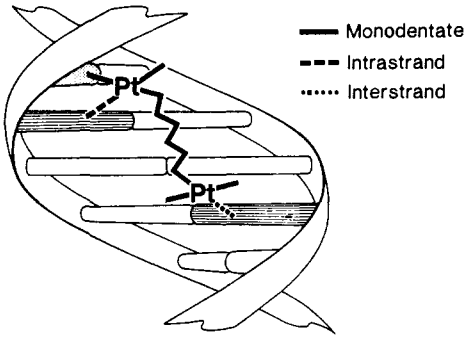

Figure 8. Possible pathways of reaction of 2,2/c,c bis(platinum) complexes with DNA leading to an interstrand (Pt,Pt) or intrastrand cross-link (one Pt only).

to give the limiting tetrafunctional structure. If the second reaction is closing of the intrastrand cross-link, the intermediate species formed now contains one platinum bound in a bidentate manner to a relatively rigid 17-membered dinucleotide chelate.[27] This situation fixes the first platinum coordination sphere, as there is no rotation possible around the platinum-purine bonds. Only rotation around the C-C bonds of the diamine backbone can place the second platinum atom in a favorable position for bonding and thus interstrand cross-link formation.

These considerations may help to explain the relative DNA binding and antitumor activity of the two structurally different sets of bis(platinum) complexes.[2] In 2,2/c,c species, cisplatin-like activity will ensue when intrastrand adducts are formed. The relative degree of other novel adducts ("non-cisplatin") may dictate how different the activity will be in comparison to cisplatin. This difference is thus marked for the 1,1/t,t complex although the presence of a 2+ charged species may not be advantageous in a pharmacological sense because of the expected reduced cellular uptake. We note further that the formation of the interstrand cross-link will also be affected by geometry; the 1,1/t,t complex is only one of three possible isomers for bis(platinum) complexes with monodentate coordination spheres. Current synthetic efforts are aimed at developing routes to the other possible isomers.

Acknowledgment. This work is supported by an American Cancer Society research grant (CH-463). We thank L. E. Erickson and T. G. Appleton for helpful discussions.

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Design of Discriminating Hosts for Noble Metal Ions with Double Functions of Thia and Amide Donors in Macrocyclic Structures

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Abstract: A novel tetradentate, dithia diamide **9** (6,6-dimethyl-5,7-dioxo-1,11-dithia-4,8-diazacyclotetradecane, "dioxo[14]aneN_2S_2") and a pentadentate, trithia diamide macrocyclic ligand **10** (12,12-dimethyl-11,13-dioxo-1,4,7-trithia-10,14-diazacyclohexadecane, "dioxo[16]aneN_2S_3") have been synthesized and their ligand properties examined. They smoothly encapsulate only divalent noble metal ions Pt^{II} (to **17** and **19**, respectively) and Pd^{II} (to **18** and **20**, respectively) but not other typical transition-metal ions, Cu^{II}, Ni^{II}, or Co^{II}. Moreover, **9** and **10** can effectively remove Pt^{II} from *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ to yield Pt^{II}-in complexes **17** and **19**, respectively. Pt^{II} complex **19** possesses a four-coordinated, square-planar geometry with $(N^-)_2S_2$ donors (N^- denotes a deprotonated amide anion), where the central S(4) atom is not coordinated, as shown by the X-ray crystal structure resolved by the heavy-atom method with 2543 unique reflections with $|F_o| > 4\sigma(F_o)$. Final R and R_w were 0.040 and 0.060, respectively: monoclinic, space group $P2_1/c$ with a = 11.753 (6) Å, b = 9.574 (3) Å, and c = 19.183 (9) Å, β = 126.78 (3)°, and V = 1729 (1) Å^3; ρ_c = 2.096 g cm^{-3} for Z = 4, and formula weight 545.62. The cyclic voltammetry of **19** in dimethyl formamide (DMF) displays a 2e$^-$ oxidation at +0.81 V vs SCE ($Pt^{II} \rightarrow Pt^{IV}$) and a 2e$^-$ reduction at +0.32 V ($Pt^{IV} \rightarrow Pt^{II}$), implying that the Pt^{II} state is stabilized by the square-planar $(N^-)_2S_2$ coordination and that the electrochemically oxidized Pt^{IV} state requires additional axial S(4) and DMF donors for stabilization. The two amide anions in Pt^{II}-in complexes **17** and **19** are reversibly protonated to Pt^{II}-out complexes **27** and **28**. Treatment of **28** with an equimolar amount of **10** yields 2:1 macrocycle-Pt^{II} complex **29**. In **9** and **10** discriminating functions are endowed by the combination of the characteristic S donors and amide groups in the macrocyclic skeleton to concertedly work only on Pt^{II} and Pd^{II} ions.

Introduction

We have already introduced the amide-containing macrocyclic polyamines **1**[1-6] and **2**[7-9] as novel ligands having hybrid features of oligopeptides (e.g. triglycine **3**) and polyamines **4** and **5**, respectively. As with triglycine complexes **6**,[10] these macrocyclic ligands interact with several divalent transition-metal ions such

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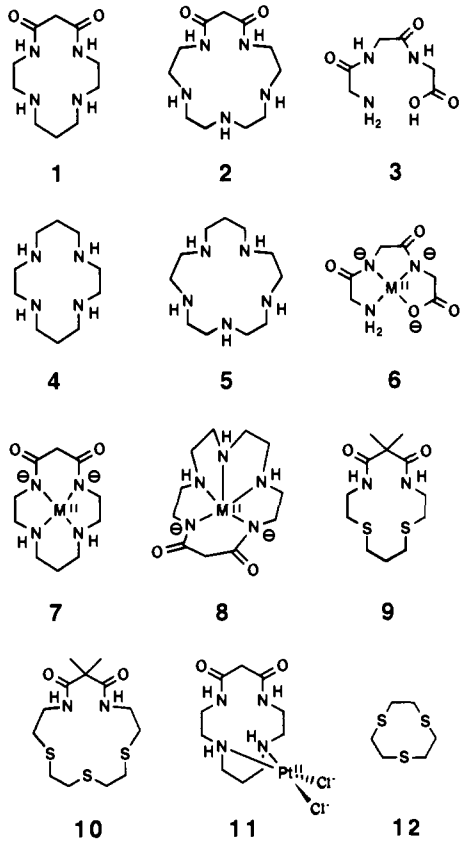
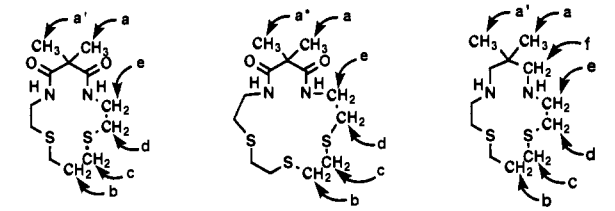
Chart I



as Cu^{II},[1-4] Ni^{II},[3,4,7-9] Co^{II},[5,6] Pd^{II},[11] Pt^{II},[12] etc., with concomitant dissociation of the two amide protons. The ligand fields of the resulting complexes **7** and **8** are analogous to the deprotonated peptides (e.g. **6**) and hence metal ions included behave similarly. For instance, in **6**,[10,13] **7**,[3,4] and **8**,[7-9] Cu^{III} and Ni^{III}, that otherwise are unusual oxidation states, are greatly stabilized. However, the advantage of macrocycles over peptides is that the structures can be easily modified through ring expansion, change in donor atoms, and increase in donor atoms, etc.[11] We have thus synthesized a number of oxo macrocyclic polyamines, which have found very broad and versatile applications. For example, dioxocyclam **1** bearing a lipophilic long alkyl chain is useful as an active transport carrier for Cu^{II}, which is counter-transported with protons,[14] or the square-pyramidal Ni^{II} complex **8** offered the first model for the Ni^{II}-bound O_2 system, whereby benzene was converted into phenol at room temperature.[7-9,15]

Divalent noble metal ions Pd^{II} and Pt^{II} are known to possess somewhat mixed properties of hard and soft acids. Toward peptide ligands (to form square-planar complexes like **6**) their hard acidities are greater than those of Cu^{II} and Ni^{II}, so that Pd^{II} and Pt^{II} can displace the amide protons at lower pH than Cu^{II} or Ni^{II}

Chart II



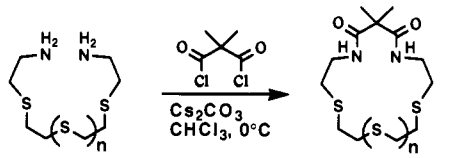
9 **10** **16**

can.[13,16] Toward soft ligands (e.g. sulfur donor) these noble metal ions become soft acids and better fit than Cu^{II} or Ni^{II}.[17] With these basic facts in mind, we have designed a new class of oxo macrocyclic ligands, 6,6-dimethyl-5,7-dioxo-1,11-dithia-4,8-diazacyclotetradecane ("dioxo[14]aneN$_2$S$_2$" **9**) and 12,12-dimethyl-11,13-dioxo-1,4,7-trithia-10,14-diazacyclohexadecane ("dioxo[16]N$_2$S$_3$" **10**). They are composed of a potential hard base donor, amide, and a soft base donor, thiaether group.

We have already reported on isolation of the Pt^{II}-in complex with the 6-methyl derivative of **7**[12] and its X-ray crystal structure, along with its precursor **11**.[18] It was also shown that a lipophilic dioxocyclam can pick up Pt^{II} ion from *cis*-[$Pt^{II}(NH_3)_2Cl_2$] (anticancer drug, cisplatin).[12] With the present sulfur counterparts **9** and **10**, the interest was whether they can better distinguish noble metal ions than the dioxocyclams **1** and **2**, and if so how they accommodate M^{II} ions. Moreover, we were interested in how **9** and **10** in reference to **1** react with *cis*-[$Pt^{II}(NH_3)_2Cl_2$], which would involve a new substitution reaction on Pt^{II}. With dioxo[16]aneN$_2$S$_3$ **10** an additional question was whether the S_3 part can be an independent ligand like [9]aneS$_3$ **12** and how the amide part can participate in the metal interaction. Previously we have communicated preliminary results with **9**.[19] Here we describe a whole account of this new class of macrocyclic ligands with mixed functional donors, thia and amide.

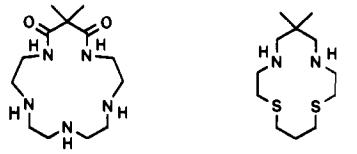
Results and Discussion

Ligand Synthesis. The new ligands **9** and **10** have been synthesized by the reaction of dimethylmalonyl dichloride with 1,9-diamino-3,7-dithianonane (**13**)[20] and 1,13-diamino-4,7,10-trithiadodecane (**14**),[21] respectively, in the presence of 1.7 equiv of Cs_2CO_3 in $CHCl_3$ at 0 °C for 1 h. The reactions were neat,



13: n=0
14: n=1

9: n=0
10: n=1



15 **16**

as shown by an appearance of only the products **9** on TLC (R_f

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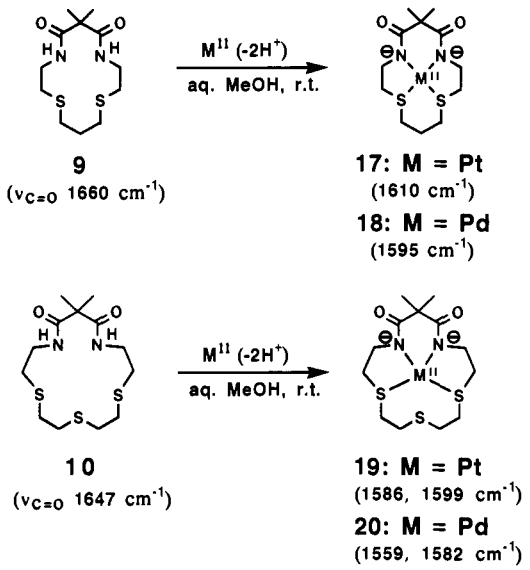
= 0.5; eluent, 20:1 CH_2Cl_2/CH_3OH) and **10** (R_f = 0.6) with simultaneous disappearance of the starting materials (R_f = 0.3; eluent, 5:2:0.1 CH_2Cl_2/CH_3OH/28% NH_3). However, the reactions halted before completion with recovery of the starting materials. Cs^+ ion is essential for the cyclization, as is well-recognized in the synthesis of thiacrown ethers.[22]

In analogous reactions with the non- and monosubstituted malonyl dichlorides, the cyclization did not occur. With the dimethylmalonyl dichloride the steric repulsion between the methyl groups would favorably work for the cyclization. A similar reaction of 1,11-diamino-3,6,9-triazaundecane (tetren) yielded the amine analogue **15**.[23]

To examine the role of the amide groups at chelation, the amide carbonyl groups of **9** were reduced by B_2H_6 in tetrahydrofuran to obtain [14]aneN_2S_2 ligand **16**, which was purified as 2 HCl salts. These new ligands were identified by ^1H NMR, IR (Table I), mass spectra, and elemental analyses.

Selective Inclusion of Pt^{II} and Pd^{II} by 9 and 10. The treatment of **9** and **10** with $K_2Pt^{II}Cl_4$ in aqueous methanol at room temperature for 12 h yielded Pt^{II}-inclusion complexes **17** (yield 86%) and **19** (yield 84%), respectively. The very simple reactions of **9** and **10** with almost quantitative yields of **17** and **19** are quite a contrast to the complex reactions of an amine counterpart **1** with occurrence of Pt^0-black precipitates and the much poorer yield (~10%) of **7** (M = Pt). The complexation of Pd^{II} occurred more quickly (within 1 h) in CH_3CN at room temperature to yield **18** (yield 90%) and **20** (yield 85%), respectively. The amide-de-



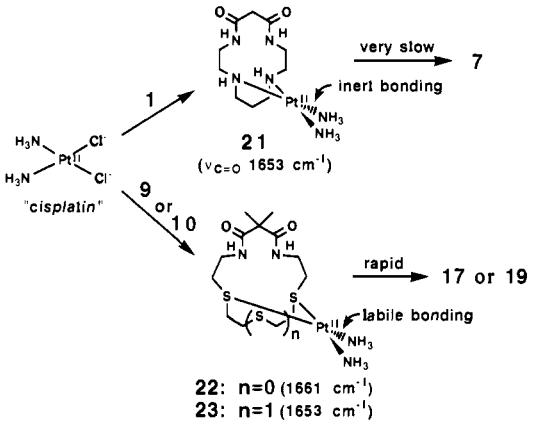
protonated structures were immediately assigned by the decreased $\nu_{C=O}$ (from ~1660 cm^{-1} for the free ligands to ~1600 cm^{-1} for the complexes) and strong charge-transfer bands ($N^- \rightarrow Pt^{II}$) in the UV regions, as previously found for **7** (M = Pt)[12] (see Table I). The square-planar coordination of **19** was established by the following X-ray study.

The most interesting finding with **9** and **10** is that *they are selective for the noble metal ions but do not recognize at all other divalent metal ions Cu^{II}, Ni^{II}, or Co^{II}* in aqueous methanol solution with recovery of the ligands even at elevated temperature to 60 °C or at higher pH (up to 11). On the other hand, the nitrogen counterparts **1** and **2** smoothly and quantitatively accommodate Cu^{II}, Ni^{II}, and Co^{II} to **7** and **8**, respectively, under the same conditions.[1-9]

Among amide-containing macrocycles, such a highly selective recognition of Pt^{II} and Pd^{II} against Cu^{II}, Ni^{II}, and Co^{II} ions has no precedent.[24] This present unique feature should arise from the combined action of the sulfur donors and amide donors lying in the macrocyclic skeleton. At the first step of the reaction, the S_2 chelate donors better accept the softer Pt^{II} and Pd^{II} ions than the harder Cu^{II}, Ni^{II}, or Co^{II} ions.[17] At the second step, the Pt^{II} and Pd^{II} ions of the stronger acids accepted can better remove the amide protons to form M^{II}–N^- bonds than Cu^{II}, Ni^{II}, or Co^{II} ions of the weaker acids.[25] It should be emphasized that the contingent donor function of the amide group (effective only after the thia group coordination) in **9** and **10** is very important for the selective Pt^{II} and Pd^{II} uptake. *An oxo-free N_2S_2 analogue ligand **16**, which lacks such an orderly double function, loses such Pt^{II} and Pd^{II} selectivity* (as described later).

Pt^{II} Uptake from *cis*-[$Pt^{II}(NH_3)_2Cl_2$]. One of our long-range objectives was to design good ligands for the Pt^{II}-uptake from *cis*-[$Pt^{II}(NH_3)_2Cl_2$] ("cisplatin").[26] Previously we found that dioxocyclam **1** removes Pt^{II} from cisplatin at low pH in the presence of $Na_2S_2O_3$.[12]

*The new ligands **9** and **10** have been demonstrated to remove Pt^{II} from cisplatin much more efficiently and rapidly than dioxocyclam **1** does (to **7**) to yield the Pt^{II}-in complexes **17** and **19** without any external additives.* The isolation yields of Pt^{II}-in complexes are 40% for **17**, 38% for **19**, and below 1% for **7** in CH_3OH–HEPES buffer (pH = 7) at a 1:1 ligand/cisplatin ratio and 35 °C for 24 h.



The labile chloride ions in cisplatin are first attacked by the sole available donors (i.e. secondary amines in **1** or thia donors in **9** and **10**) to give intermediates **21–23**, respectively, which were independently isolated and characterized. Of these, an earlier isolated tetraamine complex **21**[19] is inert and hardly proceeds to **7** (M = Pt). In contrast, the Pt^{II}–NH_3 bondings in **22** and **23** should be labilized under the trans effect of the two thia donors. Independent conversions of **22** (or **23**) to **17** (or **19**) occurred in the yields of ~40% at pH = 5 for 24 h, as followed by ^1H NMR, UV absorption, and TLC behaviors. These second reactions are reminiscent of anionic (X) replacement of the labilized NH_3 (under the trans effect of Me_2S) in *cis*-[$Pt^{II}(Me_2S)_2(NH_3)_2]^{2+}$ to give *cis*-[$Pt^{II}(Me_2S)_2(X)_2$].[27]

In overall reactions of **9** and **10** the first steps to **22** and **23** were faster and quantitative. The TLC spots of the free ligands (eluent, 20:1 CH_2Cl_2/CH_3OH, R_f = 0.5 for **9** and 0.6 for **10**) disappeared in 3 h with simultaneous appearance of the intermediates (eluent, CH_3OH; R_f = 0.7 for **22** and 0.8 for **23**). The second processes were much slower when the gradual rupture of the Pt^{II}–S bonds concurrently occurred to recover the free ligands, resulting in the reduced ~40% yields of the final complexes **17** and **19** (eluent, CH_3OH; R_f = 0.3 for **17** and 0.5 for **19**). In these Pt^{II} incor-

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Table I. Comparison of Spectroscopic Data for Ligands and Their Complexes

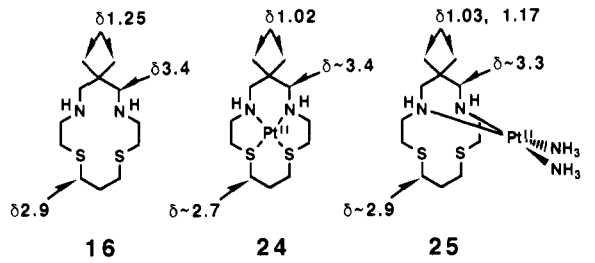
compd	IR (KBr), $\nu_{C=O}$, cm^{-1}	UV[a] λ_{max}, nm (ϵ)	solvent	^{1}H NMR,[b] δ, ppm (splitting pattern, J in Hz)					
				H_a	$H_{a'}$	H_b	H_c	H_d	H_e
				Dioxo[14]aneN_2S_2 Derivative					
9	1660	no peak	CD_3OD	1.44 (s)		1.84 (q, 6.0)	2.70 (t, 6.0)	2.77 (t, 6.0)	3.49 (t, 6.0)
22	1661, 1653	no peak (H_2O)	D_2O[c]	1.47 (s)	1.49 (s)	2.1–2.2 (m)	2.7–2.8 (m)	3.2–3.6[d] (m)	
27	1684	308 (510)	CD_3CN[e]	1.42 (s)	1.43 (s)	2.0–2.1 (m)	2.8–2.9 (m)	3.3–3.6[d] (m)	
17	1610	255 (12500)	CD_3OD	1.37 (s)	1.53 (s)	1.81 (q, 6.0)	2.7–2.8 (m)	3.1–3.2 (m)	3.7–3.8 (m)
18	1595	225 (24500)	CD_3OD	1.32 (s)	1.57 (s)	1.8–1.9 (m)	2.7–2.9 (m)	3.0–3.1 (m)	3.6–3.7 (m)
				Dioxo[16]aneN_2S_3 Derivative					
10	1647	no peak	CD_3OD	1.43 (s)		2.75 (t, 6.0)	~2.8[d] (m)		3.42 (q, 6.0)
23	1653	no peak (H_2O)	D_2O[c]	1.45 (s)		3.0–3.1 (m)	3.1–3.2[d] (m)		3.6–3.7 (m)
28	1653	323 (590)	CD_3CN[e]	1.39 (s)	1.43 (s)	2.9–3.0 (m)	3.1–3.2 (m)	3.4–3.5 (m)	3.6–3.7 (m)
19	1586, 1599	264 (10800)	CD_3OD	1.43 (s)	1.47 (s)	2.7–2.8	3.1–3.2 (m)	3.2–3.4 (m)	3.6–3.7 3.9–4.0 (m)
20	1559, 1582	230 (22900)	CD_3OD	1.47 (s)	1.48 (s)	2.7–2.8 (m)	3.1–3.2 (m)	3.4–3.5 (m)	3.6–3.7 3.8–3.9 (m)
31	1578	249 (15000)	D_2O	1.45 (s)	1.48 (s)	3.56 (q, 4.0)	3.64 (d, 4.0)	3.67 (d, 4.0)	3.7–3.8 (m)
29	1657	301 (520)	CD_3CN	1.35 (s)		2.1–2.2 (m)	3.17 (t, 6.0)	3.27 (m)	3.35 (q, 6.0)
30		421 (130)	CD_3CN	1.38 (s)	1.39 (s)	2.0–2.1 (m)	2.9–3.0 (m)	3.5–3.7[f] (m)	

[14]aneN_2S_2 Derivative

compd	IR (KBr), $\nu_{C=O}$, cm^{-1}	UV[a] λ_{max}, nm (ϵ)	solvent	^{1}H NMR,[b] δ, ppm (splitting pattern, J in Hz)					
				$H_a/H_{a'}$	H_b	H_c	H_d	H_e	H_f
16		no peak (H_2O)	D_2O	1.25 (s)	2.0–2.1 (m)	2.92 (t, 6.0)	3.09 (t, 6.0)	3.37 (s)	3.50 (t, 6.0)
25		no peak (H_2O)	D_2O	1.03 (s) 1.17 (s)	2.0–2.1 (m)	2.9–3.0 (m)	3.1–3.2 (m)	3.2–3.3 (m)	3.4–3.5 (m)
24a		291 (300) (H_2O)	D_2O	1.02 (s)	1.8–2.0 (m)	2.6–2.8 (m)	2.9–3.1 (m)	3.3–3.5 (m)	3.5–3.7 (m)
24b		241 (25000) (H_2O)	D_2O	1.04 (s)	1.8–2.0 (m)	2.6–2.8 (m)	2.9–3.0 (m)	3.2–3.4 (m)	3.4–3.5 (m)

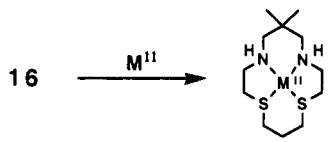
[a] In CH_3OH, except where noted. [b] The position assignments correspond with the structure shown in Chart II. [c] **22** and **23** were not sufficiently soluble in CD_3OD and were stable in D_2O for NMR experiment. [d] Complicated signals were observed in this region. [e] In D_2O or CD_3OD, **27** and **28** were unstable due to the Pt^{II}-out and -in equilibrium.

Chart III



poration processes, the dissociated H^+ (from the amide) may assist the NH_3 dissociation from Pt^{II} ion.

Reactivity of the Oxo-Less [14]aneN_2S_2 Ligand, 16. The saturated N_2S_2 tetradentate ligand **16** reacts with Cu^{II}, Ni^{II}, Pt^{II}, and Pd^{II} ions to give the corresponding metal inclusion complexes **24**. **16** reacts with Cu^{II}, Ni^{II}, and Pd^{II} straight to **24** in almost



quantitative yields (see Experimental Section). However, with $K_2Pt^{II}Cl_4$, a pink Magnus-type salt $[PtL]^{2+}[PtCl_4]^{2-}$ resulted at room temperature in H_2O (pH ~1). Because of insolubility of this salt in any common solvents, no further structural information was available. To obtain the Pt^{II}-inclusion complex **24** (M = Pt, yield ~100%), this salt was treated with an equimolar amount of $SnCl_2$[28] in H_2O (pH ~7) at room temperature for 1 h. The structure of the resulting Pt^{II}-in complex **24** (M = Pt) was established by its ^{1}H NMR spectrum, which was similar to that of Pd^{II}-in complex **24** (M = Pd).

Reaction of **16** with *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ in D_2O (pD ~1) at room temperature for 24 h seemed to produce only tetraamine complex **25** (yield ~60%), as so assigned from comparison of its ^{1}H NMR spectrum with those of **16** and **24** (Table I and Chart III). The reaction did not proceed to Pt^{II}-in complex **24** even at elevated temperatures to 60 °C or at higher pD (up to 9) with $SnCl_2$. This fact best illustrates the critical role of the amides of **9** to make **17** special to *cis*-$[Pt^{II}(NH_3)_2Cl_2]$.

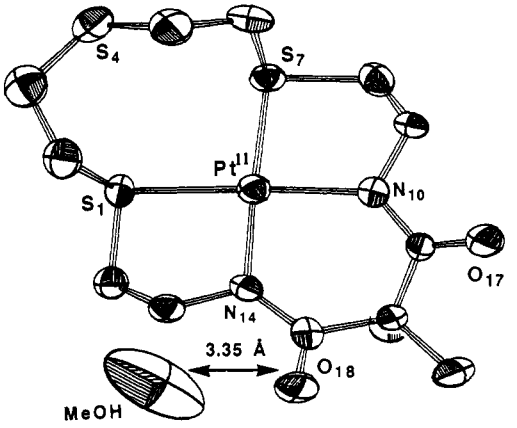


Figure 1. ORTEP drawing of **19**. Atoms are drawn with 50% probability ellipsoids.

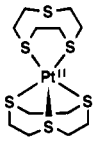
Table II. Bond Distances (Å) and Bond Angles (deg) around the Pt^{II} of **19**

	Bond Distances, Å		
Pt-S(1)	2.298 (2)	Pt-S(7)	2.280 (2)
Pt-N(10)	2.015 (8)	Pt-N(14)	2.022 (8)
	Bond Angles, deg		
S(1)-Pt-S(7)	95.8 (1)	S(1)-Pt-N(10)	177.2 (2)
S(1)-Pt-N(14)	86.2 (2)	S(7)-Pt-N(10)	86.0 (2)
S(7)-Pt-N(14)	177.7 (2)	N(10)-Pt-N(14)	92.0 (3)

(28) McCrindle, R.; Ferguson, G.; McAlees, A. J.; Parvez, M.; Ruhl, B. L.; Stephenson, D. K.; Wieckowski, T. *J. Chem. Soc., Dalton Trans.* **1986**, 2351–2359.

X-ray Crystal Structure of Pt^{II}-In Complex 19. An important question about **10** is whether or not the Pt^{II} (d^8) has a five-coordinate square-pyramidal structure with the central thia donor S(4) in an axial position. This was clarified by the X-ray analysis of **19**. Figure 1 shows that the platinum ion is square-planar with N(10), N(14), S(1), and S(7) donors, but the *S(4) donor is not involved in the coordination.* The selected bond distances and bond angles around Pt^{II} are summarized in Table II.

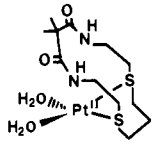
The average distances of S–Pt and N^-–Pt are 2.29 and 2.02 Å, respectively. The comparison of **19** with 6-methyl dioxocyclam Pt^{II}-in complex **7**[18] (where NH–Pt = 2.05 Å and N^-–Pt = 1.98 Å) seems to disclose the "trans effect" of the two sulfur donors that makes the N^-–Pt bond distance of **19** longer than that of **7**. The S–Pt bond lengths in **19** are close to those (2.25–2.30 Å) of $Pt^{II}([9]aneS_3)_2^{2+}$ **26**, where Pt^{II} is five-coordinated.[29]



26

Moreover, 0.5 CH_3OH molecule provides a weak hydrogen bond (3.354 Å) with the carbonyl oxygen O(18) but does not interact with Pt^{II}. The distances of two carbonyl C=O bonds are the same (1.22 Å), but the bond angles are different [O(18)–C(13)–C(12) = 119.3° and O(17)–C(11)–C(12) = 120.5°]. These different environments of the two carbonyl groups may be reflected on the two $\nu_{C=O}$ of 1586 and 1599 cm^{-1}.

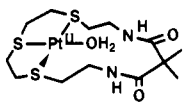
Pt^{II}-In (17 and 19) and Pt^{II}-Out Complexes (27 and 28). With dioxocyclam **1** Pt^{II}-in complex **7** ($\nu_{C=O}$ 1596 cm^{-1}) was formed via Pt^{II}-out complex **11** ($\nu_{C=O}$ 1660 cm^{-1}), both of which were isolated and characterized by X-ray analysis.[18] The Pt^{II}-in complexes with the present sulfur analogues **17** ($\nu_{C=O}$ 1610 cm^{-1}) and **19** ($\nu_{C=O}$ 1586, 1599 cm^{-1}), just as **7**, are stable in aqueous solution at pH >1. However, in 1 M $HClO_4$ aqueous solution, protonation to the imide nitrogens occurs to generate crystalline Pt^{II}-out complexes **27** ($\nu_{C=O}$ 1684 cm^{-1}) and **28** ($\nu_{C=O}$ 1653 cm^{-1}) as perchlorate salts, respectively. Under the same conditions, **7** (M = Pt) was dissociated to free ligand **1** and Pt^{II} ion. These Pt^{II}-out complexes are the intermediate products in the reaction of $K_2Pt^{II}Cl_4$ with the ligands, as was described.



27
($\nu_{C=O}$ 1684 cm^{-1})

pH = 9 ⇌ 1M $HClO_4$

17
(1610 cm^{-1})



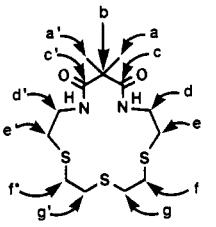
28
($\nu_{C=O}$ 1653 cm^{-1})

pH = 9 ⇌ 1M $HClO_4$

19
(1586, 1599 cm^{-1})

The Pt^{II}-out structures were also characterized by elemental analyses and IR and UV spectra. The ^1H and ^{13}C NMR spectra of **28** suggest a four-coordinate, (most likely) square-planar structure composed of S_3 and H_2O coordinations. The facts that signals of the methylene protons and carbons next to three S donors showed low-field shifts, as in Tables I and III, are strong evidence for the S_3–Pt^{II}-type structure of **28** (Cf. no shift with those around the uncoordinating S(4) of **19**). The Pt^{II}-out complexes **27** and **28** immediately returned to the starting Pt^{II}-in complexes **17** and **19** at pH = 9, which were monitored by the UV spectral changes (308 nm for **27** → 255 nm for **17**, 323 nm for **28** → 264 nm for **19**) and the TLC behaviors. These Pt^{II}-in and -out equilibria could be repeated without any degradation.

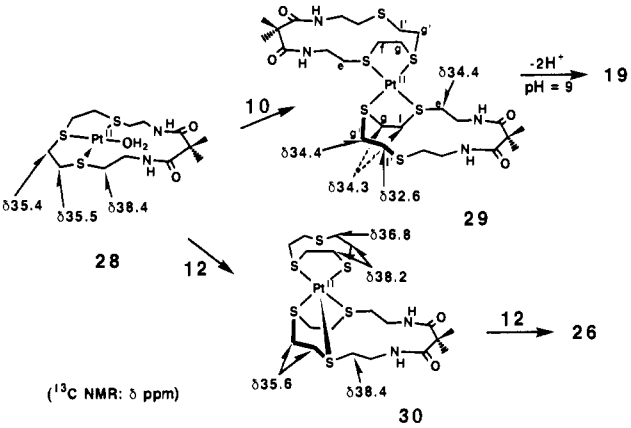
Table III. Comparison of ^{13}C NMR Chemical Shifts for **10** and Complexes



compd	^{13}C NMR,[a] δ, ppm						
	$C_a/C_{a'}$	C_b	$C_c/C_{c'}$	$C_d/C_{d'}$	$C_e/C_{e'}$	$C_f/C_{f'}$	$C_g/C_{g'}$
10: ligand (L)	24.0	50.5	174.6	40.0	33.1	32.4	32.2
19: Pt^{II}-in	27.1 29.1	52.8	180.5	51.9	39.2	38.4	30.8
28: Pt^{II}-out	22.0 26.8	50.4	175.7	38.6	38.4	35.5	35.4
29: $Pt^{II}(L)_2$	24.0	50.6	174.6	39.6 39.5	32.6 34.4	32.6 34.3	34.3 34.4
30: $Pt^{II}(L)(L')$[b]	21.9 26.9	50.6	176.1	38.7	38.4	35.6	35.6

[a] In CD_3CN. The position assignments correspond with the above structure. [b] L' = $[9]aneS_3$.

Scheme I



The present ligands **9** and **10** react with $K_2Pt^{II}Cl_4$ in CH_3OH–20% H_2O (v/v) in two consecutive steps, which were confirmed by using isolated intermediates, **27** and **28** (see Experimental Section). The first step yields Pt^{II}-out complexes **27** or **28**, and the second step yields Pt^{II}-in complexes **17** or **19**. The second-order rate constants k_1 for the initial steps (**9** to **27** and **10** to **28**) at pH = 3 and 35 °C in aqueous methanol were 0.78 ± 0.02 and 3.22 ± 0.02 M^{-1} s^{-1}, respectively. The pseudo-first-order rate constants k_2 for the following intramolecular reactions (**27** to **17** and **28** to **19**) at pH = 9 and 35 °C in aqueous methanol were 10.0 ± 0.2 × 10^{-3} and 7.8 ± 0.2 × 10^{-3} s^{-1}, respectively. These observations would reflect the participation of more sulfur donors in **10** for the initial uptake of Pt^{II} ion as well as the necessity of the Pt–S(4) bond cleavage in the process **10** to **28**. The direct comparison between the first and second reaction rates was difficult. The qualitative TLC observations for the thorough processes at pH = 9 and room temperature showed that the first steps were much slower and rate limiting.

In contrast, the thorough reactions of the amine counterparts **1** and **2** with $K_2Pt^{II}Cl_4$ under the same conditions seemed much slower and complex with other side reactions resulting in Pt^0-black precipitation. Complicated spectrophotometric changes were continuing even after 24 h. Hence, we gave up the detailed kinetic

(29) Blake, A. J.; Gould, R. O.; Holder, A. J.; Hyde, T. I.; Lavery, A. J.; Odulate, M. O.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1987**, 118–120.

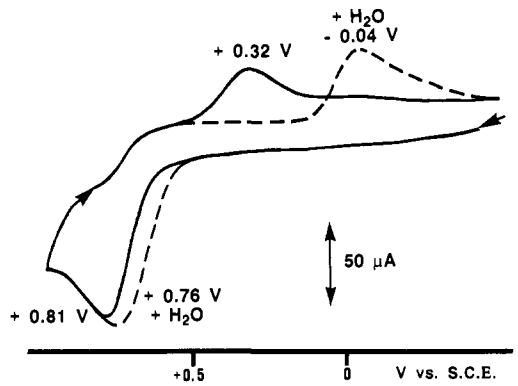


Figure 2. Cyclic voltammograms of the Pt^{II} complex **19** in DMF, 25 °C, and I = 0.1 (Et_4NClO_4): in the absence (solid line) and presence (broken line) of 2% H_2O (v/v).

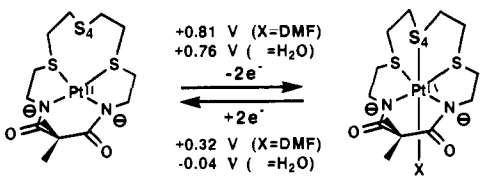
comparison of the reactions of the thia and amine ligand.

2:1 Macrocycle–Pt^{II} Complexes. Treatment of Pt^{II}-out complex **28** with **10** in CH_3OH at room temperature for 24 h gave a $Pt^{II}(\mathbf{10})_2$ complex, **29** (Scheme I). Its 2:1 stoichiometry was established by elemental analysis. The ^1H and ^{13}C NMR spectra of **29** suggest a four-coordinated, square-planar structure composed of an identical S_2 coordination from each ligand, where the significant low-field shifts were observed for both ^1H and ^{13}C peaks assignable to methylene moieties next to Pt^{II}-coordinated sulfur atoms, as depicted (Tables I and III). A square-planar structure with S_4 out of S_6 donors was reported for Pt^{II}([18]aneS$_6$).[30] While a similar sandwich-type complex of Pt^{II}([9]aneS$_3$)$_2$ **26** met with the stereochemical and electronic requirements for ready generation of d^7 Pt^{III} ($E_{1/2}$ = +0.39 V vs Fc/Fc$^+$),[29] our 2:1 complex of **29** has more difficulty generating Pt^{III}, as is so concluded from the absence of the corresponding redox waves in cyclic voltammograms in any solvents tested. Upon dissolution in alkaline solution, **29** (λ_{max} = 301 nm, ϵ 520) immediately turned to the Pt^{II}-in complex **19** (λ_{max} = 264 nm, ϵ 10 800) as a more stable form, accompanied by release of free ligand **10**, which was monitored by the UV spectral changes and TLC behaviors.

The reaction of the Pt^{II}-out complex **28** with equivalent [9]aneS$_3$ **12** analogously gave a mixed-ligand complex **30** in situ, as proved by ^1H and ^{13}C NMR and TLC behaviors [eluent, 1:1 10% NaCl/CH_3OH; R_f = 0.3 for **26**, 0.4 for **30** (main spot), and 0.5 for **29**]. Addition of [9]aneS$_3$ **12** to **29** gave both **30** and **26**, which were finally converged to **26**. These results show that Pt^{II}-([9]aneS$_3$)$_2$ **26** is thermodynamically more stable than **29** and **30**.

Electrochemistry of Pt^{II} Complexes. The cyclic voltammogram of **19** in CH_3CN as a solvent did not give any redox waves. However, in DMF it showed a 2e$^-$ oxidation at +0.81 V to Pt^{IV} and a 2e$^-$ reduction at +0.32 V to regenerate Pt^{II} (see Figure 2). The peak potential of the reduction process ($Pt^{IV} \rightarrow Pt^{II}$) varied significantly in the presence of 2% H_2O (v/v) to −0.04 V. By the controlled potential coulometry at +0.90 V, the Pt^{II} complex underwent a 2e$^-$ oxidation. The results are well-interpreted that $(N^-)_2S_2$ square-planar Pt^{II} **19** is electrochemically coupled with $(N^-)_2S_2$·X (X = DMF or H_2O) octahedral Pt^{IV} **31** that involves a rapid structural exchange. CH_3CN is a weaker donor and could not stabilize Pt^{IV} as DMF and H_2O can. In the absence of an extra S donor, Pt^{II} complex **17** did not yield Pt^{IV} electrochemically at all.

Finally, isolation of Pt^{IV} complex **31** was attempted. Addition of Br_2[31] to Pt^{II} complex **19** ($\nu_{C=O}$ 1586, 1599 cm^{-1}) yielded an oxidation–addition product **31** as orange prisms (X = Br, $\nu_{C=O}$ 1578 cm^{-1}). The convincing evidence that **31** has the axial sulfur donor S(4) came from its ^1H NMR spectrum. Chemical shifts



19 **31**

for the four methylene protons next to the S(4) atom of **31** (δ, 3.56 ppm in D_2O) moved to lower magnetic field, and the splitting pattern changed from singlet to quartet (J = 4 Hz). (cf. for **19**: s, δ 2.51 ppm in D_2O). The cyclic voltammogram of **31** in DMF is the same as that of **19**.

Conclusion

The newly synthesized macrocyclic ligands containing thia and amide donors, **9** and **10**, are Pt^{II} and Pd^{II} selective. Among amide-containing macrocycles, such a clear-cut recognition of Pt^{II} and Pd^{II} against Cu^{II}, Ni^{II}, and Co^{II} ions had been unknown. These new ligands efficiently take Pt^{II} from *cis*-[$Pt^{II}(NH_3)_2Cl_2$]. These functions are endowed by the cooperative function of each characteristic property of thia and amide donors. On the other hand, oxo-free N_2S_2 ligand **16** takes Cu^{II}, Ni^{II}, Pt^{II}, and Pd^{II} and cannot remove Pt^{II} from *cis*-[$Pt^{II}(NH_3)_2Cl_2$]. Moreover, **10** yields Pt^{II} complexes with various modes of coordination as summarized in Scheme I. The most stable form is doubly deprotonated, $(N^-)_2S_2$ complex **19**, whose square-planar structure is determined by X-ray crystal study. The concept of the present macrocyclic ligands tactically placing mixed donor functions would be quite useful in designing discriminating host molecules for acidic metal ions. These molecules work efficiently in recognizing the guest nobel metal ions such as Pt^{II} and Pd^{II}, and their various functions can be controlled by simply changing the medium pH.

Experimental Section

General Methods. All commercially available chemicals were of analytical reagent grade and were used without further purification. ^1H and ^{13}C NMR spectra were obtained on a JEOL GX-400 spectrometer (400 MHz, 35 °C, tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as reference). IR and UV spectra were recorded on a Shimadzu FTIR-4200 and a Hitachi U-3200 spectrophotometer, respectively. Mass spectra were obtained on JEOL JMS-SX102 and JMS-01SG-2 instruments. Flash and thin-layer chromatography (TLC) were carried out on Wakogel C-300 (silica gel) and Merck Art. 5554 TLC plates (silica gel 60 F_{254}), respectively.

Synthesis of 6,6-Dimethyl-5,7-dioxo-1,11-dithia-4,8-diazacyclotetradecane (9) and 12,12-Dimethyl-11,13-dioxo-1,4,7-trithia-10,14-diazacyclohexadecane (10). The new ligands **9** and **10** were synthesized by the reaction of dimethylmalonyl dichloride (170 mg, 1.0 mmol) with 1,9-diamino-3,7-dithianonane (**13**)[20] (200 mg, 1.0 mmol) and 1,13-diamino-4,7,10-trithiadodecane (**14**)[21] (240 mg, 1.0 mmol), respectively, in the presence of Cs_2CO_3 (550 mg, 1.7 mmol) in 100 mL of dry $CHCl_3$ at 0 °C for 1 h. The reaction mixtures were filtrated to remove Cs_2CO_3 and CsCl and the filtrate was washed with H_2O (50 mL × 3), from which the unreacted linear amino thioethers were recovered. The $CHCl_3$ layers were further washed with NaCl-saturated aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. Flash chromatography on silica gel column (eluent, 20:1 CH_2Cl_2/CH_3OH) afforded **9** and **10** as colorless crystals, after recrystallization from CH_3CN. TLC (eluent, 20:1 CH_2Cl_2/CH_3OH) R_f = 0.5 for **9** and 0.6 for **10**. For **9**: colorless prisms; yield 27%; mp 130.0–130.5 °C; m/z 290 (M^+). Anal. Calcd (Found) for $C_{12}H_{22}N_2S_2O_2$: C, 49.62 (49.64); H, 7.63 (7.78); N, 9.65 (9.70). For **10**: colorless needles; yield 42%; mp 180.0–181.0 °C; m/z 337 (M^+). Anal. Calcd (Found) for $C_{13}H_{24}N_2S_3O_2$: C, 46.40 (46.50); H, 7.19 (7.25); N, 8.33 (8.32). IR, UV, and ^1H NMR spectroscopic data are summarized in Table I.

Synthesis of 6,6-Dimethyl-1,11-dithia-4,8-diazacyclotetradecane (16). A 1 M solution of BH_3·THF (20 mL, 20 mmol) was added dropwise to a solution of **9** (290 mg, 1.0 mmol) in 50 mL of THF at 0 °C. The reaction mixture was stirred for 1 h at room temperature and was allowed to warm to 65 °C for 24 h. Unreacted borane was decomposed by the addition of 5 mL of H_2O and then 10 mL of 4 N HCl. The resulting solution was warmed at 60 °C for 1 h, concentrated under a reduced pressure, and, after cooling, treated with 40 mL of 2 N NaOH to raise the pH to 13. The product was extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with NaCl-saturated

(30) Blake, A. J.; Gould, R. O.; Lavery, A. J.; Schröder, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274–276.
(31) Chassot, L.; Müller, E.; Zelewsky, A. *Inorg. Chem.* **1984**, *23*, 4249–4253.
(32) Appleton, T. G.; Berry, R. D.; Davis, C. A.; Hall, J. R.; Kimlin, H. A. *Inorg. Chem.* **1984**, *23*, 3514–3521.

aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. Recrystallization from 6 N 1:1 HCl/EtOH afforded the 2 HCl salts of **16** (260 mg, yield 76%) as colorless prisms: TLC (eluent, 5:2:0.1 $CH_2Cl_2/CH_3OH/28\%NH_3$) $R_f = 0.5$. Anal. Calcd (Found) for $C_{12}H_{26}N_2S_2 \cdot 2HCl \cdot 2H_2O$: C, 38.80 (38.92); H, 8.68 (8.48); N, 7.54 (7.59).

Preparation of Pt^{II}-In Complexes 17 and 19. A solution of K_2CO_3 (190 mg, 1.4 mmol) in 10 mL of H_2O was added dropwise to a solution of **9** (410 mg, 1.4 mmol) and $K_2Pt^{II}Cl_4$ (580 mg, 1.4 mmol) in 120 mL of 5:1 CH_3OH/H_2O and the reaction mixture was stirred at room temperature for 12 h. After concentration under a reduced pressure, the residue was purified by silica gel column chromatography (eluent, 10:1 CH_2Cl_2/CH_3OH) to obtain **17** (580 mg, yield 86%) as colorless needles, followed by recrystallization from H_2O/CH_3CN; TLC (eluent, CH_3OH) $R_f = 0.3$. Anal. Calcd (Found) for $C_{12}H_{20}N_2S_2O_2Pt \cdot H_2O$: C, 28.74 (28.55); H, 4.42 (4.37); N, 5.59 (5.52). **19**: A solution of K_2CO_3 (69 mg, 0.5 mmol) in 5 mL of H_2O was added dropwise to a solution of **10** (170 mg, 0.5 mmol) and $K_2Pt^{II}Cl_4$ (210 mg, 0.5 mmol) in 50 mL of CH_3CN/H_2O (1:1), and the reaction mixture was stirred at 50 °C for 1 h. After concentration, the residue was purified by silica gel column chromatography (eluent, 10:1 CH_2Cl_2/CH_3OH) to obtain **19** (220 mg, yield 84%) as colorless prisms after recrystallization from CH_3CN; TLC (eluent, CH_3OH) $R_f = 0.5$. Anal. Calcd (Found) for $C_{13}H_{22}N_2S_3O_2Pt$: C, 29.48 (29.46); H, 4.19 (4.08); N, 5.29 (5.27). A single crystal suitable for X-ray analysis was obtained by recrystallization from CH_3OH.

Preparation of Pd^{II}-In Complexes 18 and 20. A solution of **9** (290 mg, 1.0 mmol) or **10** (340 mg, 1.0 mmol) in 100 mL of CH_3CN was mixed with $Pd^{II}(CH_3CO_2)_2$ (220 mg, 1.0 mmol), which was stirred at room temperature for 1 h. After concentration to 10 mL, the Pd^{II}-in complex precipitated was collected and dried in vacuo. Recrystallization from aqueous CH_3CN solution afforded **18** (360 mg, yield 90%) or **20** (380 mg, yield 85%) as yellow needles; TLC (eluent, CH_3OH) $R_f = 0.3$ for **18** and 0.5 for **20**. **18**: Anal. Calcd (Found) for $C_{12}H_{20}N_2S_2O_2Pd \cdot H_2O$: C, 34.91 (35.16); H, 5.37 (5.50); N, 6.79 (6.94). **20**: Anal. Calcd (Found) for $C_{13}H_{22}N_2S_3O_2Pd$: C, 35.41 (35.37); H, 5.03 (4.78); N, 6.35 (6.43).

Reaction of 9 and 10 with *cis*-$[Pt^{II}(NH_3)_2Cl_2]$. A solution of **9** (29 mg, 0.1 mmol) or **10** (34 mg, 0.1 mmol) in 10 mL of CH_3OH was treated with *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ (30 mg, 0.1 mmol) in 10 mL of HEPES [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid] buffer (pH = 7), and the mixtures were stirred at room temperature for 24 h. The reactions were followed by TLC, which disclosed the formation of **17** or **19**. After concentration, the residues were subjected to short-column chromatography (silica gel; eluent, 10:1 CH_2Cl_2/CH_3OH) to obtain **17** (19 mg, yield 40%) or **19** (20 mg, yield 38%). These Pt^{II} complexes were identified by TLC and IR, and ^1H NMR spectroscopy. During these reactions *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ was partially hydrolyzed to give stable hydroxo complexes $[Pt^{II}(NH_3)_2(\mu\text{-}OH)]_n^{n+}$ ($n = 2, 3$),[32] which failed to react with **9** or **10**.

Isolation of *cis*-$[Pt(L)^{II}(NH_3)_2](ClO_4)_2$ (L = 9 and 10), 22 and 23. **22** and **23** were prepared by a modified procedure of Tobe et al.[27] *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ (26 mg, 0.086 mmol) was suspended in 6 mL of CH_3OH. Silver perchlorate (36 mg, 0.17 mmol) was added and the mixture was stirred at room temperature for 24 h. The precipitated AgCl was filtered off and to the filtrate was added ligand **9** (25 mg, 0.086 mmol) or **10** (29 mg, 0.086 mmol). After 1 h the pink product **22** (60 mg, yield = 97%) or **23** (47 mg, yield = 90%) was precipitated by addition of Et_2O and dried in vacuo. **22**: TLC (eluent, CH_3OH) $R_f = 0.7$. Anal. Calcd (Found) for $C_{12}H_{22}N_2S_2O_2 \cdot Pt(NH_3)_2(ClO_4)_2$: C, 20.06 (19.68); H, 3.93 (3.59); N, 7.80 (7.61). **23**: TLC (eluent, CH_3OH) $R_f = 0.8$. Anal. Calcd (Found) for $C_{13}H_{24}N_2S_3O_2 \cdot Pt(NH_3)_2(ClO_4)_2$: C, 20.42 (20.03); H, 3.95 (3.85); N, 7.33 (7.09).

The reaction of *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ with **9** or **10** also produced **22** and **23**, respectively, which was detected by TLC and ^1H NMR spectroscopy, but these intermediates were not crystallized.

Preparation of the Saturated N_2S_2 Complexes, 24. Cu^{II} and Ni^{II}: A solution of K_2CO_3 (21 mg, 0.15 mmol) in 1 mL of H_2O was added dropwise to a solution of **16**·2HCl (50 mg, 0.15 mmol) and $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ (56 mg, 0.15 mmol) or $Ni^{II}(ClO_4)_2 \cdot 6H_2O$ (55 mg, 0.15 mmol) in 10 mL of H_2O at room temperature, and partial removal of the solution in a desiccator for 2 days afforded Cu^{II} complex **24** (35 mg, yield 43%) as blue prisms. Anal. Calcd (Found) for $C_{12}H_{26}N_2S_2Cu(ClO_4)_2 \cdot H_2O$: C, 26.55 (26.70); H, 5.20 (4.88); N, 5.16 (5.22). However, pure Ni^{II} complex was a red oil. TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.3$ for both complexes. UV–vis (H_2O): for Cu^{II} $\lambda_{max} =$ 328 nm (ϵ 6600) and 534 nm (ϵ 470), for Ni^{II} $\lambda_{max} = 269$ nm (ϵ 130).

Pd^{II}: Ion exchange chromatography (weak cation resin, Amberlite IRA-400) of **16**·2HCl afforded free ligand **16** quantitatively. A solution of **16** (18 mg, 0.067 mmol) in 5 mL of CH_2Cl_2 was added to a solution of $Pd^{II}Cl_2$ (12 mg, 0.067 mmol) in 5 mL of CH_3CN at room temperature. The reaction mixture was warmed at 60 °C for 2 h. After the mixture was cooled the dark brown precipitate (Pd^0 black) was filtered off and the filtrate was concentrated to 1 mL. Orange precipitate was collected and dried in vacuo. Anal. Calcd (Found) for $C_{12}H_{26}N_2S_2PdCl_2 \cdot H_2O$: C, 31.48 (31.27); H, 6.16 (6.08); N, 6.12 (5.90). TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.3$.

Pt^{II}: Pt^{II}-in complex **24** was prepared by a modified procedure of McCrindle et al.[28] A solution of K_2CO_3 (14 mg, 0.1 mmol) in 1 mL of H_2O was added dropwise to a solution of **16**·2HCl (34 mg, 0.1 mmol) and $K_2Pt^{II}Cl_4$ (42 mg, 0.1 mmol) in 10 mL of H_2O, and the reaction mixture (pH ~5) was stirred at room temperature for 1 h. Insoluble pink $[Pt^{II}L][Pt^{II}Cl_4]$ (L = **15**) ("Magnus-type salts") formed and was collected and dried in vacuo (40 mg, yield 98%). Anal. Calcd (Found) for $C_{12}H_{26}N_2S_2Pt \cdot PtCl_4 \cdot H_2O$: C, 17.74 (17.78); H, 3.47 (3.45); N, 3.45 (3.45). The reaction of the Magnus-type salts (40 mg, 0.1 mmol) with $Sn^{II}Cl_2 \cdot 2H_2O$ (12 mg, 0.05 mmol) in H_2O (pH ~7) for 1 h quantitatively afforded Pt^{II}-inclusion complex **24**, which was estimated by ^1H NMR spectroscopy. However, purification of **24** produced only colorless oil. TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.3$.

Reaction of 16 with *cis*-$[Pt^{II}(NH_3)_2Cl_2]$. The reaction of **16**·2HCl (3.0 mg, 0.9 mmol) with *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ (2.7 mg, 0.9 mmol) in 1 mL of 0.1 N DCl/D_2O (pD ~1) was followed by ^1H NMR spectroscopy. The overlapping dimethyl protons of **16** (δ 1.25 ppm) began to separate after 2 h, and the separation was completed after 24 h (δ 1.03 and 1.17 ppm). From the ratio of the signal intensities, the yield of **25** was estimated to be 60%. TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.5$. However, purification of **25** produced only colorless oil. **25** did not change to Pt^{II}-in complex **24** even with warming to 60 °C and addition of $SnCl_2$ or NaOD to pD ~9.

Isolation of Pt^{II}-Out Complexes 27 and 28. Pt^{II}-in complex **17** (48 mg, 0.1 mmol) or **19** (53 mg, 0.1 mmol) was dissolved in 10 mL of 1 N 1:1 $HClO_4/CH_3OH$. Partial concentration of the solution in a $CaCl_2$ desiccator overnight at room temperature afforded **27** (65 mg, yield 95%) as colorless needles or **28** (73 mg, yield 97%) as yellow needles, respectively: TLC (eluent, CH_3OH) $R_f = 0.7$ for **27** and 0.8 for **28**. **27**: Anal. Calcd (Found) for $C_{12}H_{22}N_2S_2O_2 \cdot Pt(ClO_4)_2$: C, 21.06 (21.00); H, 3.24 (3.33); N, 4.09 (3.91). **28**: Anal. Calcd (Found) for $C_{13}H_{24}N_2S_3O_2Pt(ClO_4)_2 \cdot H_2O$: C, 20.86 (20.57); H, 3.50 (3.52); N, 3.74 (3.71).

Preparation of 2:1 Macrocycle–Pt^{II} Complexes. 29: A solution of **28** (37 mg, 0.05 mmol) in 5 mL of 0.1 N $HClO_4$ was treated with **10** (17 mg, 0.05 mmol) in 5 mL of CH_3OH, and the mixture was stirred at room temperature for 24 h. A colorless solid precipitated and was collected and recrystallized from CH_3OH to give **29** (26 mg, yield 49%) as colorless needles: TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.5$. Anal. Calcd (Found) for $C_{26}H_{48}N_4O_4S_6Pt(ClO_4)_2 \cdot H_2O$: C, 28.78 (28.84); H, 4.65 (4.49); N, 5.16 (5.11).

30: A solution of **28** (37 mg, 0.05 mmol) in 5 mL of 0.1 N $HClO_4$ was treated with **12** (9 mg, 0.05 mmol) in 5 mL of CH_3OH, and the mixture was stirred at room temperature for 1 h. **30** was a major product as detected by ^1H NMR spectroscopy and TLC behaviors. Minor products were **26** and **29**, both of which seem more stable and better crystalline than **30**. The solvents were removed under a reduced pressure to afford **26** and **29** (but not **30**) as brown prisms and colorless needles, respectively. TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.3$ for **26**, 0.4 (major spot) for **30**, and 0.5 for **29**. **26** was prepared separately from $K_2Pt^{II}Cl_4$ and [9]aneS$_3$ **12**.[29]

Oxidation of Pt^{II}-In Complex 19 with Br_2. A solution of Br_2 (1.5 g, ca. 10 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a solution of **19** (53 mg, 0.1 mmol) in 10 mL of CH_3OH under nitrogen, and the mixture was stirred at room temperature for 10 min. The precipitated orange solid was recrystallized from 0.1 M $NaClO_4$ aqueous solution to obtain **31** (73 mg, yield 98%) as orange prisms; TLC (eluent, 1:1 10% NaCl/CH_3OH) $R_f = 0.4$. Anal. Calcd (Found) for $C_{13}H_{22}N_2O_2S_3Pt(ClO_4)$-$Br \cdot 2H_2O$: C, 20.96 (21.08); H, 3.52 (3.37); N, 3.76 (3.84).

Crystallographic Study. A colorless crystal of **19** with dimensions 0.3 × 0.3 × 0.1 mm^3 was used for data collection (Table IV). The lattice parameters and intensity data were measured on a Rigaku AFC-5 diffractometer with graphite monochromated Cu Kα radiation and used with absorption correction by the empirical method.[33] The structure was solved by the heavy atom method and refined anisotropically to give $R = 0.040$ and $R_w = 0.060$ for 2543 independent observed reflections. In a difference density map, one higher peak near an inversion point was found. We assumed that the two molecules of **19** oriented to each other were superimposed, the midpoints of respective C–O bonds lying approximately on the inversion point, with an equal occupancy. Therefore, the atomic scattering factor of the atom, represented by CH_3, was assigned as $0.5(F_c + F_o)$.

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Table IV. Summary of Crystal Data, Intensity Collection, and Refinements

formula	$C_{13}H_{22}N_2O_2S_3Pt \cdot 0.5CH_3OH$
formula wt	545.62
crystal system	monoclinic
space group	$P2_1/c$
a, b, c, Å	11.753 (6), 9.574 (3), 19.183 (9)
β, deg	126.78 (3)
V, Å^3	1729 (1)
Z	4
ρ_{calcd}, g cm^{-3}	2.096
cryst color	colorless
cryst dimens, mm	0.3 × 0.3 × 0.1
radiation	Cu Kα (λ = 1.54178 Å)
μ, mm^{-1}	188.3
$2\theta_{max}$, deg	130
refinement	anisotropic block-diagonal least-squares method
no. of unique reflcns	2940
no. of obsd reflcns $[\|F_o\| > 4\sigma(F_o)]$	2603
no. of reflcns used	2543
R	0.040
R_w	0.060

Kinetic Measurements. The complexation of ligands **9** and **10** with $K_2Pt^{II}Cl_4$ in CH_3OH-20% H_2O (v/v) involves two separate steps, which were confirmed by the ^1H NMR spectroscopy and TLC methods. We isolated and identified all the intermediates and products. The first step is the reaction from **9** (or **10**) to Pt^{II}-out complex **27** (or **28**). The second step goes from the Pt^{II}-out complex to Pt^{II}-in complex **17** (or **19**).

The first reaction between **9** (or **10**) (0.49-1.87 mM) and $K_2Pt^{II}Cl_4$ (0.025 mM) in CH_3OH-20% KCl (v/v)-HCl buffer (pH = 3.0) at 35.0 ± 0.1 °C and I = 0.2 (KCl) was spectrophotometrically monitored by UV absorption increase at 300 nm (or 320 nm) due to the formation of Pt^{II}-out complex **27** (or **28**). Under the employed conditions the hydrolysis of $[Pt^{II}Cl_4]^{2-}$[34] and formation of 2:1 macrocycle-Pt^{II} complex **29** (see the preceding paragraph) were negligible. The reactions were carried out under pseudo-first-order conditions with a large excess of the ligands over $K_2Pt^{II}Cl_4$, where the rate constants k_{obs} (s^{-1}) were obtained by a log plot method. A plot of k_{obs} vs ligand concentration gave a straight line ($r > 0.99$), and from the slope we determined the second-order rate constant k_1 (M^{-1} s^{-1}).

The succeeding reactions from Pt^{II}-out complexes **27** and **28** (0.10 mM) in CH_3OH-20% borate buffer (pH = 9.0) were spectrophotometrically monitored at 255 and 265 nm by measuring the increase in absorbance of the final products **17** and **19** at 35 ± 0.1 °C and I = 0.2 ($NaClO_4$). The first-order rate constants k_2 (s^{-1}) were obtained by a log plot method, because of a low steady-state concentration of the monoamide-deprotonated species.[10]

Electrochemical Measurements. Electrochemical experiments were performed with a Yanaco P-1100 system at 25.0 ± 0.1 °C and I = 0.1 (Et_4NClO_4). The working and the counter electrodes were a glassy-carbon electrode and a platinum wire, respectively. The saturated calomel reference electrode (SCE) was checked periodically against the Ni^{III}/Ni^{II} couple ($E_{1/2}$ = +0.495 V) of the Ni^{II}-cyclam complex in 0.1 $NaClO_4$ aqueous solution at 25 °C. Controlled-potential coulometry was carried out with a three-electrode system on a Yanaco VE-9 potentiostat and a Yanaco V10-CM coulometer. The working electrode was made of platinum gauze, and the working compartment was separated from the counter compartment by a sintered-glass disk.

Supplementary Material Available: Tables of anisotropic temperature factors and thermal parameters, crystallographic details, bond distances, and bond angles (6 pages); listing of observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

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Friedel-Crafts Acetylation of Bis(trimethylsilyl)- and Bis(tributylstannyl)ferrocene: Implications on the Mechanisms of Acylation and Proton Exchange of Ferrocene Derivatives[1]

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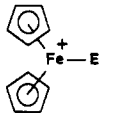
Abstract: The first unequivocal examples of intermolecular Friedel-Crafts reactions of ferrocene derivatives proceeding via exo attack of the electrophile are reported. Treatment of 1,1'-bis(trimethylsilyl)- (**5a**) or 1,1'-bis(tributylstannyl)ferrocene (**5b**) with acetyl chloride in the presence of $AlCl_3$ affords a mixture of three isomeric acetylferrocenes, 1'-acetyl- (**6**), 2-acetyl- (**7**), and 3-acetyl-1-(trialkylsilyl and -stannyl)ferrocene (**8**). Acetylation of 3,3'-dideutero-1,1'-bis(trimethylsilyl)ferrocene (**5aD$_2$**) under identical conditions generates the corresponding dideuterated products **6aD$_2$**-**8aD$_2$**. Both **6aD$_2$** and **7aD$_2$** contain 1.0 deuterium atom in each cyclopentadienyl ring whereas **8aD$_2$** contains 0.5 deuterium atom in the substituted ring and 1.5 deuterium atoms in the "unsubstituted" ring. This demonstrates that the products are formed via exo attack of the electrophile followed by an intramolecular, interannular proton transfer. The lack of scrambling of the deuterium label also suggests that protonation of ferrocenes could also occur through the exo attack of a proton rather than direct protonation at the metal center.

Introduction

Notwithstanding the plethora of synthetic and theoretical studies of ferrocene and its derivatives over the past four decades, the mechanisms of two fundamental reactions, namely the Friedel-Crafts acylation and the proton exchange, are still subject to debate.[2] The central questions of this controversy are the following: (1) Does electrophilic substitution of ferrocenes occur via an exo or an endo attack of the cyclopentadienyl ring? (2) What role, if any, does the cationic C_{2v} ferrocenium species **1** play in such electrophilic substitution reactions?

The intermediacy of **1** in electrophilic substitution reactions of ferrocenes was first proposed by Rosenblum et al.[3] in 1963. In a study of competitive acetylation, they observed that ferrocene



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