# Structural and Kinetic Studies on the Formation of Platinum(II) and Palladium(II) Complexes with L-Cysteine-Derived Ligands

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Complex-formation reactions of the L-cysteine-derived ligands $^{\alpha}$*N*-acetyl-*S*-methylene-(2′-pyridine)-L-cysteine (py-$CH_2$-accys) and $^{\alpha}$*N*-acetyl-*S*-ethylene-2-(2′-pyridine)-L-cysteine (py-$C_2H_4$-accys) with $[Pt(en)(H_2O)_2]^{2+}$ and $[Pd(en)(H_2O)_2]^{2+}$ were investigated structurally by NMR spectroscopy and kinetically by UV−vis and stopped-flow spectrophotometry. The complexes $[Pt(en)(py\text{-}CH_2\text{-}accys\text{-}S,N)](NO_3)_2$ (**1**) and $[Pt(en)(py\text{-}C_2H_4\text{-}accys\text{-}S,N)](NO_3)_2$ (**2**) were isolated and purified by reversed-phase HPLC. NMR spectroscopy revealed an *S*-thioether, *N*-pyridyl chelation mode with five- and six-membered chelate rings for **1** and **2** and their Pd(II) analogues **3** and **4**. The amino acid functional group is not involved in coordination. Comparison of the second-order rate constants for the complex-formation reactions resulted in $k_{Pd(II)}/k_{Pt(II)}$ ratios of $3.7 \times 10^4$ for py-$CH_2$-accys and $2.4 \times 10^4$ for py-$C_2H_4$-accys. In the presence of excess ligand, the trans effect of the Pd-coordinated sulfur donor induced labilization of the coordinated en ligand with successive displacement to give $[Pd(py\text{-}CH_2\text{-}accys)_2]$ and $[Pd(py\text{-}C_2H_4\text{-}accys)_2]$. The displacement reactions were shown to be in accordance with a preequilibrium behavior consisting of reversible formation of the ring-opened intermediate followed by successive irreversible ring closure. The results are discussed in reference to available literature data for related systems.

## Introduction

Interactions of Pt(II) anticancer drugs and their Pd(II) analogues with sulfur containing amino acid side chains have attracted much attention in studies on the biological activity of cisplatin[1,2] and carboplatin.[3] These compounds usually prefer soft sulfur donors over nitrogen donors. At neutral pH, monofunctional $[Pt(dien)(H_2O)]^{2+}$ and $[Pt(dien)I]^{+}$ complexes have a greater affinity for L-cysteine and glutathione than for guanosine 5′-monophosphate,[4] which is known to be the final target for antitumor-active complexes. A direct substitution mechanism of $[Pt(dien)Cl]^{+}$ with glutathione and *S*-methylglutathione without prior aquation suggested that in the blood S-containing peptides are the main targets.[5,6] Monodentate S-bound amino acids[7,8] and certain S,O-bound ligands[9] can be displaced by guanine, whereas bidentate S,N-bound amino acids were thought to be substitution inert. However, evidence for the displacement of S,N-bound *N*-acetyl-L-methionine by guanine adducts was recently found.[10] Another study reported that, at neutral pH, the rate of guanosine 5′-monophosphate binding to cisplatin increases in the presence of L-methionine.[11] This was attributed to the displacement of an ammine ligand by guanosine 5′-monophosphate, since it is labilized by the trans effect of the sulfur-coordinated L-methionine. Pd(II) complexes were also found to form chelate complexes with peptides and further promote hydrolysis of the amide bonds.[12]

Due to their $10^4-10^5$ times higher reactivity, Pd(II) analogues of Pt(II) complexes are well suited for kinetic and mechanistic studies by application of rapid-mixing techniques. Work in our laboratories has focused on the interaction of complexes of the type $[Pd(R_4en)Cl_2]$ (R = H, Me, Et) with L-methionine and *S*-methyl-L-cysteine[13] and DNA building blocks.[14] Varying the substituents R systematically from H to Et enabled us to control the reactivities of the complexes by steric effects. Electronic effects, such as the introduction of a metal−sulfur bond as investigated for $[Pd(L\text{-methionine})Cl_2]$[15] or a metal−carbon bond[16,17] resulted in a significant labilization of the trans position in aqueous solution. The introduction of a $\pi$-accepting heteroaromatic nitrogen base resulted in a decrease in the p$K_a$ of coordinated $H_2O$ ligands and an increase in reactivity.[18]

(1) Iakovidis, A.; Hadjiliadis, N. *Coord. Chem. Rev.* **1994**, *135/136*, 17.
(2) Pettit, L. D.; Bezer, M. *Coord. Chem. Rev.* **1985**, *61*, 97.
(3) Barnham, K. J.; Djuran, M. I.; Murdoch, P. d. S.; Ranford, J. D.; Sadler, P. J. *Inorg. Chem.* **1996**, *35*, 1065.
(4) Bose, R. N.; Moghaddas, S.; Weaver, E. L.; Cox, E. H. *Inorg. Chem.* **1995**, *34*, 5878.
(5) Djuran, M. I.; Lempers, E. L. M.; Reedijk, J. *Inorg. Chem.* **1991**, *30*, 2648.
(6) Lempers, E. L. M.; Inagaki, K.; Reedijk, J. *Inorg. Chim. Acta* **1988**, *152*, 201.
(7) Barnham, K. J.; Djuran, M. I.; Murdoch, P. d. S.; Sadler, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 721.
(8) van Boom, S. S. G. E.; Reedijk, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1397.
(9) Pasini, A.; Moroni, M. *J. Chem. Soc., Dalton Trans.* **1997**, 1093.
(10) Barnham, K. J.; Guo, Z.; Sadler, P. J. *J. Chem. Soc., Dalton Trans.* **1996**, 2867.
(11) Barnham, K. J.; Djuran, M. I.; Murdoch, P. d. S.; Ranford, J. D.; Sadler, P. J. *J. Chem. Soc., Dalton Trans.* **1995**, 3721.
(12) (a) Parac, T. N.; Kostic, N. M. *J. Am. Chem. Soc.* **1996**, *118*, 51. (b) Chen, X.; Zhu, L.; Yan, H.; You, X.; Kostic, N. M. *J. Chem. Soc., Dalton Trans.* **1996**, 2653.
(13) Suvachittanont, S.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **1995**, 2027.
(14) Rau, T.; van Eldik, R. In *Metal Ions in Biological Systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker: New York, 1996; Vol. 32, p 339.
(15) Prinsloo, F. F.; Pienaar, J. J.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **1995**, 3581.
(16) Schmülling, M.; Ryabov, A. D.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **1994**, 1257.
(17) Schmülling, M.; Grove, D. M.; van Koten, G.; van Eldik, R.; Veldman, N.; Spek, A. L. *Organometallics* **1996**, *15*, 1384.
(18) Rau, T.; Shoukry, M.; van Eldik, R. *Inorg. Chem.* **1997**, *36*, 1454.

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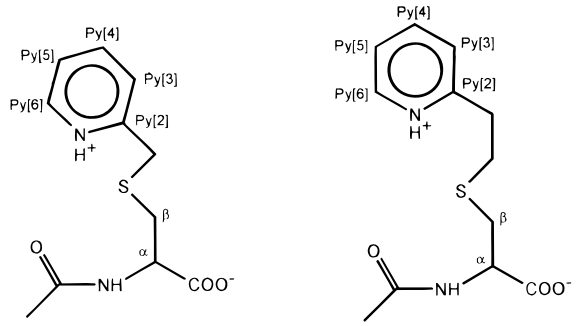
**Chart 1**




Here we report structural information and kinetic studies on the reactivity of newly developed sulfur-containing amino acid ligands.[19] These ligands consist of the amino acid L-cysteine covalently linked to a pyridyl moiety to provide specific binding sites as shown in Chart 1. We will report that the trans labilization of inert amine ligands induced by sulfur donors[20] can be used as a tool to tune the reactivity of Pt(II) and Pd(II) complexes in an electronic way. The amino acid functional group is intended to serve as a linkage to small peptides, proteins, or other pharmaceutically relevant groups.[21,22]

## Experimental Section

**Materials.** $K_2PtCl_4$ was obtained from ABCR Chemicals, and $PdCl_2$ was a donation from Degussa. $[Pd(en)Cl_2]$[23] and $[Pt(en)Cl_2]$[24] were prepared by standard methods and converted into the diaqua complexes for kinetic studies by treating them with 1.98 equiv of $AgNO_3$ under light exclusion. $NaClO_4$ was purchased from Fluka and trifluoracetic acid (TFA) from Aldrich. py-$CH_2$-accys and py-$C_2H_4$-accys were prepared as described elsewhere.[19] Demineralized water was used for all preparations and kinetic studies.

**HPLC.** A Kontron 420 pump equipped with a Rheodyne sample injector and a Spectra Physics SP 8480 XR UV−vis detector were used. Analytical work was carried out on a C18 reversed-phase Grom-Sil 80 ODS-2 FE column (250 mm × 4 mm), and semipreparative work was performed on a C18 reversed-phase Grom-Sil 80 ODS-2 FE column (250 mm × 20 mm) with detection of the products at 250 nm. A 90% $H_2O$/10% MeOH (v/v) eluent containing 0.05% TFA or $HNO_3$, shown to be suitable buffers for such systems,[25] was used for the isocratic runs. Both buffers gave similar results. The complexes [Pt(en)(py-$CH_2$-accys-*S*,*N*)]$(NO_3)_2$ (**1**) and [Pt(en)(py-$C_2H_4$-accys-*S*,*N*)]$(NO_3)_2$ (**2**) were obtained within the first fractions. The solvents and buffers from semipreparative samples were removed by rotary evaporation at 25 °C under vacuum. Chemical analyses were performed on a Carlo Erba 1108 elemental analyzer.

**Spectroscopy.** $^1H$ and $^{13}C$ NMR studies were performed in 5 mm tubes at 25 °C on a Bruker Avance DPX 300 spectrometer at 300.1 and 75.5 MHz, respectively, and a Bruker Avance DRX 400 spectrometer at 400.1 and 100.6 MHz, respectively, using $D_2O$ or 95% $H_2O$/5% $D_2O$ (v/v) as solvent. $^1H$ and $^{13}C$ spectra were referenced with respect to TSP (sodium 3-trimethylsilylpropionate) as the internal standard. $^{195}Pt$ specta were measured in 100% $H_2O$ on a Bruker Avance DRX 400 spectrometer at 85.8 MHz and referenced with respect to chloroplatanic acid (1 M in $D_2O$) in an inserted tube as the external standard. A typical $^{195}Pt$ experiment included the following parameters: 16 $\mu$s pulse, 0.5 s delay time, 0.2 s acquisition time, and 64K data points.

Assignment of $^1H$ and $^{13}C$ resonances was aided by $^1H$ COSY and $^{13}C-^1H$ HCOSY experiments. Variable-temperature NMR experiments were carried out on the Bruker Avance DRX 400 spectrometer. Band shape analyses were performed using the Bruker WIN-KUBO software package (Bruker-Franzen Analytik GmbH, Bremen, Germany). To prepare $[Pd(en)(D_2O)_2]^{2+}$, the dichloro complex $[Pd(en)Cl_2]$ was treated with 1.9 equiv of $AgNO_3$ in $D_2O$. After the AgCl precipitate was filtered off over a cotton wool plug, a yellow solution of $[Pd(en)(D_2O)_2]^{2+}$ was obtained.

IR spectra were recorded on a Mattson Polaris FT IR spectrophotometer using KBr pellets. UV−vis spectra were recorded on a Cary 1 spectrophotometer. Raman spectra of the solid samples were measured in glass tubes under ambient conditions using a DILOR XY multichannel spectrometer, equipped with an $Ar^+$ ion laser, Spectra Physics Stabilite 2014 (514.5 nm, ∼100 mW).

**pH Measurements.** pH values for kinetic investigations were measured with a Mettler-Toledo electrode on a Metrohm 632 pH meter. The electrode was filled with NaCl instead of KCl to prevent precipitation of $KClO_4$. Standard buffers of pH 1.68, 4.00, and 6.87 were used for calibration. pH measurements of NMR samples in $D_2O$ were recorded directly in the NMR tube with an Aldrich 4 mm combination electrode. pH* values, uncorrected for the deuterium isotope effect, were adjusted using diluted $DNO_3$ and NaOD solutions in $D_2O$.

The p$K_a$ values of the ligands py-$CH_2$-accys and py-$C_2H_4$-accys were determined by plotting the $^1H$ resonances of the aromatic protons versus the pH*. The p$K_a$ values measured in $D_2O$ and $H_2O$ are virtually the same.[26]

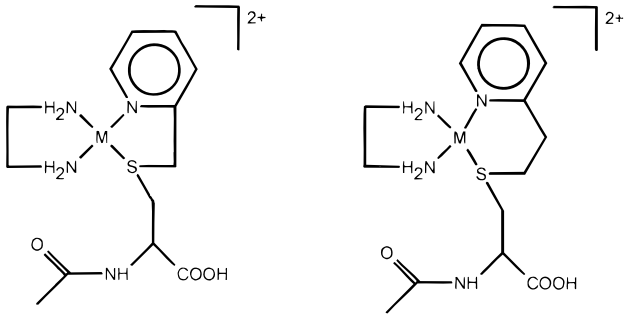
**Kinetic Measurements.** Fast kinetic measurements were performed on a Durrum D 110 or an Applied Photophysics stopped-flow instrument coupled to on-line data aquisition systems. For slower reactions, UV−vis absorbance−time traces were obtained from spectra collected on a Cary 1 spectrophotometer. The kinetic traces were evaluated using the OLIS KINFIT (Bogart, GA) or the Applied Photophysics (Leatherhead, U.K.) set of programs including the Global Analysis software package. The pH of the solutions was adjusted with $HClO_4$ and NaOH, and no buffers were employed. Unless otherwise stated, kinetic measurements were carried out at a complex or nucleophile concentration of $1.0 \times 10^{-4}$ M for Pt and $0.5 \times 10^{-4}$ M for Pd and a pH of 3.00 at 25.0 ± 0.1 °C and 0.10 M ionic strength, which was adjusted with $NaClO_4$. All kinetic measurements were performed under pseudo-first-order conditions; i.e., at least a 10-fold excess of nucleophile or metal complex was used.

**Preparation of Complexes. (a) ($^{\alpha}N$−Acetyl-*S*-methylene-(2′-pyridine)-L-cysteine)(ethylenediamine)platinum(II)nitrate, [Pt(en)(py-$CH_2$-accys-*S*,*N*)]$(NO_3)_2$ (1).** A 275.8 mg (0.846 mmol) sample of $[Pt(en)Cl_2]$ and 278.5 mg (1.639 mmol) of $AgNO_3$ were suspended in 30 mL of $H_2O$, and the mixture was stirred for 24 h at room temperature in the dark. After the white AgCl precipitate was filtered off, 214.6 mg (0.845 mmol) py-$CH_2$-accys dissolved in 10 mL of $H_2O$ was added to the colorless filtrate, and the mixture was then stirred for 24 h. After removal of the solvent by rotary evaporation, a colorless product was obtained, which was dissolved in 1 mL of $H_2O$ and purified by HPLC. A 342.0 mg (0.540 mmol; 64%) yield of **1** was obtained as a transparent solid. Anal. Calcd for $C_{13}H_{22}N_6SO_9Pt$: C, 24.65; H, 3.50; N, 13.27; S, 5.06. Found: C, 24.86; H, 3.70; N, 12.80; S, 5.06.

**(b) ($^{\alpha}N$−Acetyl-*S*-ethylene-2-(2′-pyridine)-L-cysteine)(ethylenediamine)platinum(II)nitrate, [Pt(en)(py-$C_2H_4$-accys-*S*,*N*)]$(NO_3)_2$ (2).** A 391.4 mg (1.200 mmol) sample of $[Pt(en)Cl_2]$ and 387.0 mg (2.278 mmol) of $AgNO_3$ were suspended in 40 mL of $H_2O$, and the mixture was stirred for 24 h at room temperature in the dark. After the white AgCl precipitate was filtered off, 318.8 mg (1.190 mmol) py-$C_2H_4$-accys dissolved in 10 mL of $H_2O$ was added to the colorless filtrate, and the mixture was then stirred for 24 h. The solvent was removed by rotary evaporation at 25 °C, and a colorless product was obtained.

(19) Alsfasser, R.; van Eldik, R. *Inorg. Chem*. **1996**, *35*, 628.
(20) Appleton, T. G.; Connor, J. W.; Hall, J. R.; Prenzler, P. D. *Inorg. Chem.* **1989**, *28*, 2030.
(21) Lippard, S. J. In *Bioinorganic Chemistry*; Bertini, I., Gray, H. B., Lippard, S. J., Valentine, J. S., Eds.; University Science Books: Mill Valley, CA, 1994; p 505.
(22) Keppler, B. K. *Nachr. Chem. Tech. Lab.* **1987**, *35*, 1029.
(23) Hohmann, H.; van Eldik, R. *Inorg. Chim. Acta* **1990**, *174*, 87.
(24) Dhara, S. C. *Indian J. Chem.* **1970**, *8*, 193.
(25) Siebert, A. F. M.; Sheldrick, W. S. *J. Chem. Soc., Dalton Trans.* **1997**, 385.
(26) Scheller, K. H.; Scheller-Krattiger, V.; Martin, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 6833.

**Chart 2**




[M(en)(py-$CH_2$-accys-S,N)]$^{2+}$
**(1)** M = Pt, **(3)** M = Pd

[M(en)(py-$C_2H_4$-accys-S,N)]$^{2+}$
**(2)** M = Pt, **(4)** M = Pd

**Table 1.** $^1$H and $^{195}$Pt NMR Chemical Shifts (ppm) of Complexes **1**−**4** ($\delta$($^1$H), 400 MHz, 95% $H_2O$/5% $D_2O$; $\delta$($^{195}$Pt), 85.8 MHz, $H_2O$)

| | **1**, pH* 1.4 | **2**, pH* 1.4 | **3**, pH* 1.9 | **4**, pH* 2.0 |
|---|---|---|---|---|
| Py[6] | 8.55 d | 8.75 d<br>8.71 d | 8.25 d | 8.62 d |
| Py[4] | 8.21 t | 8.12 tt | 8.14 t | 8.13 t |
| Py[3] | 7.90 d | 7.74 dd | 7.79 d | 7.76 d |
| Py[5] | 7.55 t | 7.52 tt | 7.56 t | 7.59 t |
| NH[amide] | 8.50 d[b]<br>8.61 [b] | 8.51 dd[b] | *a* | *a* |
| NH[en] | 6.44−5.82[b] | 6.20−5.44[b] | *a* | *a* |
| H[α] | 4.85<br>4.91 | 4.74<br>5.01 | 4.42 dd | 4.65 br |
| $CH_2$ | 4.73−4.56 | 3.70−3.23 | 4.84 | *c* |
| H[$\beta$] | 3.41−3.09 m | 2.80−2.60 | 3.50−3.10 m | 2.69−2.63 br |
| $CH_2$[en] | 2.89 | 2.88 | 2.96 br | 2.95 br |
| $CH_3$ | 2.08<br>1.99 | 2.08<br>2.05 | 2.08<br>2.02 | 2.05 br |
| $^{195}$Pt | −3177 | −3308<br>−3289 | | |

[a] Not observed; fast HD exchange. [b] Measured in $H_2O$. [c] Appear as broad multiplets.

Purification by HPLC yielded 532 mg (0.815 mmol; 68%) of **2** as a transparent solid. Anal. Calcd for $C_{14}H_{24}N_6SO_9Pt$: C, 25.97; H, 3.74; N, 12.98; S, 4.95. Found: C, 25.60; H, 3.68; N, 12.45; S, 4.54.

## Results and Discussion

**Spectroscopic Measurements. (a) $^1$H NMR Data for the Pt(II) Complexes.** Since acidic conditions were used for the isolation of **1** and **2** by HPLC, the complexes were obtained with protonated carboxylic acid groups (the p$K_a$ of cysteine is 1.86[27]). The $^1$H NMR data for **1** and **2** in $D_2O$ are summarized in Table 1.

The spectra for both complexes exhibit two sets of peaks in the aliphatic region, indicating the presence of two diastereomers due to the chiral coordinated sulfur, which are slowly interconverting. This is typically observed for Pt(II) complexes of sulfur-containing amino acids.[28,29] From integration of the $^1$H NMR spectra, it follows that the diastereoisomers are present in nearly equal amounts. Two doublets of doublets between 4.7 and 5.0 ppm are observed for the H[α] of **1** and **2** at pH* 1.4, respectively. Upon an increase of the pH* to 3.6, the carboxylic acid function becomes deprotonated, resulting in a concomitant shift of the H[α] signal of ca. 0.3 ppm to higher field. The $C(O)CH_3$ groups exhibit two signals which are nearly unshifted with respect to the signals of the free ligands at 1.98 and 2.02 ppm for py-$CH_2$-accys and py-$C_2H_4$-accys, respectively, from which an amide coordination can be ruled out. Due to the chiral sulfur center, the $CH_2$ groups of the chelate and the two H[$\beta$] protons appear as unresolved peaks close to the signals of H(en) which are shifted to lower field with respect to $[Pt(en)(H_2O)_2]^{2+}$, exhibiting a resonance at 2.5 ppm.

A four-resonance 1:1:1:1 pattern is found in the aromatic region, corresponding well to similar complexes reported in the literature.[30] Due to Pt(II) coordination of pyridine, the resonances of Py[5], Py[4], and Py[3] are shifted to higher field when compared with those of the free ligands (0.19, 0.37, 0.42 ppm (**1**); 0.35, 0.37, 0.79 ppm (**2**)), whereas the Py[6] signal is shifted downfield by 0.07 (**1**) and 0.10 ppm (**2**) with respect to that of the free ligand. Pt(II) coordination of the pyridyl moiety is also indicated by a slight broadening of the Py[6] signal. This is a result of the enhanced chemical shift anisotropy relaxation of the $^{195}$Pt satellites at the high magnetic field strength.[31]

At low pH*, where the carboxylic acid group is protonated, the two diastereoisomers become distinguishable in the aromatic region. Upon a change in the pH* from 3.6 to 1.6, the initial doublet of Py[6] (pH* 3.6) splits into two doublets (pH* 1.6) with $^3J$(CH[6]−CH[5]) of 5.1 and 5.9 Hz, respectively. A small singlet at 3.36 ppm indicates the presence of free $enH_2^{2+}$, which is liberated under these conditions due to the trans-labilizing effect of the coordinated sulfur. This effect has previously been reported for *S*-methylglutathione coordinated to $[Pd(en)]^{2+}$ in acidic solution.[32] When the $^1$H NMR spectra were measured in 95% $H_2O$/5% $D_2O$, the four NH protons of the en ligand and the amide proton were resolved as shown in Table 1.

When the temperature of **2** in acidic solution is raised to 333 K, the two signals for the $CH_3$ groups collapse to give one signal due to fast inversion at the sulfur center. A coalescence temperature of 322 K at 400 MHz with $k_{coal} = 56\ s^{-1}$ was derived. From band shape analysis of spectra recorded between 278 and 333 K, an activation energy $\Delta G^{\ddagger}$ of 68.5 kJ mol$^{-1}$ was calculated for the inversion at the coordinated sulfur, which is well within the range of those for other six-membered Pt(II) chelate complexes.[33]

This contrasts with the behavior of **1**, which does not exhibit coalescence of the $CH_3$ signals at temperatures up to 343 K. This is in accordance with larger activation energies commonly observed for inversion in five-membered chelate rings.[34]

Only one sharp signal is observed for the $CH_3$ groups of the free ligands. We therefore conclude that amide rotation of the S,N-chelated complexes around the C−N bonds is fast on the NMR time scale. The broadening of the $CH_3$ resonances is asssumed to be solely due to sulfur inversion.

A dissociation and recombination process for **2** can also be excluded, since the signals of H[$\beta$] and the $CH_2$ groups are significantly shifted with respect to those of the free ligands. This is further confirmed by $^{195}$Pt spectra and will be discussed in section d.

The p$K_a$ values of the free ligands py-$CH_2$-accys and py-$C_2H_4$-accys were determined by plotting the $^1$H resonances of

(27) Beyer, H.; Walter, W. *Lehrbuch der Organischen Chemie*; S. Hirzel: Stuttgart, Germany, 1988; p 823.
(28) Appleton, T. G.; Connor, J. W.; Hall, J. R. *Inorg. Chem.* **1988**, *27*, 130.
(29) Gummin, D. D.; Ratilla, E. M. A.; Kostic, N. M. *Inorg. Chem.* **1986**, *25*, 2429.
(30) Markies, B. A.; Wijkens, P.; Boersma, J.; Kooijman, H.; Veldman, N.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 3244.
(31) Lallemand, J.-Y.; Soulié, J.; Chottard, J.-C. *J. Chem. Soc., Chem. Commun.* **1980**, 436.
(32) Zhu, L.; Kostic, N. M. *Inorg. Chim. Acta* **1994**, *217*, 21.
(33) Abel, E. W.; Bhargava, S. K.; Orrell, K. G. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; John Wiley: New York, 1984; Vol. 32, p 1.
(34) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1989; Vol. 6, p 268.

**Table 2.** $^{13}$C NMR Chemical Shifts (ppm) of the Complexes **1** and **2** (95% $H_2O$/5% $D_2O$)

| | **(1)** pH* 1.4 | **(2)** pH* 1.3 |
|---|---|---|
| C(O)NH | 175.1 | 173.6 |
| | 174.7 | 173.9 |
| COOH | 177.3 | 171.0 |
| | | 171.6 |
| Py[2] | 164.1 | 157.1 |
| | 164.4 | |
| Py[6] | 154.1 | 151.3 |
| Py[4] | 144.6 | 141.3 |
| Py[3] | 128.3 | 127.1 |
| | | 127.3 |
| Py[5] | 128.9 | 125.1 |
| | | 125.3 |
| C[α] | 54.5 | 50.3 |
| | 53.7 | 50.7 |
| C[en] | 51.7 | 48.1 |
| | 48.9 | |
| C−S | 46.9 | 46.4 |
| C[*β*] | 41.4 | 40.0 |
| | 39.4 | 41.0 |
| C−Py | | 38.7 |
| $CH_3$ | 24.7 | 21.3 |
| | 24.8 | 21.4 |

the aromatic protons versus the pH* as shown in supporting Figure S1. Values of $4.69 \pm 0.01$ and $5.47 \pm 0.01$ were found for py-$CH_2$-accys and py-$C_2H_4$-accys, respectively. These values are in good agreement with those for similar 2-(thiaalkyl)-pyridine compounds.[34]

**(b) $^{13}$C NMR Data for the Pt(II) Complexes.** Table 2 summarizes the $^{13}$C chemical shifts for the Pt(II) complexes **1** and **2**. The $^{13}$C spectra under acidic conditions show two resonances for most carbon atoms due to the presence of the two diastereoisomers. In the low-field region, we assigned two resonances to the C(O) of the *N*-acetyl groups and two resonances to the carboxylic acid groups. The aromatic region exhibits peaks for Py[2] to Py[6], confirming the presence of the diastereoisomeric forms, since they are split into two sets of signals differing by 0.1−0.2 ppm. Two resonances are also observed for C[α] and the C[*β*]. Upon an increase in the pH* to 3.6, deprotonation of the carboxylic acid groups causes the resonances of the C(O)O, C[α], and C[*β*] carbon atoms to be shifted to lower field by about 2 ppm, whereas the other $^{13}$C peaks remain unchanged.

**(c) $^{195}$Pt NMR Data for the Pt(II) Complexes.** The $^{195}$Pt spectrum of **2** exhibits two peaks of nearly identical intensities at −3308 and −3289 ppm representing the two diastereoisomeric forms. For complex **1**, only one resonance at −3177 ppm is detected. These chemical shifts correspond well to those reported for similar compounds with a $PtN_3S$ coordination sphere where the thioether is not bridging between two Pt centers.[35,36]

On recording spectra of **1** at 5 °C and **2** at 55 °C, we observed no significant change in line width and shape. The absence of line broadening in the $^{195}$Pt spectra for **2** can be accounted for as follows. From the separation of the two $^{195}$Pt signals of 19 ppm (1590 Hz) for **2**, a value for $k_{coal}$ of ca. 3500 $s^{-1}$ is calculated.[37] It is evident that coalescence of both signals into one due to fast inversion of the sulfur center must occur at much higher temperatures than accessible in the $^1$H NMR spectra (see part a), since for $k_{coal}$ a value of only 56 $s^{-1}$ at 322 K was found. Thus much higher rates would be needed in order to detect a significant line broadening in the $^{195}$Pt spectra.

A dissociation and recombination processs can be ruled out, since the difference in shift of only 19 ppm between the two $^{195}$Pt signals of **2** is very small with respect to the chemical shift span of 15 000 ppm[38] observed for the $^{195}$Pt nucleus and can therefore not be attributed to a change in the $PtN_3S$ coordination sphere.

However, for **1** only one signal is observed, which is in contrast to the $^1$H NMR data clearly showing the presence of two diastereoisomers. This can only be related to the $^{195}$Pt shifts of **1** exhibiting a much smaller shift difference than those of **2**, making them indistinguishable and leading to a lower coalescence temperature. For **1** though, it is assumed that fast inversion has already been reached in the $^{195}$Pt spectrum.

**(d) $^1$H NMR Data for the Pd(II) Complexes.** Attempts to isolate the Pd(II) complexes [Pd(en)(py-$CH_2$-accys-*S*,*N*)]$(NO_3)_2$ (**3**) and [Pd(en)(py-$C_2H_4$-accys-*S*,*N*)]$(NO_3)_2$ (**4**) failed, since decomposition occurred due to labilization of ethylenediamine. The Pd(II) adducts were generated directly in the NMR tube by reacting equimolar solutions of $[Pd(en)(D_2O)_2]^{2+}$ with py-$CH_2$-accys and py-$C_2H_4$-accys between pH* 1.6 and 3.0. The $^1$H NMR spectra with a metal-to-ligand ratio of 1:1 exhibit chemical shifts similar to those of the purified Pt(II) complexes **1** and **2** (see Table 1). The $CH_2$ resonances of the en ligand shift from 2.63 ppm for $[Pd(en)(D_2O)_2]^{2+}$ to 2.95 ppm for the amino acid complexes **3** and **4**. The chemical shifts of the pyridine resonances for the Pd complexes **3** and **4** and the Pt complexes **1** and **2** are nearly identical as is apparent in Table 1. Small amounts of liberated $enH_2^{2+}$ are observed at 3.36 ppm in the spectra of both complexes.

On reaction of 2 equiv of $[Pd(en)(D_2O)_2]^{2+}$ with 1 equiv of ligand at pH* 1.6, only the formation of 1:1 S,N-chelated complexes and 1 equiv of uncoordinated $[Pd(en)(D_2O)_2]^{2+}$ were observed in the $^1$H NMR spectra. No indication for coordination of the carboxylic acid or the amide groups to the remaining $[Pd(en)(D_2O)_2]^{2+}$ was found for both ligands. Upon an increase in the pH* above 3 to deprotonate the carboxylic acid groups, the spectrum of **3** still shows only resonances for the 1:1 complex and free $[Pd(en)(D_2O)_2]^{2+}$.

The spectra are more complicated when the complex-to-ligand ratio is decreased to 1:2 with $[Pd^{2+}] = 10$ mM, [ligand] = 20 mM, and pH* ≈ 2.0. Here the $^1$H NMR spectra show that **3** and **4** slowly decompose to give free $enH_2^{2+}$ and react further with a second amino acid to give a mixture of *cis*- and *trans*-bis(amino acid) complexes. From a comparison of the relative rates of formation of the bis(amino acid) complexes, obtained from time-dependent $^1$H NMR spectra, it is evident that formation of [Pd(py-$CH_2$-accys)$_2$], completed after ca. 2 h, is ca. 10 times faster than formation of [Pd(py-$C_2H_4$-accys)$_2$], completed after ca. 24 h. These observations are in good agreement with the kinetic observations (under kinetics section c).

In addition to the formation of the 1:2 complexes, side products are also formed to a lesser extent. The spectrum of **3** (1:2 mixture) contains signals indicative of a complex containing a coordinated carboxylic acid group. Hereby the H[α] signal is shifted downfield to 5.30 ppm, and the $CH_3$ group appears as a broad signal at 1.81 ppm. The formation of a tridentate S,N,O-chelate as a side product seems a likely explanation for this observation.

(35) Mitchell, K. A.; Jensen, C. M. *Inorg. Chem.* **1995**, *34*, 4441.
(36) Norman, R. E.; Ranford, J. D.; Sadler, P. J. *Inorg. Chem.* **1992**, *31*, 877.
(37) $k_c = \pi\delta\nu/\sqrt{2}$: Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.
(38) Kidd, R. G. *Annu. Rep. NMR Spectrosc.* **1980**, *10A*, 1.

**(e) IR and Raman Spectra of the Pt(II) Complexes.** The IR spectra of [Pt(en)(py-$CH_2$-accys-*S*,*N*)]$(NO_3)_2$ (**1**) and [Pt(en)(py-$C_2H_4$-accys-*S*,*N*)]$(NO_3)_2$ (**2**) show strong $\nu$(COO) stretching bands at 1732 and 1734 $cm^{-1}$, respectively, due to the uncoordinated protonated carboxylic acid function.[39,40] Bands at 1661 and 1665 $cm^{-1}$ for both complexes were assigned to the $\nu$(C═O) stretching modes of the C(O)$CH_3$ groups. $\delta(NH_2)$ bands at 1541 and 1543 $cm^{-1}$ indicate the presence of coordinated ethylenediamine. Strong $\nu$(N−O) bands in the Raman spectra at 1038 and 1048 $cm^{-1}$ and in the IR spectra from 1300 to 1400 $cm^{-1}$ are assigned to the nitrate counterions.[41] In the Raman spectra, $\nu$(Pt−N) bands are observed at 480−580 $cm^{-1}$ for both complexes.[42] Raman bands at ca. 330 and 334 $cm^{-1}$ for **1** and **2**, respectively, are most probably due to the $\nu$(Pt−S) stretching mode.[44]

**Kinetic Measurements. (a) Reactions of py-$CH_2$-accys and py-$C_2H_4$-accys with an Excess of $[Pt(en)(H_2O)_2]^{2+}$.** At pH 3.00, the complex-formation reactions of py-$CH_2$-accys and py-$C_2H_4$-accys with an excess of $[Pt(en)(H_2O)_2]^{2+}$ are slow enough to be followed by UV−vis spectroscopy. As shown in supporting Figure S2, the reaction with py-$C_2H_4$-accys was accompanied by a decrease in absorbance at 262 nm and an increase at 243 nm with an isosbestic point at 251 nm that is not very clean, since a slow subsequent reaction was observed. For the reaction with py-$CH_2$-accys, spectra were obtained which exhibited three isosbestic points at 281, 267, and 258 nm, with the largest absorbance change at 238 nm.

A single-exponential function can be fitted to the absorbance−time traces obtained from the spectra, which is ascribed to the formation of the S,N-chelated complexes [Pt(en)(py-$CH_2$-accys-*S*,*N*)]$^+$ (**1**) and [Pt(en)(py-$C_2H_4$-accys-*S*,*N*)]$^+$ (**2**) as outlined in reaction 1.

$$\text{nu} + [\text{M(en-}N,N\text{)(H}_2\text{O)}_2]^{2+} \xrightarrow{k_{1M}} [\text{M(en-}N,N\text{)(nu-S)(H}_2\text{O)}]^{2+} + \text{H}_2\text{O} \quad (1a)$$

$$[\text{M(en-}N,N\text{)(nu-S)(H}_2\text{O)}]^{2+} \xrightarrow{\text{fast}} [\text{M(en-}N,N\text{)(nu-}S,N\text{)}]^{+} + \text{H}_3\text{O}^{+} \quad (1b)$$

M = Pt, Pd; nu = py-$CH_2$-accys, py-$C_2H_4$-accys

After coordination of the thioethers, a proton of the ligands, which are mostly present in their zwitterionic forms (Chart 1), is consequently released on or prior to coordination of the pyridyl N.

Following the complex-formation reaction, a slow increase in absorbance was observed, e.g. at the isosbestic points (see supporting Figure S2). This process is very slow with respect to the initial complex-formation reaction, and it is assumed that slow decomposition, initiated by loss of en, takes place. Since the absorbance changes and rate constants ($k_{obs} \approx 10^{-6}$ $s^{-1}$) are very small, this process is neglected for the Pt complexes, but it will be discussed in more detail for the more labile analogous Pd complexes (see part c).

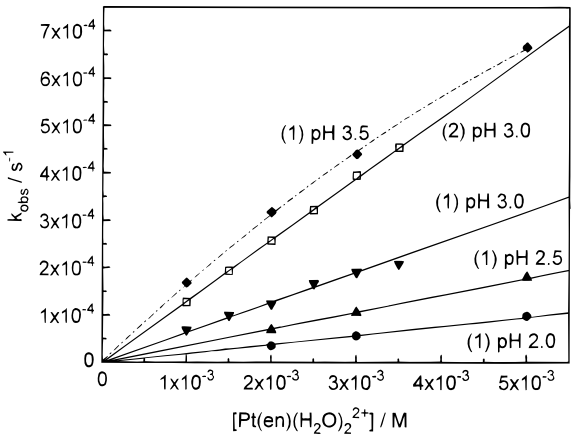



**Figure 1.** Plots of $k_{obs}$ versus $[Pt(en)(H_2O)_2^{2+}]$ for the Reactions with py-$CH_2$-accys (solid points) and py-$C_2H_4$-accys (open points) at different pH values. Experimental conditions: [nu] = $1 \times 10^{-4}$ M, $I$ = 0.1 M, $\lambda$ = 245 nm, $T$ = 25 °C.

**Table 3.** Rate Constants and Activation Parameters for the Reactions of py-$CH_2$-accys and py-$C_2H_4$-accys with Excess $[M(en)(H_2O)_2^{2+}]$[a]

| | | $k_{1Pt}$, $M^{-1}$ $s^{-1}$ | |
|---|---|---|---|
| | | py-$CH_2$-accys | py-$C_2H_4$-accys |
| $[Pt(en)(H_2O)_2]^{2+}$ | pH 2.0 | $(1.92 \pm 0.06) \times 10^{-2}$ | $(4.2 \pm 0.1) \times 10^{-2}$ |
| | pH 2.5 | $(3.56 \pm 0.05) \times 10^{-2}$ | $(7.20 \pm 0.09) \times 10^{-2}$ |
| | pH 3.0 | $(6.38 \pm 0.01) \times 10^{-2}$ | $(1.30 \pm 0.01) \times 10^{-1}$ |

| | | $k_{1Pd}$, $M^{-1}$ $s^{-1}$ | |
|---|---|---|---|
| | | py-$CH_2$-accys | py-$C_2H_4$-accys |
| $[Pd(en)(H_2O)_2]^{2+}$ | pH 3.0 | 2130 ± 11 | 3100 ± 15 |
| $\Delta H^{\ddagger}_{1Pd}$, kJ $mol^{-1}$ | | 47 ± 2 | 37.7 ± 0.2 |
| $\Delta S^{\ddagger}_{1Pd}$, J $K^{-1}$ $mol^{-1}$ | | −26 ± 5 | −53 ± 1 |

[a] M = Pt, $\lambda$ = 245 and 262 nm, respectively; M = Pd, $\lambda$ = 270 nm. [nu] = $0.5 \times 10^{-4}$ and $1.0 \times 10^{-4}$ M for reactions with Pd and Pt, respectively; $I$ = 0.1 M; $T$ = 25 °C.

Linear dependences of $k_{obs}$ on the Pt(II) concentration were obtained for the complex-formation reactions of both ligands as shown in Figure 1. This can be expressed by the rate law[43]

$$k_{obs} = k_{1Pt}[\text{Pt(II)}] \quad (2)$$

at pH ≤ 3.0. The rate constants (Table 3) obtained from the slopes of the plots clearly demonstrate that py-$C_2H_4$-accys is reacting faster than py-$CH_2$-accys by a factor of ca. 2 with $k_{1Pt}$ values of $(1.30 \pm 0.01) \times 10^{-1}$ and $(6.38 \pm 0.01) \times 10^{-2}$ $M^{-1}$ $s^{-1}$, respectively, at 25 °C and pH 3.0. Only one substitution step was observed under all conditions, which is attributed to the coordination of the thioether S to Pt(II), followed by fast ring closure,[44] as outlined in reaction 1. By introduction of the 2+ charged metal complex onto the ligand, the acidity of the pyridyl N is assumed to increase, which will favor deprotonation accompanied by a fast ring-closure reaction. A major contribution from initial coordination of the pyridine N is excluded at pH 3.0 or lower, since it is expected to be mostly protonated ($pK_a$ values for py-$CH_2$-accys and py-$C_2H_4$-accys are 4.69 ± 0.01 and 5.47 ± 0.01, respectively) under these conditions and 2-substituted pyridines are known to react very slowly with Pt(II).[45] This inertness led to the application of 2-substituted pyridines as buffers in kinetic studies of Pt(II) complexes.[46]

(39) Theodorou, V.; Photaki, I.; Hadjiliadis, N.; Gellert, R. W.; Bau, R. *Inorg. Chim. Acta* **1982**, *60*, 1.
(40) Caubet, A.; Moreno, V.; Molins, E.; Miravitlles, C. *J. Inorg. Biochem.* **1992**, *48*, 135.
(41) Weidlein, J.; Müller, U.; Dehnicke, K. *Schwingungsfrequenzen I*; Georg Thieme: Stuttgart, Germany, 1981.
(42) Weidlein, J.; Müller, U.; Dehnicke, K. *Schwingungsfrequenzen II*; Georg Thieme: Stuttgart, Germany, 1986.
(43) Hohmann, H.; Suvachittanont, S.; van Eldik, R. *Inorg. Chim. Acta* **1990**, *177*, 51.
(44) Skibsted, L. H. *Adv. Inorg. Bioinorg. Mech.* **1986**, *4*, 137.
(45) Marzilli, L. G.; Hayden, Y.; Reily, M. D. *Inorg. Chem.* **1986**, *25*, 974.
(46) Arpalahti, J.; Lehikoinen, P. *Inorg. Chem.* **1990**, *29*, 2564.

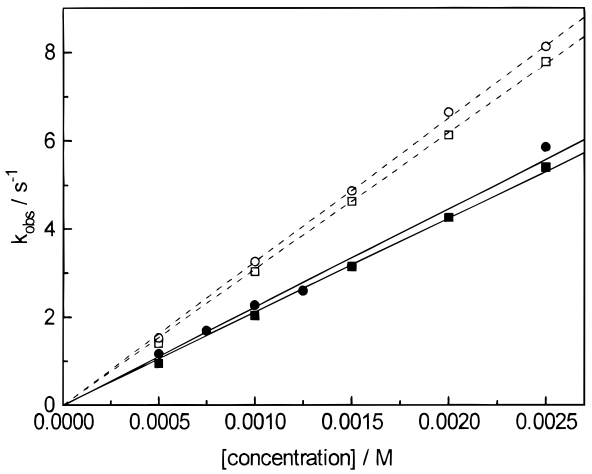



**Figure 2.** Plots of $k_{obs}$ versus concentration for reactions outlined in (1). (a) ■, [Pd(II)] > [py-$CH_2$-accys]; □, [Pd(II)] > [py-$C_2H_4$-accys]. (b) ●, [py-$CH_2$-accys] > [Pd(II)]; ○, [py-$C_2H_4$-accys] > [Pd(II)]. Experimental conditions: [ligand] and [Pd(II)] = $0.5 \times 10^{-4}$ M for (a) and (b), respectively, pH 3.00, $I = 0.1$ M, $\lambda = 270$ and 230 nm for (a) and (b), respectively, $T = 25$ °C.

The rate of the nucleophilic attack of the thioether increases on raising the pH as shown for py-$CH_2$-accys in Figure 1 and Table 3. Deprotonation of the pyridine leads to an increasing negative charge on the ligands, resulting in a higher affinity for the dicationic $[Pt(en)(H_2O)_2]^{2+}$ and correspondingly greater rate constants at higher pH values. The same trend is observed for py-$C_2H_4$-accys.

The experimental pH range is limited by the formation of $\mu$-OH-bridged dimeric Pt(II) complexes at pH $\geq$ 3.5.[47] The p$K_a$ values of $[Pt(en)(H_2O)_2]^{2+}$ are 5.8 for the first and 7.6 for the second deprotonation.[48] Such a dimer formation will reduce the effective concentration of $[Pt(en)(H_2O)_2]^{2+}$, causing the concentration-dependent plot (see Figure 1) to become nonlinear under such conditions. At pH 3.0 or lower, the amount of dimer can be neglected.

**(b) Reactions of py-$CH_2$-accys and py-$C_2H_4$-accys with an Excess of $[Pd(en)(H_2O)_2]^{2+}$.** The complex-formation reactions of py-$CH_2$-accys and py-$C_2H_4$-accys with an excess of $[Pd(en)(H_2O)_2]^{2+}$ were followed on the stopped-flow instrument at 270 nm, where the absorbance change is only due to the decrease in the ligand concentration. Clean isosbestic points were observed at 258 nm as evaluated from Global Analysis measurements, which are in good agreement with the spectra of the Pt complexes (supporting Figure S2). For both ligands, one exponential function could be fitted to the absorbance time traces.

This reaction step is therefore attributed to coordination of the thioethers, since it was observed under all conditions. The calculated $k_{obs}$ values of this step are reproducible within a 5−10% error limit, when one compares measurements at different wavelengths and Global Analysis measurements over all wavelengths. These values are also in good agreement with those obtained from measurements with the ligands present in excess concentrations (see part c, Figure 2, and Tables 3 and 4).

On variation of the complex concentration, linear dependences for both ligands with no significant intercepts were observed as shown in Figure 2, demonstrating the irreversibility of this process. The second-order rate constants, $k_{1Pd}$ (see Table 3), for the reactions were determined to be $2130 \pm 11$ and $3100 \pm 15$ $M^{-1}$ $s^{-1}$ for py-$CH_2$-accys and py-$C_2H_4$-accys, respectively.

**Table 4.** Rate Constants and Activation Parameters for the Reaction of $[Pd(en)(H_2O)_2]^{2+}$ with Excess py-$CH_2$-accys and py-$C_2H_4$-accys[a]

| | py-$CH_2$-accys | py-$C_2H_4$-accys |
|---|---|---|
| $k_{1Pd}$, $M^{-1}$ $s^{-1}$ (substitution) | $2240 \pm 30$ | $3260 \pm 14$<br>$2930 \pm 18$ (310 nm) |
| $\Delta H^{\ddagger}_{1Pd}$, kJ $mol^{-1}$ | $43 \pm 1$ | $41.9 \pm 0.3$ |
| $\Delta S^{\ddagger}_{1Pd}$, J $K^{-1}$ $mol^{-1}$ | $-38 \pm 3$ | $-37 \pm 1$ |

| | py-$CH_2$-accys | | py-$C_2H_4$-accys[b] |
|---|---|---|---|
| pH | $K_2$, $M^{-1}$ | $10^3 k_3$, $s^{-1}$ | $k_3$, $s^{-1}$ |
| 1.00 | $212 \pm 17$ | $0.50 \pm 0.06$ | $(5.7 \pm 0.1) \times 10^{-5}$ |
| 2.00 | $108 \pm 41$ | $1.0 \pm 0.7$ | $(7.0 \pm 0.6) \times 10^{-5}$ |
| 3.00 | $81 \pm 24$ | $1.6 \pm 0.4$ | $(1.0 \pm 0.1) \times 10^{-4}$ |

[a] $[Pd(en)(H_2O)_2 2+] = 0.5 \times 10{-}4$ M; pH 3.00; $I = 0.1$ M; $T = 25$ °C; $\lambda = 230$ nm. [b] $K_2 > 1000$ $M^{-1}$.

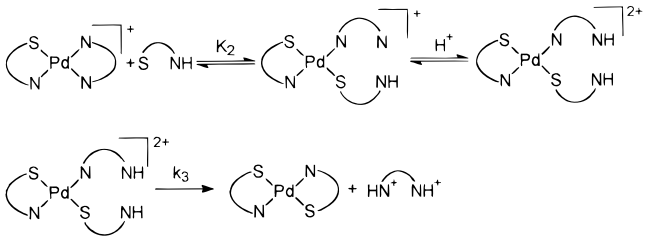
Analyzing the final products by $^1$H NMR spectroscopy showed only the presence of the S,N-chelated complexes **3** and **4** and unreacted $[Pd(en)(H_2O)_2]^{2+}$. By comparison of the reactivities of the metal ions Pd(II) and Pt(II), the following results were obtained. The ratios of the second-order rate constants $k_{1Pd}/k_{1Pt}$ were found to be $3.7 \times 10^4$ and $2.4 \times 10^4$ for py-$CH_2$-accys and py-$C_2H_4$-accys, respectively. These values correspond well to those observed for reactions of other thioethers with tetrachloropalladium and -platinum, whereas for hard donors such as N or O these ratios increase to ca. $10^6$.[49]

Activation parameters (see Table 3) were obtained from Eyring−Polanyi plots. Negative values for the activation entropies for the substitution processes strongly suggest an associative substitution mechanism, which is in line with literature data for Pd(II) complexes.[50] The larger activation enthalpy for py-$CH_2$-accys than for py-$C_2H_4$-accys is in accordance with the higher rate constants of the latter reaction. This must be due to the additional $CH_2$ group inducing more flexibility on the py-$C_2H_4$-accys ligand, thus making it sterically less hindered.

**(c) Reactions of $[Pd(en)(H_2O)_2]^{2+}$ with an Excess of py-$CH_2$-accys and py-$C_2H_4$-accys.** The reactions of $[Pd(en)(H_2O)_2]^{2+}$ with an excess of py-$CH_2$-accys and py-$C_2H_4$-accys under pseudo-first-order conditions, i.e., with the nucleophile concentration being present in at least a 10-fold excess over the complex, were accompanied by two distinct steps (see supporting Figure S3) for which the $k_{obs}$ values differ by orders of magnitude. The first process (supporting Figure S3: a → b) is fast and was followed on the stopped-flow spectrophotometer, whereas the second slow step (supporting Figure S3: b → c) was followed by recording successive UV−vis spectra. From the absorbance−time traces obtained from the stopped-flow measurements, a single-exponential function was resolved. This step ($k_{1Pd}$) is assigned to the substitution reaction of $[Pd(en)(H_2O)_2]^{2+}$ with the nucleophiles, analogous to $k_{1Pd}$ in part b, as outlined in reaction 1a. As mentioned above, the ring-closure reaction is expected to occur too fast to be measured. The rate-determining substitution step $k_{1Pd}$ (reaction a) exhibits a linear dependence on the concentration of the nucleophile with no intercept, indicating that no significant back-reaction occurs

(47) (a) Wimmer, S.; Castan, P.; Wimmer, F. L.; Johnson, N. P. J. *Chem. Soc., Dalton Trans.* **1989**, 403. (b) Lippert, B.; Lock, C. J. L.; Rosenberg, B.; Zvagulis, M. *Inorg. Chem.* **1978**, *17*, 2971.
(48) Lim, M. C.; Martin, R. B. *J. Nucl. Chem.* **1976**, *38*, 1911.
(49) Elmroth, S.; Bugarcic, Z.; Elding, L. I. *Inorg. Chem.* **1992**, *31*, 3551 and references cited herein.
(50) van Eldik, R.; Asano, T.; le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549.

**Scheme 1**



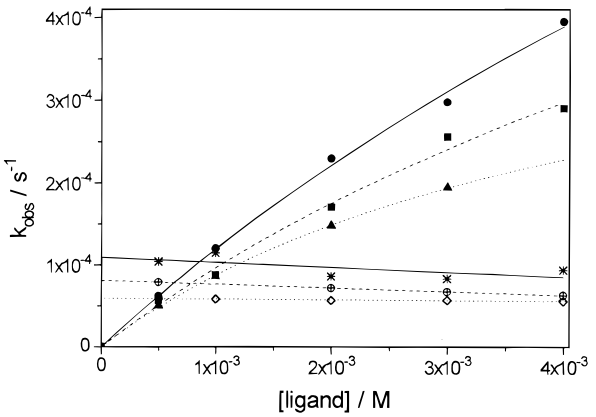



**Figure 3.** Plots of $k_{obs}$ versus [ligand] for the en labilization shown in Scheme 1 for py-$CH_2$- accys (●, ■, ▲) and py-$C_2H_4$-accys (*, ⊕, ◇) at pH 3.0, 2.0, and 1.0, respectively. Experimental conditions: [Pd(II)] = $0.5 \times 10^{-4}$ M, $I = 0.1$ M, $\lambda = 305$ nm, $T = 25$ °C.

as shown in Figure 2. From the slope of the plots, $k_{1Pd}$ values of 2240 ± 30 and 3260 ± 14 $M^{-1}$ $s^{-1}$ were calculated for the reactions of $[Pd(en)(H_2O)_2]^{2+}$ with py-$CH_2$-accys and py-$C_2H_4$-accys, respectively (see Table 4). At 310 nm, $k_{1Pd}$ was calculated to be 2930 ± 18 $M^{-1}$ $s^{-1}$ for the reaction with py-$C_2H_4$-accys. Considering the experimental error, this value is the same as that determined at 230 nm. These values are in the typical range for such substitution processes[51] and in good agreement with those determined for excess Pd complex (section b).

Since the sulfur atom coordinated to palladium has a strong labilizing effect on the ligand in the trans position and the nucleophiles are available in excess, the en ligand is displaced by a second py-$CH_2$-accys or py-$C_2H_4$-accys to give the complexes $[Pd(py\text{-}CH_2\text{-}accys)_2]$ and $[Pd(py\text{-}C_2H_4\text{-}accys)_2]$, respectively, which has already been discussed in the spectroscopic part (section d). This step (Scheme 1) is very slow with respect to the reactions of the diaqua complex. On variation of the ligand concentrations, a linear dependence of $k_{obs}$ reaching saturation at higher concentrations was observed for py-$CH_2$-accys, whereas for py-$C_2H_4$-accys no significant dependence on the concentration was found, as shown in Figure 3. With decreasing pH, i.e., increasing $[H^+]$, both dependences exhibited smaller $k_{obs}$ values.

The data were fitted to the mechanism shown in Scheme 1, which involves the reversible formation of a ring-opened intermediate ($K_2$) followed by ring closure ($k_3$), using rate law 3. The linear concentration dependence observed for py-$CH_2$-accys at low ligand concentrations, reaching saturation at higher concentrations, provides evidence that direct attack of the nucleophile is the main reaction step rather than aquation involving protonation of en. From Table 4 it follows that $K_2$ increases in going to lower pH values, which is in accordance with the stabilization of the ring-opened intermediate via protonation of the free N under these conditions. The rate constant $k_3$ of the ring closure decreases at lower pH, since the reaction is hindered by protonation of the pyridyl N of the ring-opened intermediate. However, rates for the formation of the six-membered chelate complex $[Pd(py\text{-}C_2H_4\text{-}accys)_2]$ were found to be practically independent of [ligand]. With increasing concentration, the difference in the rates between py-$CH_2$-accys and py-$C_2H_4$-accys becomes larger (see Figure 3), which is in good agreement with the $^1H$ NMR investigations (part d). It is assumed that saturation is already reached at low [ligand], where $k_3$ is rate-determining. In this case the preequilibrium constant $K_2$ must be much larger, which is in accordance with the higher rates observed for py-$C_2H_4$-accys in the substitution reactions of the diaqua complexes.

$$k_{obs} = \frac{K_2 k_3 [\text{ligand}]}{1 + K_2[\text{ligand}]} \qquad (3)$$

The difference in the ring-closure reaction ($k_3$) which is ca. 10 times faster for the formation of the five-membered chelate ring $[Pd(py\text{-}CH_2\text{-}accys)_2]$ than for the six-membered chelate ring $[Pd(py\text{-}C_2H_4\text{-}accys)_2]$ is in good agreement with results obtained by Romeo et al. for the ring-closure reactions of ethylenediamine and 1,3-diaminopropane as well as for 2-(aminomethyl)pyridine and 2-(aminoethyl)pyridine, where the same factor was reported.[52] The lower p$K_a$ value observed for py-$CH_2$-accys will also favor a faster ring-closure reaction ($k_3$), since the pyridine will be deprotonated much more easily than for py-$C_2H_4$-accys. The initial nucleophilic attack of the corresponding ligands was not influenced significantly by the chelate size and was reported to take place at comparable rates, which is also in agreement with this study.

At [ligand] ≈ 1 mM and lower, the absorbance−time traces were fitted to only one exponential function as shown in supporting Figure S4. At higher concentrations (≈4 mM), a second reaction step ca. 1 order of magnitude faster was observed that became the major reaction with the larger contribution to the overall absorbance change. This step is probably related to the attack of a second ligand on the ring-opened intermediate, preventing ring closure.

The rate constants for the displacement of en by S nucleophiles correspond well to those reported earlier for the reaction of $[Pd(en)(H_2O)_2]^{2+}$ with *S*-methylglutathione.[33] These rates for en labilization are remarkably slow in comparison to those of the usual substitution reactions of Pd(II) complexes in aqueous solution.

## Conclusions

The newly developed modified amino acids py-$CH_2$-accys and py-$C_2H_4$-accys have been shown to be suitable ligands for designing new complexes of transition metals with square-planar coordination spheres. The S,N-chelation mode of these ligands is of importance, since only the side chain of the amino acid is involved in metal coordination, whereas the amino acid function remains uncoordinated, leaving this functional group accessible for the attachment of other amino acids or peptides. The Pt(en)-derived complexes were isolated and shown to be stable under acidic and neutral conditions. Substitution reactions of the Pd(II) complexes were shown to be 4−5 orders of magnitude faster than those of the corresponding Pt(II) complexes. The

(51) Shi, T.; Elding, L. I. *Inorg. Chem.* **1996**, *35*, 5941.

(52) Romeo, R.; Alibrandi, G.; Arena, G.; Scolaro, L. M.; Plutino, M. R. *Inorg. Chim. Acta* **1995**, *235*, 281.

strong trans labilization induced by the sulfur donor coordinated to Pd(II) results in displacement of the ethylenediamine ligand by other nucleophiles. This process is very slow with respect to the usual substitution reactions of $[Pd(en)(H_2O)_2]^{2+}$, and the rate constants reach magnitudes which are usually found for reactions of Pt aqua complexes. The substitution process reported here was shown to be 7 orders of magnitude slower than the initial substitution of the corresponding diaqua complex. Thus, the reactivity of the complexes $[Pd(en)(py\text{-}CH_2\text{-}accys\text{-}S,N)]^+$ (**3**) and $[Pd(en)(py\text{-}C_2H_4\text{-}accys\text{-}S,N)]^+$ (**4**) was decreased to such an extent that it is in the range of Pt(II) aqua complexes. This may be interesting for the biological activity of **3** and **4**, since Pd(II) complexes are generally known to react too fast to be applied as antitumor agents.[53] A similar decrease in reactivity was achieved previously by increasing the steric hindrance on the amine ligands.[54]

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**Supporting Information Available:** Plots of the $^1H$ chemical shifts of the aromatic protons of py-$CH_2$-accys and py-$C_2H_4$-accys versus pH* (Figure S1), repetitive scan spectra for reaction 1 (Figure S2), repetitive scan spectra for the reaction in Scheme 1 (Figure S3), and a typical absorbance−time trace for the en labilization (Figure S4) (5 pages). Ordering information is given on any current masthead page.

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(53) Gill, D. S. In *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nijhoff Publishing: Boston, MA, 1984; p 267.

(54) Kotowski, M.; van Eldik, R. In *Inorganic High Pressure Chemistry*; van Eldik, R., Ed.; Elsevier Science Publishers: Amsterdam, 1986; p 219.