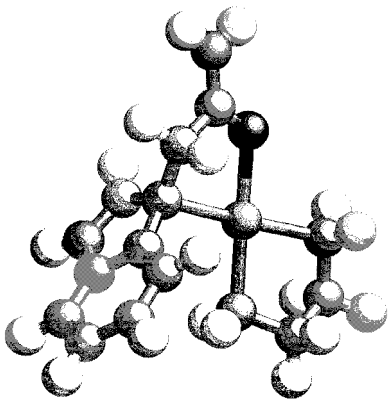


Figure 1. Structure of the *R* enantiomer of the complex cation *cis*-[Pt(en)(indole-3-acetamide)]$^{2+}$ (**3**), as calculated by molecular mechanics (CHARMM) and optimized by quantum mechanics (density-functional theory, program package ADF). The figure was drawn with the program RasMol2.

Table 1. Observed Rate Constant (k_{obs}) for the Reaction in Eq 3, Displacement of the Solvent Ligands in *cis*-[Pt(en)(sol)$_2$]$^{2+}$ by Indole-3-acetamide and Its Amino Acid Derivatives as Bidentate Ligands[a]

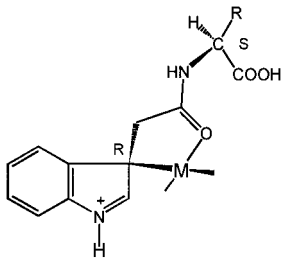
NHX	structure	$k_{obs} \times 10^3$ min^{-1}	NHX	structure	$k_{obs} \times 10^3$ min^{-1}
NH_2	**3**	120 ± 22	L-Val	**6**	46.5 ± 4.9
L-Ala	**6**	125 ± 18	L-Ile	**6**	48.1 ± 5.8
L,D-Asp	**6**	67.6 ± 4.1	L-Phe	**6**	10.6 ± 1.5
L-Leu	**6**	45.7 ± 3.9			

[a] The initial concentrations of *cis*-[Pt(en)(sol)$_2$]$^{2+}$ and the bidentate ligand were 0.094 and 0.0094 M, respectively. The temperature was 296 K, and the solvent was acetone-d_6.

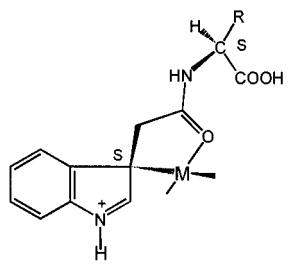
binding to platinum(II) creates a new chiral center, the only one in complex **3**.

Reactions of Amino Acid Containing Indole Derivatives with *cis*-[Pt(en)(sol)$_2$]$^{2+}$. The structural difference between indole-3-acetic acid and tryptophan is that the former lacks a methylene group and an amino group. Nevertheless, condensation of the carboxylic group of indole-3-acetic acid and the amino group of an amino acid yields compounds that are similar to tryptophanyl-(amino acid) dipeptides. These dipeptide-like bidentate ligands can displace two solvent molecules from the coordination sphere of platinum(II) and form complexes **6** that are structurally similar to **3**; their spectroscopic properties are given in Tables S1−S5. Because the amino acid moiety contains a noninverting carbon atom of *S* (or L) configuration and the indole C(3) atom can have either *R* or *S* configuration, the new spiro complexes form diastereomers **6a** and **6b**, shown below and in Figure S3. Indeed, ^{1}H NMR spectra show two sets of resonances of similar intensities; see Tables S1 and S2. This doubling is not caused by restricted rotation around the amide C−N bond because *N*-(3-indolylacetyl)-glycine, which lacks a chiral amino acid moiety, forms only one product with *cis*-[Pt(en)(sol)$_2$]$^{2+}$. The fact that the relative concentrations of the two diastereomers are approximately equal shows that the coordination is rather insensitive to the chirality of the amide substituent. In other words, the two chiral atoms are too far apart for chiral discrimination.

Steric Effect on Coordination of the Amino Acid Containing Indole Derivatives to *cis*-[Pt(en)(sol)$_2$]$^{2+}$. The observed rate constants for the reaction in eq 3 were determined by ^{1}H NMR spectroscopy, as described in the Experimental Section. The coordination is inhibited by the steric bulk of the amide substituent X, as Table 1 shows. The bulkier the substituent X,

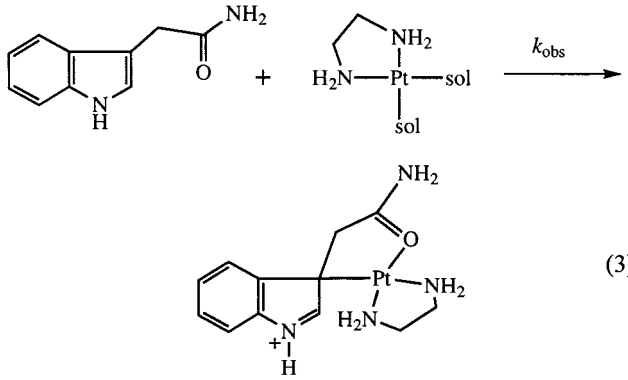


6a



6b

the greater the shielding of the amide oxygen from the platinum(II) complex and the slower the displacement of the two solvent ligands by the dipeptide-like ligand. Complex [Pt(bpy)(sol)$_2$]$^{2+}$, which contains a bulky bipyridyl ligand, does not bind to indole-3-acetamide and *N*-(3-indolylacetyl)-L-alanine.



(3)

Importance of Chelation for Coordination of the Indolyl Group to Platinum(II). Tables 1 and 2 show that only the derivatives of indole-3-acetamide bind to *cis*-[Pt(en)(sol)$_2$]$^{2+}$ to an appreciable extent. Other indole derivatives bind to a small or undetectable extent. For example, the alcohol tryptophol does not coordinate even in the presence of a 10-fold molar excess of the complex. Indeed, the hydroxyl group is an extremely weak ligand for platinum(II).[65] Therefore, chelation via the indole C(3) atom and the hydroxyl group, similar to that in **3**, does not occur.

Because in our experiments H^+ concentration is 1×10^{-3} to 1×10^{-4} M, indole-3-acetic and indole-3-propionic acids are electroneutral and are weaker nucleophiles and poorer ligands than the corresponding carboxamides. Unreactivity of the ethyl ester supports this conclusion.

Table 2 shows that indole and its derivatives cannot bind to platinum(II) as unidentate ligands; coordination of the C(3) atom alone is not sufficient. A second donor group, with correct electronic properties and steric disposition, is required. Indole derivatives bind as bidentate ligands to platinum(II).

The Rate Law for Coordination. Indole-3-acetamide is well-suited to mechanistic studies because reactions of this ligand with *cis*-[Pt(en)(sol)$_2$]$^{2+}$, according to eq 3, are fast and are not complicated by the formation of diastereomers. This reaction is of first order with respect to the entering ligand, as Figure 2 shows. The slope of the plot yields a first-order rate constant of $(1.20 \pm 0.22) \times 10^{-1}$ min^{-1}.

The reaction of indole-3-acetamide and *cis*-[Pt(en)(sol)$_2$]$^{2+}$ is independent of the concentration of the platinum(II) complex, as Figure 3 shows. Experiments in which the concentration of *cis*-[Pt(en)(sol)$_2$]$^{2+}$ was 10−100 times higher than the concentration of the entering ligand gave the result $k_{obs} = (1.36 \pm$

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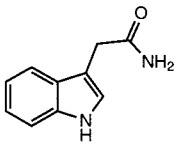
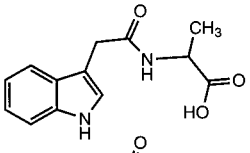
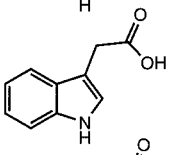
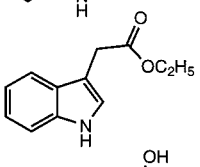
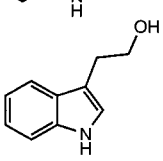
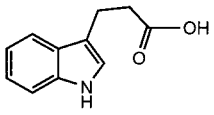
Table 2. Observed Rate Constants (k_{obs}) for the Achieved or Attempted Displacement of the Solvent Ligands in *cis*-$[Pt(en)(sol)_2]^{2+}$ by Various Derivatives of Indole[a]

indole derivative	k_{obs}, min^{-1}
	1.20×10^{-1}
	1.25×10^{-1}
	$< 5.0 \times 10^{-5}$
	$< 1.0 \times 10^{-4}$
	$<< 5.0 \times 10^{-6}$
	$< 1.0 \times 10^{-4}$

[a] For the reaction conditions, see Table 1.

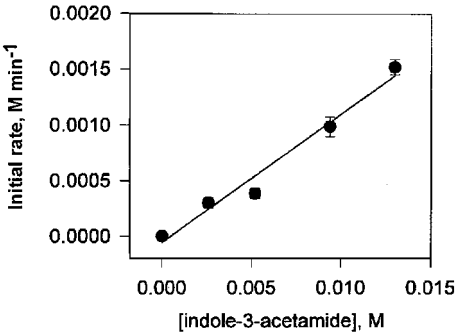


Figure 2. Initial rate for the coordination of indole-3-acetamide to platinum(II), according to eq 3, depends on the initial concentration of the entering ligand. The initial concentration of *cis*-$[Pt(en)(sol)_2](ClO_4)_2$ was 0.094 M. The solvent was acetone-d_6, and the temperature was 296 K.

$0.24) \times 10^{-1}$ min^{-1}. Experiments in which concentrations of the two reactants were similar gave the result $k_{obs} = (1.70 \pm 0.12) \times 10^{-1}$ min^{-1}. In both series of experiments, the counteranion was ClO_4^-. In similar experiments with $CF_3SO_3^-$ as the counteranion, the result was $k_{obs} = (1.62 \pm 0.43) \times 10^{-1}$ min^{-1}. The three values are the same, within the margins of error.

The displacement of the two solvent molecules from platinum(II) by indole-3-acetamide is complete. When the initial concentrations of the entering ligand and the complex were 0.094 and 0.0094 M, respectively, the final concentration of the product, complex **3**, was 0.0094 M. When the mole ratio of

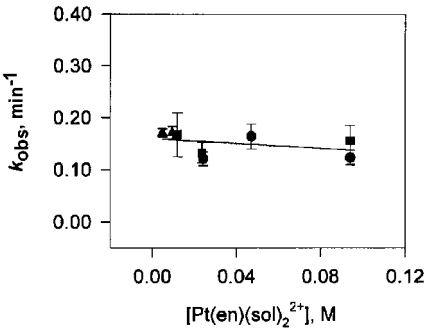


Figure 3. Observed rate constant for the coordination of indole-3-acetamide to platinum(II), according to eq 2, does not depend on the initial concentration of the *cis*-$[Pt(en)(sol)_2]^{2+}$complex. Combined are the results from three sets of experiments: 0.0047 and 0.0094 M in *cis*-$[Pt(en)(sol)_2](ClO_4)_2$ (▲), 0.027−0.094 M in *cis*-$[Pt(en)(sol)_2](ClO_4)_2$ (●), and 0.014−0.094 M in *cis*-$[Pt(en)(sol)_2](CF_3SO_3)_2$ (■). The initial concentration of indole-3-acetamide was always 0.0094 M. The solvent was acetone-d_6, and the temperature was 296 K.

cis-$[Pt(en)(sol)_2]^{2+}$ and the free ligand was varied, the final concentration of **3** was always equal to the starting concentration of the limiting reagent. No exchange between free and bound indole-containing ligand was detected.

Figures 2 and 3 support the rate law in eq 4 for the substitution reaction in eq 3.

$$d[\mathbf{3}]/dt = k_{obs}\,[\text{ligand}]^1[Pt(en)(sol)_2^{2+}]^0 \qquad (4)$$

Mechanism of Coordination. Because the rate law in eq 4 shows zeroth order with respect to the *cis*-$[Pt(en)(sol)_2]^{2+}$ complex, we conclude that the rate-limiting step does not involve this complex. The mechanism in eq 5 under certain conditions satisfies the observed rate law. The first step is the displacement of the first solvent ligand by indole, designated I. Considering the structure of **3**, the first step in eq 5 probably is the unidentate coordination of indole-3-acetamide via the amide oxygen atom.

$$Pt(en)(sol)_2^{2+} + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Pt(en)(sol)I^{2+} + sol \xrightarrow{k_2} \mathbf{3} + sol \qquad (5)$$

This initial anchoring is followed by closing of the chelate ring to yield the spiro compound **3** as the final product. Careful examination of ^1H NMR spectra reveal a higher concentration of the Pt(II)-bound amide oxygen than of the Pt(II)-bound C(3) atoms. This finding supports our view about the mechanism of coordination and the structure of $[Pt(en)(sol)I]^{2+}$. The equilibrium constant K was estimated from ^1H NMR spectra. Only the O-bound species is observed when 0.10 M indole-3-acetamide and 0.10 M *cis*-$[Pt(en)(sol)_2]^{2+}$ are mixed in acetone solution. Therefore, the concentration of free indole-3-acetamide is lower than 1×10^{-3} M. The value of $K > 10^5$ M^{-1} agrees with the previous studies.[66] This equilibrium, for which $K = k_1/k_{-1}$, is shifted to the right, especially in the presence of an excess of the platinum(II) complex.

The second step is the rearrangement of the initial complex to **3**, with the displacement of the second solvent ligand. Under the pre-equilibrium approximation, eq 6, the observed rate constant for the formation of **3** is given in eq 7. Because the equilibrium constant K is relatively large, as stated in eq 8, eq 7 reduces to eq 9. Because the concentration of the platinum(II) complex is not a factor in eq 9, this simple expression agrees with the evidence in Figure 3.

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$$k_{-1} + k_1[\text{Pt(en)(sol)}_2^{2+}] \gg k_2 \quad (6)$$

$$k_{obs} = \frac{Kk_2[\text{Pt(en)(sol)}_2^{2+}]}{K[\text{Pt(en)(sol)}_2^{2+}] + 1} \quad (7)$$

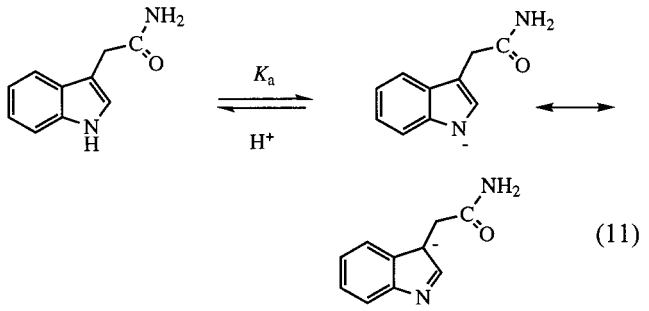
$$K[\text{Pt(en)(sol)}_2^{2+}] \gg 1 \quad (8)$$

$$k_{obs} = k_2 \quad (9)$$

The alternative mechanism, involving an equilibrium between two forms of indole-3-acetamide followed by the coordination of one of these forms to *cis*-$[Pt(en)(sol)_2]^{2+}$, is shown in eq 10. Under particular conditions (see the Supporting Information), this mechanism can also satisfy the experimental results. The equilibrium in eq 10 clearly is not amide-to-iminol tautomerization because both the entering ligand, indole-3-acetamide,

$$I_1 \overset{K}{\rightleftharpoons} I_2 \xrightarrow[Pt(en)(sol)_2^{2+}]{k_2} \mathbf{3} \quad (10)$$

and the final product, complex **3,** exist as amides. Similarly, tautomerism between the indole and 3*H*-indolenine forms of the ligand[19,65,67] probably is not involved, because it would favor platinum(II) binding to indole nitrogen and such binding is not observed. Deprotonation and formation of the indolyl anion,[19] shown in eq 11, can, in principle, result in **3**, because in the second resonance form[19,68,69] chelation via the C(3) and amide oxygen atoms is favorable.



(11)

We tested this hypothesis by examining the effects of acid on the coordination. Because addition of NaOH to the reaction mixture in acetone-d_6 caused precipitation of platinum(II),[70] the effects of base on the rate of coordination could not be determined. Fortunately, the effects of acid were amenable to study and gave useful mechanistic information. In the standard reaction mixture for kinetic experiments with indole-3-acetamide (see the preceding subsection), the concentration of strong acid ($HClO_4$) was 5×10^{-4} M and k_{obs} (in eq 3) was $(1.20 \pm 0.22) \times 10^{-1}$ min^{-1}. In three additional series of experiments, the reaction mixtures were 0.10, 0.30, and 0.78 M in CF_3COOH, so that the concentration of strong acid was varied 1600-fold overall. Higher concentrations of the acid had to be avoided because the ethylenediamine ligand could be displaced from the complex. The new k_{obs} values were $(1.86 \pm 0.37) \times 10^{-1}$, $(1.92 \pm 0.37) \times 10^{-1}$, and $(6.0 \pm 1.0) \times 10^{-3}$ min^{-1} for the three concentrations, respectively. Evidently, k_{obs} does not significantly depend on the acid concentration. The first three values (at 5×10^{-4} M $HClO_4$ and 0.10 and 0.30 M CF_3COOH) are the same, within the error margins. The fourth one, at very high acid concentration, decreased 25-fold. The mechanism in eq 10 requires that k_{obs} be inversely proportional to the acid concentration; therefore, the fourth value should be 1600 times smaller than the first. The experimental results disagree with this mechanism because the fourth value (at 0.78 M CF_3COOH) is only 25 times smaller than the first. We favor the mechanism in eq 5 for coordination of indole-3-acetamide to the platinum(II) atom.

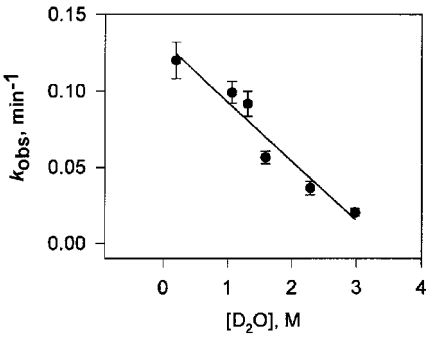


Figure 4. Observed rate constant for the coordination of indole-3-acetamide to platinum(II), according to eq 3, depends on the concentration of water. Initial concentrations of indole-3-acetamide and *cis*-$[Pt(en)(sol)_2]^{2+}$ were 0.0094 and 0.094 M, respectively. The solvent was acetone-d_6, and the temperature was 296 K.

Inhibition of Coordination by Water. Addition of water inhibits the coordination of indole-3-acetamide to *cis*-$[Pt(en)(sol)_2]^{2+}$, as Figure 4 shows. We consider two possible causes of this inhibition. First, competition between water and the amide oxygen of indole-3-acetamide for binding to platinum(II) would lower the binding constant *K*. Such effects of water have been previously observed.[71] Second, acetone, a weakly basic solvent, favors formation of the indolyl anion in **3**, whereas water is notoriously incompatible with carbanions and other very strong bases.[72] Both factors are likely to contribute to the inhibiting effect of water on the coordination.

Activation Parameters for Coordination. Because the observed rate constant for the reaction in eq 3 corresponds to k_2 in eq 5, the activation parameters for the second step in eq 5 could be determined. The results in Figure 5 were fit to the Eyring equation. The $\Delta H^{\ddagger}$ values of 78.2 ± 9.2 and 61.4 ± 22.0 kJ mol^{-1} and the $\Delta S^{\ddagger}$ values of -37.5 ± 25.0 and -96.0 ± 74.0 J K^{-1} mol^{-1} were obtained for indole-3-acetamide and *N*-(3-indolylacetyl)-L-alanine, respectively. The relatively high values of $\Delta S^{\ddagger}$ indicate that the transition state is only slightly more ordered than the substrate.[73] This finding is consistent with the unimolecular closing of the spiro ring.

Change in the Rate-Limiting Step in the Case of a Bulky Entering Ligand. Figure 6 shows that the rate of entry of the bulkiest ligand, *N*-(3-indolylacetyl)-L-phenylalanine, depends on the concentration of the platinum(II) complex. In this case, the experimentally determined rate law is given in eq 12, which differs from eq 4. In the case of bulky entering ligands, the binding constant *K* is lowered and eq 8 does not apply. Indeed,

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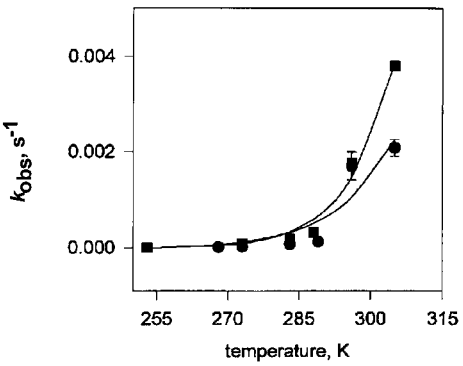

Figure 5. Temperature dependence of the observed rate constants for the coordination of indole-3-acetamide (■) and *N*-(3-indolylacetyl)-L-alanine (●) to platinum(II), according to eq 3. Initial concentrations of indole-3-acetamide, *N*-(3-indolylacetyl)-L-alanine, and *cis*-[Pt(en)(sol)$_2$]$^{2+}$ were 0.0094, 0.0094, and 0.094 M, respectively. The solvent was acetone-d_6.

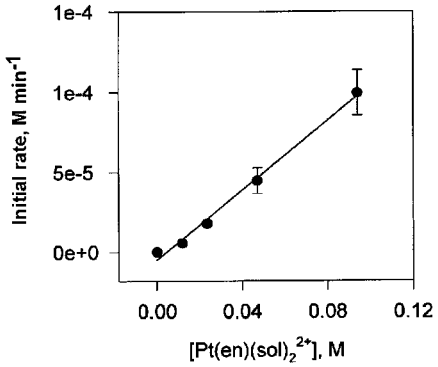

Figure 6. Initial rate for the coordination of *N*-(3-indolylacetyl)-L-phenylalanine to platinum(II) depends on the initial concentration of the platinum(II) complex. The initial concentration of *N*-(3-indolylacetyl)-L-phenylalanine was 0.0094 M. The solvent was acetone-d_6, and the temperature was 296 K.

integration of the ^{1}H NMR amide resonances of the free and O-bound *N*-(3-indolylacetyl)-L-phenylalanine yield the result $K = 3.3 \times 10^{-3}$ M^{-1}. Therefore, eq 7 is reduced to eq 13, which corresponds to the rate law in eq 12. The second-order observed

$$d[\mathbf{6}]/dt = k_{obs}\,[\text{ligand}]^1[\text{Pt(en)(sol)}_2^{2+}]^1 \qquad (12)$$

rate constant, $k_{obs} = Kk_2$, determined from the slope of the plot in Figure 6 and the initial concentration of *N*-(3-indolylacetyl)-L-phenylalanine, is $(1.16 \pm 0.05) \times 10^{-1}$ M^{-1} min^{-1}.

$$k_{obs} = Kk_2[\text{Pt(en)(sol)}_2^{2+}]_0 \qquad (13)$$

The rate law in eq 12 was tested further in experiments with added CF_3COOH, a strong acid. When its concentration was 5×10^{-4}, 0.1, 0.3, and 0.78 M, the rate constant at 296 K of the reaction with this bulky ligand was $(1.16 \pm 0.05) \times 10^{-1}$, $(1.16 \pm 0.08) \times 10^{-1}$, $(1.13 \pm 0.05) \times 10^{-1}$, and $(1.01 \pm 0.09) \times 10^{-1}$ M^{-1} min^{-1}, respectively. Evidently, the rate constant is practically independent of the acid concentration. We conclude that, even when the entering ligand is bulky, the rate-limiting step does not involve proton exchange. Again, the evidence is inconsistent with the mechanism in eq 10. We favor the mechanism in eq 5.

Stability of Complex 3. As Table 3 shows, some unidentate ligands do and others do not displace indole-3-acetamide in complex **3**. Most of the reactions were too slow or too fast for accurate kinetic experiments by ^{1}H NMR spectroscopy. The results nevertheless show that the new complex, **3**, is moderately stable with respect to substitution.

Table 3. Second-Order Rate Constant (k_{dis}) for the Displacement of Indole-3-acetamide from *cis*-[Pt(en)(indole-3-acetamide)]$^{2+}$ (**3**) by Various Potential Ligands[a]

ligand	k_{dis}, M^{-1} min^{-1}	ligand	k_{dis}, M^{-1} min^{-1}
2-aminoethanol	>5.0	CNO^-	$<3 \times 10^{-6}$
$(CH_3)_2SO$	2.0	CH_3COO^-	$<1 \times 10^{-6}$
2-methylimidazole	1.0	CH_3CN	$<1 \times 10^{-6}$

[a] The initial concentration of *cis*-[Pt(en)(indole-3-acetamide)]$^{2+}$ was 0.0094 M. The temperature was 296 K, and the solvent was acetone-d_6.

Coordination of Indole-3-acetamide to Palladium(II) Complexes. Because of the general similarity between platinum(II) and palladium(II),[74] complexes of palladium(II) analogous to those of platinum(II) discussed above also react with indole-3-acetamide and form complexes of the type **3**. Their spectroscopic properties are given in Tables S5−S7. But the coordination to palladium(II) is faster; the reaction is nearly complete in 0.5 min under the same conditions for which coordination to platinum(II) required 30 min. The slowness of the latter reactions is convenient, for it allowed the kinetic and mechanistic studies presented above. Such studies with palladium(II) complexes were unfeasible.

We also examined the reaction of indole-3-acetamide with *cis*-[Pd(Me$_4$en)(sol)$_2$]$^{2+}$ and [Pd(dien)(sol)]$^{2+}$, complexes whose platinum counterparts we did not study. The products of these two reactions were structurally different from **3**. The product with the Me$_4$en ligand shows downfield movement of the ^{1}H NMR resonances of the amide and C(8)H$_2$ groups and no change in those of the indole moiety. These facts indicate that indole-3-acetamide coordinates as a unidentate ligand via the amide oxygen atom.[58,59] Large downfield movement of the carbonyl resonance and invariance of the other ^{13}C resonances corroborate this conclusion.[59] This unidentate coordination is incomplete, and a large fraction of indole-3-acetamide remains free in solution even if *cis*-[Pd(Me$_4$en)(sol)$_2$]$^{2+}$ is present in excess. Both ^{1}H and ^{13}C NMR spectra of indole-3-acetamide remain unchanged even after a 20-h incubation with [Pd(dien)(sol)]$^{2+}$ at 296 K. The unidentate coordination in the former case and lack of coordination in the latter case result from steric repulsion and the relative lability of palladium(II) complexes.

Conclusion

Reactions of platinum(II) and palladium(II) complexes with indole-3-acetamide and its derivatives produced new complexes of unusual structure. Various NMR, UV, IR, and mass spectra revealed bidentate coordination via the indole carbon C(3) and the amide oxygen. The indolyl group in the derivatives containing substituents at the C(3) atom cannot coordinate to platinum(II) as a unidentate ligand. If this inability also applies to tryptophan and to other transition metals, this study may help explain why tryptophan residue has not been found bound to transition-metal ions that are intrinsic to proteins. Our recent discovery of such binding and selective cleavage of tryptophan-containing peptides[18] opens new directions for research into the bioinorganic and biological chemistry of tryptophan.

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Supporting Information Available: NMR spectral properties of indole derivatives, ^{1}H and ^{13}C chemical shifts for the products of the reactions in eq 3, a representative $^{1}H-^{13}C$ spectrum, ^{195}Pt chemical shifts and dependence of some of them on temperature, molecular masses and *m*/*z* ratios of Pt(II) and Pd(II) complexes with indole-3-acetamide and its amino acid derivatives, commentary on the mechanism in eq 10, absolute intensities of the ^{1}H resonances, calculated structures of the diastereomers **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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