rically, rapid mixing procedures would be needed.

The result quoted above that $[V^{II}(trpy)(bpy)]^{2+}$ has a low affinity for CH_3CN, which is expected to be a better π acid than Cl^-, suggests that back-bonding does not play an important role in its binding to a sixth ligand. This does not mean, however, that back-bonding is unimportant in the chemistry of V(II), but must only mean that the back-bonding capacity of $[V^{II}(trpy)(bpy)]^{2+}$ is depleted by the π-acid polypyridyl groups already attached. The degree to which V(II)(πd^3) participates in back-bonding compared to that for the much more completely studied πd^6 cases is a point of some interest. The potentials of the V(III/II) couples for the different cases have a bearing on this, but because the potentials also involve the V(III) state, it is not as direct a measure as would be desirable. Nevertheless, it is of interest to compare the changes in the potentials for corresponding Ru, Os, and V couples (Table II). For the change from $M(trpy)_2^{2+}$ to $M(trpy)(bpy)Cl^+$, $-\Delta E_{1/2}$ values for the three systems are 0.46, 0.53, and 0.29 V, respectively; for the change from $M(trpy)(bpy)Cl^+$ to $M(bpy)_2Cl_2$, $-\Delta E_{1/2}$ values are 0.51, 0.48, and 0.45 V. If the change in potential absent back-bonding is much the same for the three cases, as seems likely because the same oxidation states are involved, the results can be taken to show that the stabilization of V(II) by back-bonding is substantial even though only three πd electrons are involved in this case.

The data for the continued reduction of the $M(trpy)_2$ moiety support the conclusion reached earlier, on other grounds, that the reduced states in the case of vanadium are more strongly metal based than in the case for either Ru or Os.

Taguchi et al. have shown that O_2 oxidizes species such as $[V^{IV}(\beta\text{-dik})(bpy)(O)]^+$ to V(V) on the time scale of hours.[31] Because of the stabilization of the V(V) product by the negative charge of the coordinated diketonate ion, the resulting V(V) species is expected to be less reactive as an oxidizing agent than the products resulting from the oxidation of $[V^{IV}(trpy)(bpy)(O)]^{2+}$. Cationic V(V) is a quite potent oxidant. In acidic aqueous solution, 1 M H^+ and above, the dominant form of V(V) is VO_2^+. For the reaction of VO_2^+ with cyclobutanol (aldehyde as product) in 1 M $HClO_4$ at 25 °C, the specific rate is measured as 2.1×10^{-3} M^{-1} s^{-1}.[32] Although aqueous V(V) does not oxidize benzene, it oxidizes aromatic compounds such as naphthalene[33] and toluene.[34] For the oxidation of toluene in 2 M H_2SO_4 at 30 °C, (product unspecified) k is reported as 5×10^{-4} M^{-1} s^{-1}.

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Equilibrium and Kinetic Studies of Monoaqua Complexes of Platinum(II). 3. Acid–Base Properties and Dimerization of $[Pt(amino\ acid)(Me_2SO)(OH_2)]^+$ Species

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The acid dissociation and dimerization reactions of platinum(II) complexes of general formula $[Pt(amino\ acid)(Me_2SO)(H_2O)]^+$, for the amino acids glycine, sarcosine, and *N*,*N*-dimethylglycine (dmg), were investigated by potentiometric and NMR methods. Data are reported for the pK_a at 35 °C and for the equilibrium (K_d) and rate constants (k_d and k_{-d}) for the dimerization reaction over a range of temperatures. Approximate values for these quantities at 35 °C are pK_a = 4, K_d = 100 M, k_d = 10^{-2} M^{-1} s^{-1}, and k_{-d} = 10^{-4} s^{-1}, with the dmg complex having the smallest pK_a and K_d and the largest k_{-d}. The significance of these data for species distribution as a function of pH, total platinum concentration, and pCl, for dimerization and trimerization of aqua species derived from cisplatin, and for potential reactions with other ligands is examined.

Introduction

Previous papers in this series have reported results of our study of the formation, by hydrolysis, of the monoaqua species formed from the monochloro species of general formula *cis*(*N*,*S*)-[Pt(amino acid)(Me_2SO)Cl][1] and of the dimerization of the monoaqua species $[Pt(dien)(H_2O)]^{2+}$.[2] This paper describes our subsequent determination of the pK_a values and the rate and equilibrium constants for the dimerization of *cis*(*N*,*S*)-[Pt(amino acid)(Me_2SO)(H_2O)]$^+$, where amino acid = glycine (gly), sarcosine (sar), or *N*,*N*-dimethylglycine (dmg). The acid–base properties of the aqua species are intimately connected with the dimerization reaction, since the dimerization is most favored at pH = pK_a. In light of that observation, the dimerization reaction is most appropriately written

$$Pt\text{–}OH + Pt\text{–}OH_2^+ \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} Pt\text{–}OH\text{–}Pt^+ + H_2O \qquad (1)$$

where $Pt\text{–}OH_2^+$ and Pt–OH denote the aqua species and its deprotonated conjugate base, while $Pt\text{–}OH\text{–}Pt^+$ denotes the μ-OH-bridged dimer. The equilibrium constant for this reaction, K_d, is given by $K_d = [Pt\text{–}OH\text{–}Pt^+]/[Pt\text{–}OH_2^+][Pt\text{–}OH] = k_d/k_{-d}$.

The pK_as of aqua species were determined by potentiometric pH titrations. Since the dimerization reactions are relatively fast under typical titration conditions, both K_d and K_a could be estimated from the titration curves by allowing pH equilibration after each addition of base.[2] Although rate data for the dimerization reaction could also be obtained from the rate of equilibration of the pH after each addition of NaOH, a more direct NMR method was ultimately employed as the preferred method to determine rate and equilibrium constants for the dimerization reaction. Both equilibrium and rate data for dimerization were also obtained as a function of temperature to permit calculation of thermodynamic data and activation parameters for the dimerization reactions.

Experimental Section

Starting Materials. The *cis*(*N*,*S*)-[Pt(amino acid)(Me_2SO)Cl] compounds were obtained as the thermodynamically favored and/or less soluble isomers in the reaction of $K[Pt(Me_2SO)Cl_3]$ with the amino acid anions in a 1:1 ratio.[3] The neutral compounds were isolated from the

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aqueous reaction mixtures after heating 5 mmol of the platinum compounds in about 20–30 mL of water to 60–70 °C for 4–5 h to ensure isomer equilibration. Further slow evaporation of water from the reaction mixture in an open beaker produced a good yield of product. For glycine and *N*-methylglycine (sarcosine), the cis(N,S) isomer was the only isomer obtained (in 60–80% yield); for *N*,*N*-dimethylglycine, slow evaporation of the reaction mixture produced the less soluble colorless cis isomer, contaminated with pale yellow trans isomer. The dried and powdered mixture was then washed three times with about 3 mL of water/g of solid to remove the more soluble trans isomer, filtered out, and dried in vacuo; yield 30–40%. Isomer purity was established by proton NMR spectroscopy. In the absence of a free-ligand catalyst (like Cl^- or Me_2SO),[3] equilibration of the cis isomer of the chloro species to a cis/trans equilibrium mixture is too slow to complicate the hydrolysis and dimerization reactions.

Potentiometric Titrations and pH Monitoring. Potentiometric pH titrations were carried out on 10.0 mL of 0.050 M aqua complex contained in a thermostated, jacketed 50-mL cell maintained at 35 °C. The aqua species was prepared by the reaction of 0.500 mmol of the corresponding chloro species with 10.0 mL of 0.0500 M $AgNO_3$ for several hours in the dark. After preliminary experiments showed that precipitated AgCl did not interfere with pH measurements, titrations were typically carried out without separating the precipitated AgCl from the dissolved aqua species. The pH after each addition of 0.50 mL of 0.100 M NaOH was determined with a combination glass/reference electrode and a Corning Model 10 pH meter connected to either a Houston Omniscribe strip chart recorder or to an ADAC system 1200 laboratory computer for later processing. Sufficient time (typically 5–20 min) was allowed after each addition of NaOH to ensure equilibration of the species by the dimerization reaction. Plots of pH vs time were available for estimating the rate of dimerization, while plots of pH vs mL of NaOH were used to determine pK_a.

NMR Study of Dimerization Reactions. Initial NMR observations were made with a Perkin-Elmer R-600 60-MHz proton spectrometer, which operated at 35 °C. Chemical shifts of ligand protons moved upfield monotonically when the aqua species was titrated with NaOH. However, at intermediate extents of titration, the spectra of the dimer species (whose chemical shifts are pH independent) were also evident. The fact that the dimer species concentration reached a maximum at pH = pK_a suggested the formulation of the dimerization equilibrium as given in (1). The data reported here were all derived from proton spectra at 300 MHz obtained with an IBM (Bruker) NF-300 spectrometer equipped with a variable-temperature probe. The variable-temperature controller was calibrated with ethylene glycol and is accurate to ±1 °C.

A 0.200 M stock solution of each aqua complex in D_2O was prepared by adding 5.00 mL of 0.100 M NaOH (0.500 mmol) to 1.00 mmol of the solid aqua species, rotary-evaporating the solution to dryness to ensure a small HDO peak in the proton spectrum, and carefully diluting the mixture to 5.00 mL in a volumetric flask. The aqua species for each solution was prepared as required by heating 1.000 mmol of the chloro species in 10 mL of 0.1000 M $AgNO_3$ to 50–60 °C for 1 h, centrifuging the solution to remove precipitated AgCl, and rotary-evaporating the filtrate to dryness.

The equilibrium constants for the dimerization reactions were then obtained from the relative concentrations of dimer (D) and monomer (M), as determined from the relative heights of corresponding peaks in the proton NMR spectrum ($S(CH_3)_2$ peaks of glycine and dmg species; the less shielded CH_2 proton peaks of the sarcosine species) of the half-neutralized 0.200 M (total Pt) stock solution. Since the pH = pK_a for these solutions, the monomer signal consisted of equal contributions from $Pt-OH_2^+$ and Pt–OH so that the concentrations of all three species in (1) could be calculated.

The temperature dependence of K_d between 5 and 95 °C was evaluated by equilibrating a sample of the stock solution in an NMR tube at the desired temperature (from 10 min at 90 °C to 24 h at 5 °C), rapidly freezing the solution in liquid nitrogen to fix the composition, and then recording the spectrum of the solution at magnet temperature immediately after it had thawed out in the NMR probe. The reliability of this technique was verified on the basis of subsequently determined rate constants. The half-life for approach to equilibrium at the unregulated sample temperature (about 23 °C) is almost 1 h, so the position of equilibrium does not shift significantly in the 20–30 s required to optimize the resolution and to record 10 scans. Nor is the rate fast enough at the highest temperatures investigated to permit any significant shift in the equilibrium in the 3–5 s required to freeze the sample in liquid nitrogen.

Rate constants for the dimerization reaction were obtained at each temperature from the first-order decrease in dimer concentration ([D])

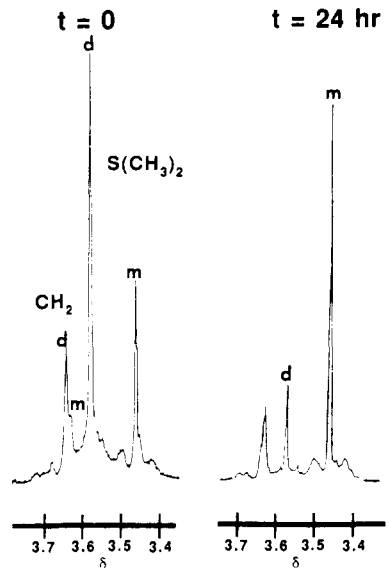

Figure 1. 300-MHz proton NMR spectra of an equilibrium mixture of monomer (m) and dimer (d) of $[Pt(D_2N-CH_2-CO_2)(Me_2SO)(OH_2)]^+$ at pH = pK_a: t = 0, immediately after dilution from 0.20 to 0.005 M (total Pt); t = 24 h, after equilibration at 305 K. Note the shift in equilibrium toward the monomer.

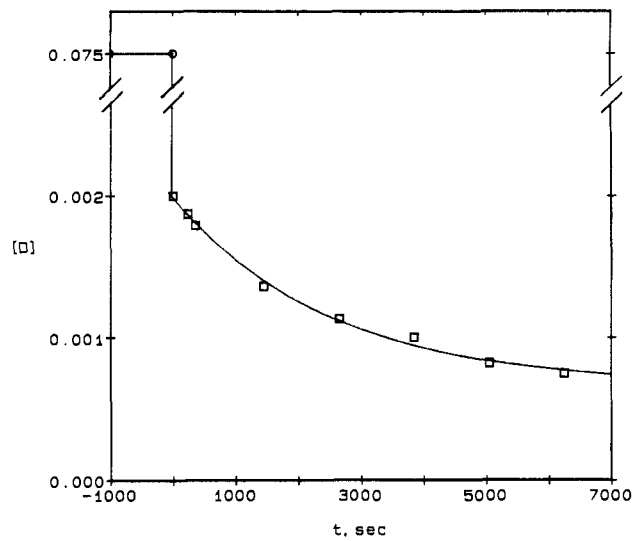

Figure 2. Shift in concentration of the dimer of $[Pt(sar)(Me_2SO)(OH_2)]^+$ before (○) and after (□) dilution of a half-neutralized solution from 0.20 to 0.005 M (total Pt) at 305 K. A regression line is drawn through the points.

following a 40-fold dilution of the stock solution used to determine K_d, from 0.200 M to 0.0050 M (total Pt). A 1.00-mL sample of D_2O in an NMR tube was thermally equilibrated in the NMR probe at the specified temperature. The spectrometer resolution was optimized for the water signal. The tube was then removed from the spectrometer long enough to inject 25 μL of 0.200 M stock solution. An automated sequence was then used to collect NMR spectra at appropriate intervals (from 30 s to 5 min) to follow the course of the reaction until the dimer had largely disappeared. The proton NMR spectral changes at 300 MHz and the shift in equilibrium concentration of dimer resulting from dilution of the glycine complex are shown in Figures 1 and 2. As in the K_d determinations, the ratio of monomer/dimer was calculated from the ratio of peak heights of corresponding peaks (which had essentially the same line widths) in the proton spectrum. Concentrations of all three species were then calculated from the total platinum concentration, the monomer/dimer ratio, and the fact that the acidic and basic forms of the monomer were at equal concentrations.

The first-order rate constant for the approach to equilibrium after dilution, k_1, was obtained by assuming that the time course of the dimer concentration, [D], is given by

$$[D] = [D]_\infty + ([D]_0 - [D]_\infty)e^{-k_1 t} \quad (2)$$

where $[D]_0$ and $[D]_\infty$ are the dimer concentrations at the time of dilution

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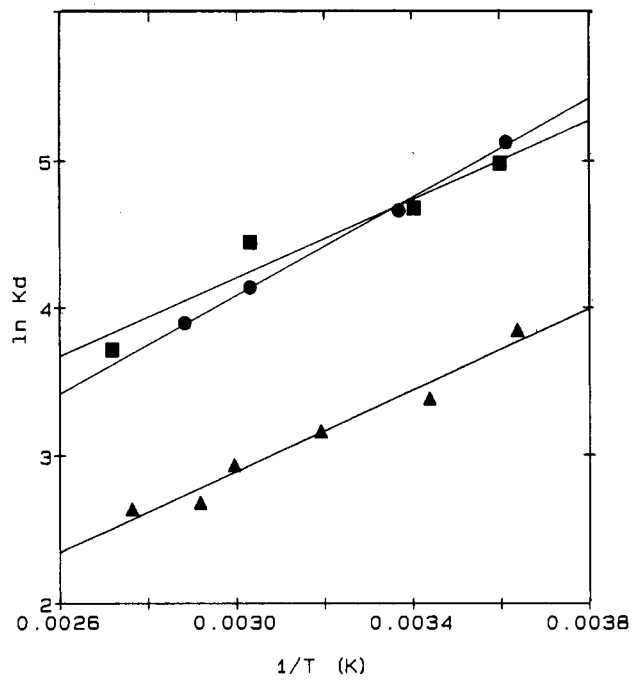

Figure 3. Plot of ln K_d vs $1/T$ for the dimerization of Pt–aqua species (all 0.200 M in total Pt): (●) [Pt(gly)(Me_2SO)(OH_2)]$^+$; (■) [Pt(sar)(Me_2SO)(OH_2)]$^+$; (▲) [Pt(dmg)(Me_2SO)(OH_2)]$^+$.

Table I. Equilibrium Constants for Acid Dissociation and Dimerization of [Pt(amino acid)(Me_2SO)(OH_2)]$^+$ Species at 35 °C Based on pH Titration Data

amino acid	pK_a	K_d/M^{-1}
gly	4.14 ± 0.05	92 ± 10 (90)[a]
sar	4.07 ± 0.05	86 ± 8 (93)[a]
dmg	3.82 ± 0.05	26 ± 5 (25)[a]

[a] Values in parentheses are interpolated from NMR-based data in Table III.

and at equilibrium, respectively. The rate constants k_d and k_{-d} were then obtained from k_1 by assuming that the rate law is

$$d[D]/dt = k_d[A][B] - k_{-d}[D] \quad (3)$$

where A, B, and D denote Pt–OH_2^+, Pt–OH, and Pt–OH–Pt$^+$, respectively. The first-order relaxation rate constant, k_1, for this system[5] is given by

$$k_1 = k_d([A]_\infty + [B]_\infty) + k_{-d} \quad (4)$$

Separate values for k_d and k_{-d} were then calculated from K_d, the total platinum concentration, and the condition that $[A]_\infty = [B]_\infty$. For example, for the glycine complex at 23 °C, $[A]_\infty = [B]_\infty = 0.00204$ M, on the basis of the value of K_d at the appropriate temperature as determined from the linear plot of ln K_d vs $1/T$ (Figure 3). These K_d values were based on NMR spectra of more concentrated solutions in which monomer and dimer concentrations are more nearly equal and therefore more accurately known. The effect of activity coefficients on the equilibrium should be negigible, since only one +1 species appears in both the numerator and denominator of K_d, so little error should be introduced by using the K_d values determined at 0.200 M total platinum.

Results

pK_a and K_d from Titration Data. The pK_a values at 35 °C for the three species are given in Table I. The values given are based on the equilibrium pH at half-neutralization. These values for K_a were used in the complete equilibrium model,[2] including the dimerization reaction, to obtain the best values of K_d at 35 °C, which are listed for each complex in Table I. The accuracy of the method for glycine and sarcosine species is somewhat compromised by a chelate ring-opening reaction that consumes another 1 mol of OH^- if the titration is carried past 1 equiv/mol of complex.[1] This prevented a reliable independent determination of the equivalence point in the titration. More reliable and extensive data on the dimerization reaction was therefore obtained by the NMR method.

(5) Bernasconi, C. F. *Relaxation Kinetics*; Academic Press: New York, 1976; Chapter 1.

Table II. Equilibrium Constants for the Dimerization of [Pt(amino acid)(Me_2SO)(OH_2)]$^+$ Species Based on NMR Data

amino acid	T/°C	K_d/M	amino acid	T/°C	K_d/M
gly	4	168	dmg	4	42
	24	105		18	29
	57	62		40	24
	74	49		61	18
sar	5	146		70	14
	21	107		89	13
	57	85			
	95	41			

Table III. Thermodynamic Data[a] for the Dimerization of [Pt(amino acid)(Me_2SO)(OH_2)]$^+$ Species at 25 °C

amino acid	$\Delta G°$/kJ mol^{-1}	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
gly	−11.6 ± 0.9	−13.9 ± 0.5	−7.6 ± 1.5
sar	−11.6 ± 4.0	−11.1 ± 2.0	1.6 ± 6.5
dmg	−8.4 ± 0.9	−11.4 ± 0.9	−10.2 ± 2.8

[a] Error estimates are based on the standard deviations in the slopes of ln K_d vs $1/T$ plots shown in Figure 3.

Table IV. Rate Constants for Formation and Dissociation of Dimers of [Pt(amino acid)(Me_2SO)(OH_2)]$^+$ Species

amino acid	T/K	10^4k_1/s^{-1}[a]	K_d/M^{-1}[b]	$100k_d$/M^{-1} s^{-1}	10^4k_{-d}/s^{-1}
gly	296	1.61 ± 0.11	111	1.23	1.10
	304	4.14 ± 0.16	99	2.90	2.9
	311	10.7 ± 0.41	89	7.00	7.9
	316	25.9 ± 2.0	83	15.9	19.2
sar	296	1.29 ± 0.13	110	0.98	0.89
	305	4.49 ± 0.51	97	3.09	3.2
	311	10.7 ± 0.87	89	6.81	7.7
	317	21.8 ± 1.2	82	13.2	16.3
dmg	296	6.86 ± 0.32	30	1.83	6.0
	304	16.7 ± 1.5	27	4.00	14.8
	311	39.8 ± 1.3	24	8.73	35.8
	316	109 ± 10	22	22.5	99.2

[a] The standard deviation in k_1 was calculated by the least-squares fit of concentration–time data based on 6–10 points at each temperature. [b] Value at each temperature were calculated from slope and intercept of ln K_d vs $1/T$ plot of data in Table II.

Equilibrium Constants for Dimerization. Equilibrium constants, K_d, for the dimerization reaction as obtained from the NMR data are given in Table II. Thermodynamic data for the reaction, calculated from these data, are summarized in Table III. Linear plots of ln K_d vs $1/T$ (Figure 3) were employed to obtain $\Delta H° = -R \times$ slope, $\Delta S° = R \times$ intercept, and $\Delta G°$ at 298 K $= -R(298)$ ln K_d. The estimated errors in $\Delta H°$ and $\Delta S°$ reported in Table III were calculated from the standard deviations in the slope and intercept of the graphs shown in Figure 3.

The K_d values at 35 °C obtained from titration data (Table I) agree well with the interpolated values for K_d obtained by the NMR method over a wider temperature range. The *N*,*N*-dimethylglycine dimer is less stable (by about a factor of 4 in K_d) than the dimers of glycine and sarcosine, which have comparable stabilities. It should be noted that K_d for the sarcosine complex is the overall constant involving total dimer concentration. For the sarcosine dimer two isomers are present, since two chiral centers are present, one for each Pt–$NH(CH_3)CH_2$– moiety. The two isomers, which are nearly equal in concentration, can be distinguished in the 300-MHz proton spectrum, as shown in Figure 4.

The modest decrease in K_d with increase in temperature for all three species is reflected in a small negative $\Delta H°$ for the dimerization reaction for each compound. Though not large (about −12 kJ/mol), this $\Delta H°$ term accounts for most of the free

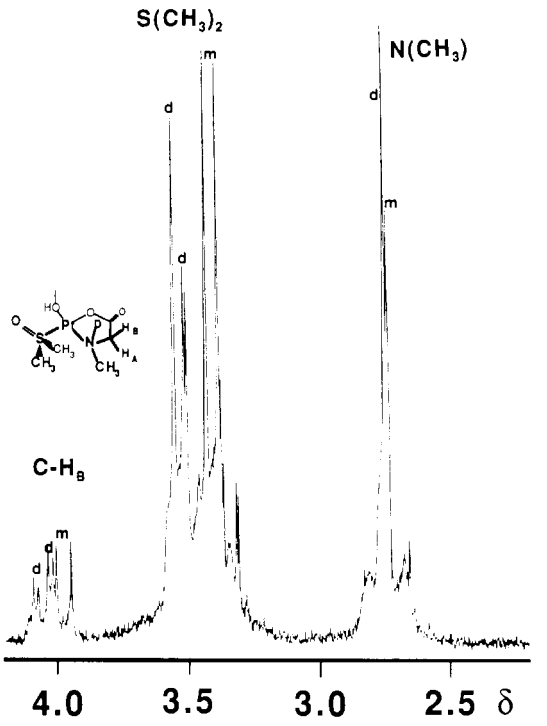

Figure 4. 300-MHz proton NMR spectrum of an equilibrium mixture of monomer (m) and dimer (d) of $[Pt(sar)(Me_2SO)(OH_2)^+]$ at pH = pK_a where acid and base forms are equal at 23 °C. Note the two doublets of the two diastereomers of the dimer in the CH_B and $S(CH_3)_2$ regions of the spectrum particularly. Peaks of H_A lie between 3.5 and 3.3 ppm, under and upfield from peaks of $S(CH_3)_2$ protons.

Table V. Activation Parameters for Formation and Dissociation of Dimers of $[Pt(amino\ acid)(Me_2SO)(H_2O)]^+$ Species

amino acid	k_i	$\Delta H^\ddagger$/kJ mol^{-1}	$\Delta S^\ddagger$/J K^{-1} mol^{-1}
gly	k_d	96 ± 11	41 ± 24
	k_{-d}	107 ± 14	41 ± 24
sar	k_d	96 ± 4	37 ± 12
	k_{-d}	106 ± 4	37 ± 12
dmg	k_d	92 ± 7	32 ± 36
	k_{-d}	104 ± 9	42 ± 36

energy of the reaction. The small entropy changes show no pattern and contribute negligibly to the driving force for the reaction.

Rate Constants for Dimerization. Rate constants for the dimerization process at several temperatures are given in Table IV. Values are given for the observed first-order relaxation rate, k_1, and for the forward and reverse reactions, k_d and k_{-d}, based on the assumed rate law. The latter were calculated from (4) by using $[A]_\infty = [B]_\infty$ calculated from the total platinum concentration and $K_d = k_d/k_{-d}$ at that temperature. Since the dissociation reaction dominates the relaxation process, the variation in relaxation rates reflects mainly the variation in the rate of dissociation of dimer (k_{-d}). In fact, the rate of dimerization for the three complexes is very similar over the whole temperature range. The only significant difference lies in the rates of dissociation of the dimers. The factor of 4–5 greater rate of dissociation of the dmg dimer is reflected in the factor of 4–5 smaller K_d observed for the dmg dimer relative to the gly and sar dimers.

Plots of ln (k_d/T) vs $1/T$ and ln (k_{-d}/T) vs $1/T$ were employed to obtain the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ according to the Eyring equation, $k_d = (kT/h)[\exp(\Delta S^\ddagger/R)][\exp(-\Delta H^\ddagger/RT)]$. Results are summarized in Table V. Again, the small differences in activation enthalpies in the series reflect the small differences in the rates.

Discussion

Comparison of Dimerization Rates of Monoaqua- and Diaquaplatinum Species. Rate and equilibrium data for the three species reported here are compared with data for other related aqua complexes of Pt(II) and Pd(II) in Table VI. The rates of dimerization for monoaqua amino acid species are significantly faster than the rate of dimerization of $[Pt(dien)(OH_2)]^{2+}$,[1] but they are 1 order of magnitude slower than the rate of dimerization of $[Pt(NH_3)_2(OH)(OH_2)]^+$ derived from cisplatin.[9] As Martin has noted,[6-8] dimerization rates of all platinum complexes are several orders of magnitude less than the rates for similar palladium complexes, though acid dissociation and dimerization constants for corresponding Pt and Pd species tend to be quite similar.

Some of the observed differences in dimerization rates of platinum complexes can probably be attributed to simple electrostatic charge effects. The more acidic species might be expected to have the strongest Pt–O bond, which should lead to more difficult loss of H_2O to form the dimer, but that is just the opposite of what is observed. The three amino acid complexes with $pK_{a_1} \cong 4$ all dimerize at comparable rates, while the dimerization rate of $[Pt(dien)(OH_2)]^{2+}$ (with $pK_a \cong 6$) is a factor of 10 slower. This slower rate of dimerization of $[Pt(dien)(OH_2)]^{2+}$ can probably be attributed in part to the effect of charge on the species involved. For these amino acid–Me_2SO complexes, Pt–OH is a neutral species, but for the dien species, the dimerization reaction is between a +2 and a +1 cation. Similar effects were noted by Bignozzi et al. in their investigation of the effect of pH (4–5 range) and concentration of complex on the rate of dimerization of $[Pt(NH_3)_2(H_2O)_2]^{2+}$.[9] From their second-order rate data, they estimated that dimerization occurs by reaction of the $[Pt(NH_3)_2(H_2O)_2]^{2+}$ species ($k_2 \cong 0.03\ M^{-1}\ s^{-1}$) as well as by reaction of the $[Pt(NH_3)_2(H_2O)(OH)]^+$ species ($k_2 \cong 0.2\ M^{-1}\ s^{-1}$). The ratio of rate constants for these two reactions is comparable to the ratio of rate constants for dimerization for $[Pt(dien)(OH_2)]^{2+}$ and the +1 amino acid species reported here, about a factor of 10.

Comparison of K_d's of Monoaqua- and Diaquaplatinum Species. Comparison of equilibrium constants for dimerization of $[Pt(NH_3)_2(H_2O)_2]^{2+}$ with those of the simpler monoaqua species is complicated by the stepwise nature of the process and by the competing acid–base equilibria that must be considered. The acid–base properties and dimerization reactions of important aqua species of platinum and palladium have been reviewed by Lippard[10] and Martin.[8] With two hydroxo bridges, the $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ dimer is very stable so that the dimerization reaction—in competition with formation of trimer, at high total platinum concentrations—goes essentially to completion in the pH range where $[Pt(NH_3)_2(OH_2)(OH)]^+$ is the dominant monomer species, even at the quite low concentrations of total platinum ($\sim 10^{-3}$ M) employed in typical UV spectral studies.

In a comparison of the simple dimers with doubly bridged species, the most appropriate comparison is between K_d as we have defined it for monoaqua species, on the basis of (1), and K_{d1} in Scheme I, which shows the two separate steps in the formation of the doubly bridged dimer from $[Pt(NH_3)_2(H_2O)(OH)]^+$. With reference to Scheme I, related dimerization constants are $K_d = K_{d1}K_{d2}$, the equilibrium constant for the overall dimerization reaction, and K_{d1}', K_{d2}', and K_d', the corresponding constants for reactions involving dimerization and proton displacement of the fully protonated species.

Both K_d and the separate stepwise constants K_{d1} and K_{d2} for $[Pt(NH_3)_2(H_2O)(OH)]^+$ can be estimated from data in the literature. In a multinuclear NMR study of the system, Appleton and co-workers[11] were able to identify both protonated monomer and singly bridged (and otherwise protonated) dimer in a 0.3 M

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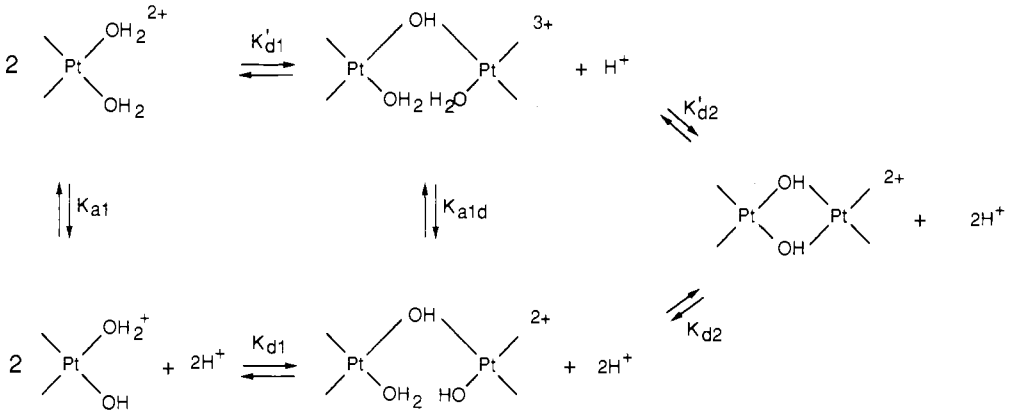
Table VI. Comparison of Equilibrium and Rate Data for Aqua Species of Pt(II) and Pd(II)[a]

species	pK_a	$k_d/M^{-1}\ s^{-1}$	k_{-d}/s^{-1}	K_d	ref
$[Pt(gly)(Me_2SO)(H_2O)]^+$	4.14	5×10^{-2}	50×10^{-5}	90	this work
$[Pt(sar)(Me_2SO)(H_2O)]^+$	4.07	4×10^{-2}	50×10^{-5}	93	this work
$[Pt(dmg)(Me_2SO)(H_2O)]^+$	3.82	6×10^{-2}	20×10^{-5}	25	this work
$[Pt(dien)(H_2O)]^{2+}$	5.85	3.3×10^{-3}	3.0×10^{-5}	108	2
$[Pd(dien)(H_2O)]^{2+}$	7.74	fast	fast	132	6
$[Pd(en)(H_2O)(OH)]^+$	7.5 (mean)	fast	fast	2000	6, 8
$[Pt(NH_3)_2(H_2O)(OH)]^+$	7.3	$\sim 10^{-1}$		<2600	9, 11
$[Pt(NH_3)_2(H_2O)_2]^{2+}$	5.6, 7.3	$\sim 10^{-2}$		?	9

[a] Amino acid and $[Pt(dien)(H_2O)]^{2+}$ data at 35 °C; other data at 25 °C.

Scheme I



solution of the dimer that had been equilibrated at pH 3. On the basis of their report of essentially equal intensities for the Pt signals from monomer and dimer at pH 3.0, $K_{d1}' = (0.15)(10^{-3})/(0.3)^2 = 1.67 \times 10^{-3}$. Since $K_{d1}' = K_{d1}K_{a1}^2/K_{a1d}$, $K_{d1} = (1.67 \times 10^{-3})(K_{a1d})/(10^{-5.8})^2 = (2.6 \times 10^7)K_{a1d}$, where K_{a1d} is the first dissociation constant of the singly bridged dimer. The failure of Appleton et al. to detect appreciable doubly bridged dimer in the pH 3.0 solution allows some limits to be placed on K_{d2} as well. Assuming that the concentration of doubly bridged dimer is less than 1% that of singly bridged dimer, $K_{d2}' = [D^{2+}][H^+]/[D^{3+}] < 0.01 \times 10^{-3} = 10^{-5}$. But $K_{d2} = K_{d2}'/K_{a1d}$, so $K_{d2} < 10^{-5}/K_{a1d}$. The value of K_{a1d} is not available, but making the reasonable assumption that it lies between K_{a1} ($pK = 5.6$) and K_{a2} ($pK = 7.3$) for $[Pt(NH_3)_2(H_2O)_2]^{2+}$ yields $K_{d1} = 650$–13 and $K_{d2} < 4$–200. Thus, the range of likely values for K_{d1} for $[Pt(NH_3)_2(H_2O)(OH)]^+$ includes the values for K_d reported here for the amino acid complexes and the values reported for other closely related monoaqua species. The value for $K_d = K_{d1}K_{d2} < 2600$, derived from this analysis, is not dependent on the unknown K_{a1d}. It is consistent with the value of $K_d = 2000$ obtained by Lim and Martin for $[Pd(en)(H_2O)(OH)]^+$, whose properties closely parallel those of $[Pt(NH_3)_2(H_2O)(OH)]^+$, from titration data of solutions equilibrated over a wide pH range.[6,8]

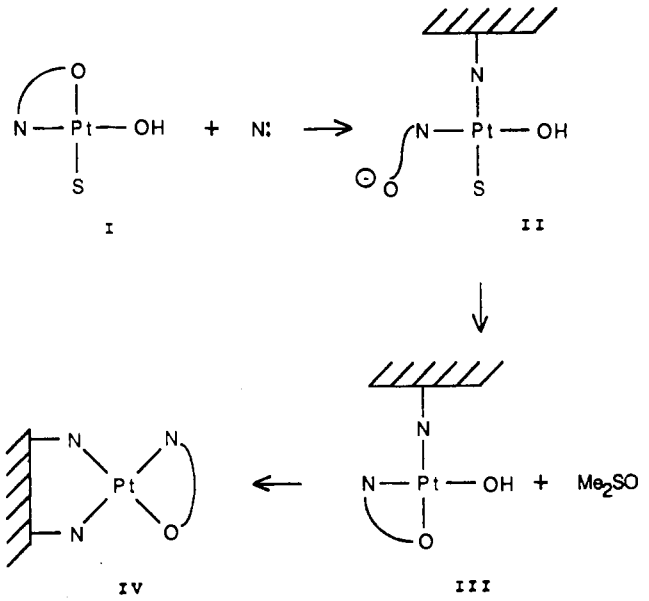
The above analysis of the factoring of K_d into K_{d1} and K_{d2} can be extended to account for the significant stability of the triply bridged trimer, T, of $[Pt(NH_3)_2(H_2O)(OH)]^+$. If K_{d1} lies toward the upper end and K_{d2} lies toward the lower end of the range estimated in our analysis of Appleton's data, the singly bridge dimer is more likely to add another monomer (if it is available) than to form the doubly bridged dimer. With both H_2O and OH present in each monomer unit, K_{d1} could easily be 200, leaving $K_{d2} < 13$. Forming the second OH bridge in the dimer involves considerable steric strain. However, such strain is not present in formation of the three OH bridges in the six-membered-ring trimer, including the last intramolecular step to form the six-membered ring. Martin also reports a value of $10^{6.5}$ for K_T, the equilibrium constant for formation of the trimer from three singly ionized monomer units for $[Pd(en)(H_2O)(OH)]^+$. The formation of the trimer can be thought of as the sum of the three separate steps, each involving loss of water between Pt–OH and Pt–OH_2 moieties. If K_d for each step in the trimerization of $[Pt(NH_3)_2(H_2O)(OH)]^+$ is 100–200, $K_T = (100\text{–}200)^3 = 10^6$–$8 \times 10^6$, in good agreement with Martin's value for the comparable Pd species. So the K_d values for the monoaqua species seem to be reasonably reliable indicators of K_d for the individual steps in formation of doubly and triply bridged species.

Dominant Species as a Function of pH. The relative concentrations of Pt–OH_2^+, Pt–OH, and Pt–OH–Pt^+ for these amino acid complexes vary with pH and total platinum concentration. For a given concentration of platinum, the dimer concentration is a maximum at pH = pK_a. However, with $K_d \cong 100$ or less, even at pH = pK_a the concentration of dimer exceeds that of monomer only at total platinum concentrations > ~0.1 M. Three pH units on either side of pK_a (cf. Figure 4 of ref 1) the dimer concentration is negligible. Thus, at pH 7, the predominant species for these aqua complexes is Pt–OH, assuming no competition from other anions. With chloride present, some Pt–Cl is also present at equilibrium, but the dimer is not a significant species.

The relative importance of Pt–OH and Pt–Cl at equilibrium can be estimated from $K_h' = [Pt\text{–}OH][Cl^-]/[Pt\text{–}Cl][OH^-] = K_hK_a/K_w$. If we use the K_h values reported eariler[1] and the K_a values from this work, for these species, $K_h' \cong 10^{-4} \times 10^{-4}/10^{-14} \cong 10^6$. Thus, in the presence of excess Cl^-, the ratio [PtOH]/[Pt–Cl] $\cong 10^8$ [OH]/[Cl^-]. At pH 7, this ratio is 0.10/[Cl^-]. So, for 0.10 M Cl^-, the Pt–Cl and Pt–OH concentrations are comparable, but for 10^{-3} M Cl^-, [Pt–OH]/[Pt–Cl] $\cong$ 100, and the Pt–OH species predominates.

Probable Reactions of [Pt(amino acid)(Me_2SO)(OH)] with Polynucleotides and Other Ligands. [Pt(dien)Cl]Cl and [Pd(dien)Cl]Cl have been employed extensively to study the interaction of platinum and palladium species with potential biologically significant ligands.[8,10] The comparative stability of the Pt(dien) fragment makes this a particularly attractive probe. Like the case for cisplatin, hydrolysis in low chloride medium makes the aqua (or hydroxo) species the important species under physiological conditions. The monoaqua species reported in this work might be employed in similar studies. The corresponding chloro species are readily prepared in good yield and the aqua species can be obtained from the chloro species readily. However, the behavior at the other three ligand binding sites would almost certainly lead to more complicated chemistry than observed for the dien species. At pH 7, the predominant species for these compounds would be the neutral species with the coordinated water deprotonated, since pK_a for coordinated water is about 4. The Pt–OH bond is rela-

Scheme II



tively inert, but replacement of OH could occur via the 0.10% of protonated species. Subsequent displacement of the cis Me_2SO could lead to a disubstituted species, which retains the chelated amino acid. A disubstituted product could also be obtained by initial displacement of Me_2SO, followed by displacement of OH, but the Pt–S bond is also not very labile in these species.[3] With $[Pt(dmg)(Me_2SO)(OH_2)]^+$, we have obtained proton NMR evidence of a clean aqua substitution reaction to an equilibrium mixture of aqua and acetate species on addition of a stoichiometric quantity of acetate anion as the basic ligand. Such displacement of coordinated water by acetate and other relatively weakly coordinating ligands is well documented.[11,12] Not surprisingly, our preliminary attempts to monitor the reactions of $[Pt(dmg)(Me_2SO)(H_2O)]^+$ with nucleotides by NMR techniques have indicated that several different products are formed.

As Farrell[13] has noted in reviewing extensive work on dimethyl sulfoxide complexes as potential therapeutic reagents and as Lippard et al. have observed in solvolysis reactions of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$,[14] the large trans effect of coordinated dimethyl sulfoxide[15] is very important in determining the course of substitution reactions. Scheme II suggests possible outcomes of the reaction of $[Pt(\text{amino acid})(Me_2SO)(OH)]^+$ with nitrogen donors of a polymeric molecule. In view of the large trans effect of coordinated dimethyl sulfoxide, a likely mode of action for the glycine and sarcosine species (but not for the *N,N*-dimethylglycine species, which lacks an N–H proton) with basic moieties at pH 7 is the ring-opening reaction that we have noted in attempting to follow the hydrolysis of Pt–Cl species by OH^-[1] and in the reaction of the aquo species with methylamine,[4] as shown in Scheme II. The precendent for the first two steps is clear. Whether species III would bind a second basic moiety in a reasonable time would depend on the lability of the Pt–OH bond of III and on the relative stability of Pt–N and Pt–OH entities. Species III also corresponds to one of the products expected in the reaction of $[Pt(\text{amino acid})Cl_2]^-$ species, followed by hydrolysis of the remaining chloride. $[Pt(dmg)(Me_2SO)(OH)]$, which is a neutral species at pH 7, might be expected to react less rapidly than the corresponding gly and sar species, since both Me_2SO and OH^- are relatively inert to substitution and the ring-opening reaction would not be facilitated by the conjugate-base mechanism[16] that is available to the gly and sar species.

Comparison of Corresponding Olefin and Me_2SO Complexes. We are also investigating the aqueous solution chemistry of parallel olefin–amino acid complexes (with olefin replacing Me_2SO), for which the cis(N,olefin) isomer is also thermodynamically favored.[17] Both qualitative and quantitative properties are quite similar for corresponding complexes with the same amino acid. However, the olefin complexes tend not to be as stable and to lose olefin more readily than sulfoxide complexes lose Me_2SO.

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Registry No. *cis*(*N,S*)-$[Pt(gly)(Me_2SO)(H_2O)]^+$, 119413-66-0; *cis*(*N,S*)-Pt(sar)$(Me_2SO)(H_2O)]^+$, 119413-67-1; *cis*(*N,S*)-$[Pt(dmg)(Me_2SO)(H_2O)]^+$, 119413-68-2.

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