Proton Magnetic Resonance Studies of Amino Acid Complexes of Platinum(II). II. Kinetics of N–H and C–H Proton Exchange

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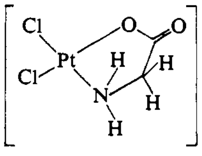
Abstract: Rates of N–H proton exchange for **1** and **2** were determined (a) by analysis of line-shape changes of H_2O solutions at pH 8–11 and (b) by analysis of the slow spectral changes of D_2O solutions observed at pD 2–6. The exchange reaction is OH^- catalyzed over the whole pH range investigated. However, H_2O catalysis contributes to the observed rate at pH <3. For **3**, in which the α-carbon atom is the asymmetric center, rates of base-catalyzed C–H proton exchange and of inversion were found to be comparable.

Sargeson, Buckingham, and coworkers have recently compared rates of proton exchange and of inversion in several Co(III) complexes.[1-3] The proton exchange rates were determined by observing the disappearance of nmr signals of protonated species in D_2O solutions of the complexes. Rates of inversion of resolved isomers were determined polarimetrically. Both processes were found to be OH^- catalyzed. It was found that the rate of exchange exceeds the rate of inversion by a factor of 10^3–10^5, *i.e.*, that the proton can be abstracted and replaced several times on the average before inversion takes place. More recently, they have extended this investigation to include effects of the solvent on this ratio.[4]

Haake and Turley, on the other hand, used nmr line-shape analyses alone to compare rates of exchange and inversion of Pt(II) complexes (*dl* and *meso*) of N,N′-dimethylethylenediamine (N,N′-dmen).[5] They found that the rates of exchange and inversion were comparable and speculated that Pt(II) complexes are somehow different from corresponding Co(III) complexes.

During this period, several studies of base-catalyzed α-proton exchange of chelate complexes of amino acids have also been reported.[6-9] In contrast to complexes in which a nitrogen atom is the center of asymmetry, the rates of inversion and exchange were found to be essentially identical.

In this and an accompanying paper[10] we report similar kinetic studies of proton exchange and inversion of Pt(II) complexes of amino acids some of whose spectra have been reported previously.[11] This paper summarizes investigations of N–H exchange rates of 1:1 complexes of glycine, **1**, and sarcosine, **2**, and of C–H exchange and racemization rates for the 2:1 complex of L-glutamate, **3**. The former investigation employed both slow spectral changes of D_2O solutions at low pD and line-shape analysis of spectra of H_2O solutions of high pH to cover a 10^7-fold range in observed exchange rates. It also included measurements of the rates of protonation of the deuterated species in H_2O at low pH.



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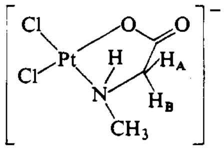

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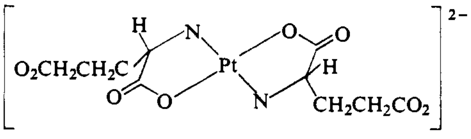

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Experimental Section

Preparation of Complexes. $KPt(Gly)Cl_2$ and $KPt(Sar)Cl_2$ were prepared as described earlier.[11] In some cases the pale yellow KCl-contaminated 1:1 salt was further purified by dissolving in a minimum of anhydrous dimethylformamide—to leave behind KCl—and reprecipitating by the addition of several volumes of absolute ethanol.

trans-$H_2Pt(L\text{-}Glu)_2$ was prepared by Grinberg's method.[12]

Other Reagents. Reagent grade chemicals were used in preparation of starting materials and buffer solutions for kinetic runs. Deuterated solvents (D_2O, D_2SO_4, DCl, NaOD) were obtained from NMR Specialties.

Procedure for Kinetic Runs. Solutions for kinetic runs were prepared by dissolving the solid complex in buffer containing KCl, if necessary, to control the ionic strength. After the pH (±0.01) at the magnet temperature was determined with a Metrohm pH meter equipped with a combination microelectrode, the solution was transferred to an nmr tube and the sample placed in the probe of a Varian A-60 nmr spectrometer for recording spectra. For slow-exchange runs in D_2O, spectra were recorded as a function of time while the sample remained in the probe or in a water bath at the same temperature. For high pH runs, the pH was varied over a small range by the addition of very small quantities of acid or base to obtain several traces near coalescence for a single sample

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[1] B. Halpern, A. M. Sargeson, and K. R. Turnbull, *J. Am. Chem. Soc.*, **88**, 4630 (1966).

[2] D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *ibid.*, **89**, 825 (1967).

[3] D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *ibid.*, **89**, 3428 (1967).

[4] D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *ibid.*, **90**, 6028 (1968).

[5] P. Haake and P. C. Turley, *ibid.*, **90**, 2293 (1968).

[6] D. H. Williams and D. H. Busch, *ibid.*, **87**, 4644 (1965).

[7] J. B. Terrill and C. N. Reilley, *Anal. Chem.*, **38**, 1876 (1966).

[8] J. B. Terrill and C. N. Reilley, *Inorg. Chem.*, **5**, 1988 (1966).

[9] D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Am. Chem. Soc.*, **90**, 5133 (1968).

[10] L. E. Erickson, H. L. Fritz, R. J. May, and D. A. Wright, *ibid.*, **91**, 2513 (1969). Note: These two papers together correspond to paper II referred to in ref 11. It was separated at the suggestion of the editor.

[11] L. E. Erickson, R. P. Clow, J. K. Howie, and J. W. McDonald, *ibid.*, **90**, 6371 (1968).

[12] A. A. Grinberg and N. N. Katz, *Izv. Sektora Platiny i Drug. Blagorodn. Metal. Inst. Obsbch. i Neorg. Khim. Akad. Nauk SSSR*, **29**, 37 (1955).

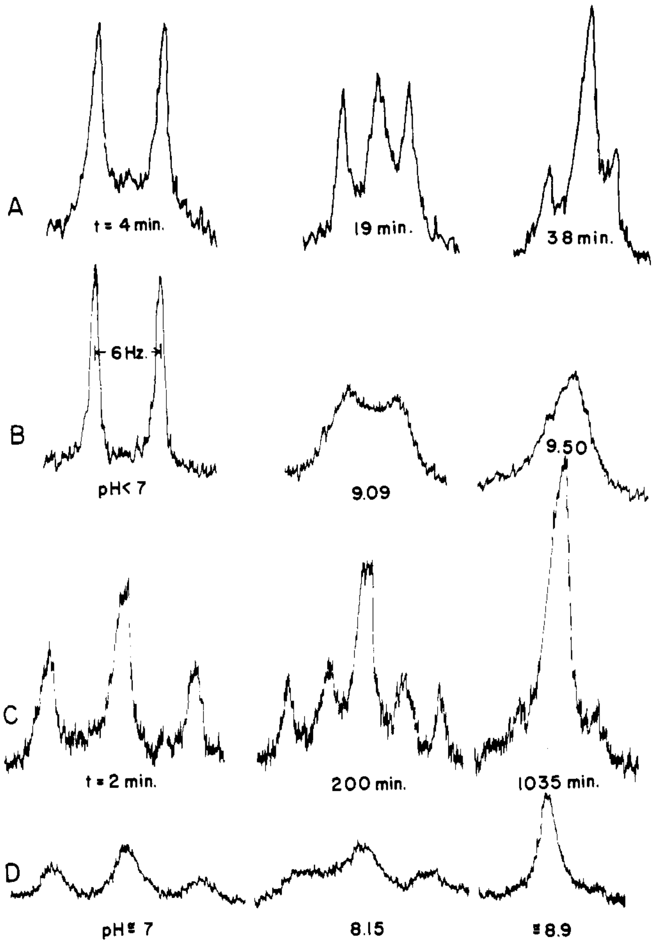

Figure 1. Nmr traces typical of those employed to obtain rates of proton exchange of $Pt(Sar)Cl_2^-$ and $Pt(Gly)Cl_2^-$: (A) $Pt(Sar)Cl_2^-$ in D_2O at pD 5.02; (B) $Pt(Sar)Cl_2^-$ in H_2O at pH values indicated; (C) $Pt(Gly)Cl_2^-$ in D_2O at pD 2.29; (D) $Pt(Gly)Cl_2^-$ in H_2O at pH values indicated.

without significant dilution. After pH adjustment, several traces were recorded and the pH was redetermined. An average of the two determinations is reported if the two readings were not identical. Traces where the discrepancy exceeded 0.1 pH unit were discarded.

For runs at other than magnet temperature, the V-6040 temperature controller was employed. However, sample temperatures were also checked by measuring the peak separation of an ethylene glycol or methanol reference standard at the same dial setting. The pH of the sample was similarly determined at the same temperature.

Racemization and proton exchange rates of **3** were determined by dissolving the salt in phosphate buffer–D_2O and following the decrease in C–H proton signal, the change in optical rotation (using a Cenco-Kern polarimeter accurate to 0.05°), and the pH of separate portions of the solution simultaneously.

Results

N-Proton Exchange of $Pt(Sar)Cl_2^-$ and $Pt(Gly)Cl_2^-$. The nmr spectrum of $Pt(Sar)Cl_2^-$ has been described earlier.[11] The methyl portion employed in these kinetic studies is shown in Figure 1A. Low pH–rate measurements were made by determining the extent of deuteration or protonation from the relative heights of methyl doublet or $Pt(Sar)Cl_2\text{-}d^-$ singlet as the exchange proceeded. Data for the deuteration rates at 33.5° are summarized in Table I. The first-order rate constant for exchange, k_{ex}, for each run was obtained from a plot of log (peak height of doublet) *vs.* time.

Table I. Rate Constants for N–H Exchange of $Pt(Sar)Cl_2^-$ at 33.5°

Buffer[a]	Ionic strength	pH (meter)	$10^{10}(OD^-)$, M[b]	$10^5 k_{ex}$, sec^{-1}
None	0.30	1.85	0.0064	3.6
KHP	0.30	3.43	0.24	6.4
KHP	0.30	3.84	0.63	12
KHP	0.30	4.13	1.23	21
KHP	0.30	4.25	1.62	29
OCH_2CO_2H	1.0	4.32	1.90	23
OCH_2CO_2H	1.0	4.53	3.09	45
OCH_2CO_2H	1.0	4.62	3.80	46
OCH_2CO_2H	1.0	4.73	4.90	79
OCH_2CO_2H	1.0	4.84	6.30	86

[a] Total buffer concentration for all runs was 0.05 M; complex, 0.25 M. [b] (OD^-) for all D_2O solutions was calculated from $pOD = pK_w(D_2O) - (pH\ (\text{from meter}) + 0.40)$, where $K_w(D_2O) = 0.195K_w(H_2O)$.[3]

For $Pt(Gly)Cl_2^-$, where two protons are exchanged, the situation can be represented as

$$NH_2 \xrightarrow{k_1} NHD \xrightarrow{k_1'} ND_2 \qquad (1)$$

where k_1 and k_1' are the pseudo-first-order rate constants for conversion of NH_2 to NHD, and NHD to ND_2, respectively. Spectral changes observed during the course of N–H exchange in D_2O for $Pt(Gly)Cl_2^-$ are shown in Figure 1C. The initial triplet (~1:2:1) is replaced by the doublet of NHD which is subsequently converted to the singlet of ND_2. NH_2 concentrations were determined by adding the peak heights of the outer components of the NH triplet since they do not overlap significantly with the NHD doublet. Plots of log (peak height) *vs.* t were satisfactorily linear over a 2–3 half-life range. For the reverse reaction, the protonation of $Pt(Gly)Cl_2\text{-}d_2^-$, it was more convenient to evaluate the rate constant k_1' from the disappearance of the NHD doublet after essentially all of the ND_2 had been converted to NHD. Since the relative concentration of NHD is quite low (~15% of total complex concentration) at this point, accuracy is lower than for the $NH_2 \rightarrow NHD$ determination. In order to determine k_1 for these runs, it was assumed that $k_1' = k_1/2$, as expected on the basis of probability arguments with a negligible secondary isotope effect.

At pH 9 in H_2O, the rate of the N–H exchange is great enough to produce a collapse of the methyl doublet of $Pt(Sar)Cl_2^-$ and the methylene triplet of $Pt(Gly)Cl_2^-$, as illustrated in Figure 1B and 1D. Rates at several different pH values were determined by adding a small drop of concentrated aqueous NH_3 to 2 ml of a solution of the complex and recording nmr traces for a portion of the sample while simultaneously monitoring the pH of the same sample at the same temperature, as the pH dropped slowly through coalescence. Data for $Pt(Sar)Cl_2^-$ were analyzed by fitting nmr traces to computer-generated curves for doublet collapse.[13] For $Pt(Gly)Cl_2^-$, exchange rates at high pH were estimated on the basis of line shapes close to coalescence, assuming that

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[13] As summarized in J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 489.

Table II. Rate Constants for Proton and Deuteron Exchange of Sarcosine and Glycine Complexes at 33.5° and Ionic Strength 1.0

Complex	Solvent, buffer[a]	No. of runs	pH (meter) range	$10^5 k_{D_2O}(k_{H_2O})$, sec^{-1}	$10^{-6} k_{OD^-}(k_{OH^-})$, l. mol^{-1} sec^{-1}
$KPt(Sar)Cl_2$	D_2O, KHP or $C_6H_5CH_2CO_2H$	10	1.8–4.8	3.6	1.2
$KPt(Sar)Cl_2$	H_2O, unbuffered	8	8.9–9.5		0.9
$KPt(Sar)Cl_2$-*d*	H_2O, $C_6H_5CH_2CO_2H$	4	1.6–4.5	0.4	1.1
$KPt(Gly)Cl_2$	D_2O, KHP	8	1.9–4.0	5.6	10
$KPt(Gly)Cl_2$	H_2O, borate	5	8.0–8.4		8
$KPt(Gly)Cl_2$-d_2	H_2O, KHP	4	2.0–3.8	~1	9

[a] Total buffer concentration for all runs was 0.05 *M*; complex, 0.25 *M*.

Table III. Proton Exchange and Racemization[a] Rates of **3** at 39°

pH (meter)	k_{ex}, sec^{-1}	k_{ex}', l. mol^{-1} sec^{-1}	k_r, sec^{-1}
12.50	5.1×10^{-4}	1.2×10^{-2}	7.3×10^{-4}
12.02	1.54×10^{-4}	1.1×10^{-2}	2.2×10^{-4}

[a] Initial α of 0.5 *M* solution of complex yields $[\alpha]^{39}D \sim -18°$.

the spectrum is approximately a 1:2:1 A_2X triplet.[14]

In the pD range 3–5 and at high pH in H_2O the observed first-order rate constants are approximately proportional to (OH^-) or (OD^-). However, for both $Pt(Sar)Cl_2^-$ and $Pt(Gly)Cl_2^-$, a solvent-catalyzed path also contributes to the observed rate at lower pH; *i.e.*, the complete rate law in D_2O is given by eq 2, where

$$\text{rate} = k_{ex}(NH) = [k_{D_2O} + k_{OD^-}(OD^-)](NH) \quad (2)$$

k_{D_2O} and k_{OD^-} are the rate constants for the catalysis by D_2O and OD^-, and k_{ex} is the observed first-order rate constant for the exchange (k_1 in eq 1) for the two-step $Pt(Gly)Cl_2^-$ exchange). Plots of k_{ex} *vs.* (OD^-) were prepared from which k_{OD^-} was obtained as the slope. The intercept, k_{D_2O}, corresponds closely to k_{ex} obtained for runs at pH <2, since the rate of the OD^- catalyzed process becomes negligible at such low pH values.

Values of k_{D_2O} and k_{OD^-} at 33.5° and ionic strength 1.0 are summarized in Table II. The values given for k_{D_2O} and k_{OD^-} for each species are based on four–ten kinetic runs (low pH) or line-shape analyses (high pH). Although data for species for which more runs were completed are somewhat more reliable, deviations from linearity in the k_{ex} *vs.* (OD^-) plots indicate an uncertainty of about ±10% for both k_{D_2O} and k_{OD^-}, except for $KPt(Gly)Cl_2$-d_2 for which k_{ex} for two low-pH runs differed by a factor of two and the method of data analysis was much less reliable.

C–H Proton Exchange and Racemization Rates of $Pt(L\text{-}Glu)_2^{2-}$. First-order rate constants for C–H proton exchange of **3**, as determined from the rate of decrease of the C–H proton signals, are summarized in Table III. First-order rate constants for racemization, k_r, and k_{ex}' are also given. The former was obtained as the slope of a plot of $\ln(\alpha - \alpha_\infty)$ *vs.* time.

Discussion

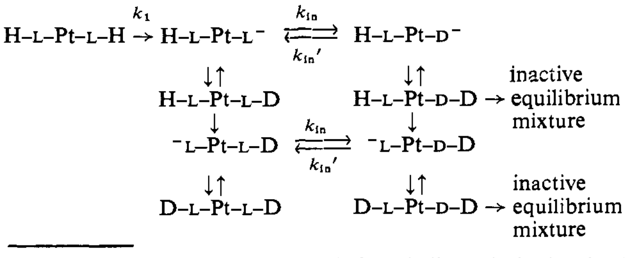
The observed decrease in k_{OD^-} from **1** to **2** no doubt reflects the decreased acidity of the N–H proton of **2** relative to **1**. Replacement of one glycine N–H by CH_3 decreases k_{OD^-} by almost a factor of 10. The analogous replacement of N–H by a methyl group increases the pK_a of the ammonium ion from 9.24 to 10.62.[15] Parallel changes are also observed for ^{195}Pt–^1H spin coupling constants between platinum and ligand CH_2 protons. These values decrease for 1:1 complexes from 38 to 35.5 (average) to 33 in going from glycine to sarcosine to N,N-dimethylglycine.[11] Similarly, for N-methyl-substituted ethylenediamine complexes, the average coupling between platinum and ligand CH_2 protons in bipyridyl complexes decreases with extent of methyl substitution,[16] in accord with known relative acidities.[17]

Comparison of data for three sarcosine complexes indicates the direction and magnitude of effects resulting from changes in ligand coordination and metal charge. A 100-fold decrease in exchange rate is observed in going from $Pt(Sar)Cl_2^-$ (**2**) to $Pt(NH_3)_3(Sar)^+$, in which the sarcosine is N coordinated.[10] By contrast, the rate of OH^--catalyzed exchange of $Co(NH_3)_4(Sar)^{2+}$ is greater than that of $Pt(Sar)Cl_2^-$ by almost a factor of 10. These effects, which can also be accounted for in terms of changes in acidities of N–H protons, might be expected to follow a similar pattern in other complexes.

The data obtained for **1** and **2** suggest that isotope effects on rates of hydroxide ion catalysis are not very large. This conclusion is qualified by the empirical approach used to obtain OH^- and OD^- concentrations, but it appears to be sufficiently reliable to permit valid comparisons of relative values of rate constants obtained in D_2O and H_2O.

C–H Exchange and Racemization. The fact that the observed rate constant for racemization of **3**, k_r, exceeds the observed rate constant for exchange, k_{ex}, can be accounted for in terms of Scheme I, in which H′–L–Pt–L–H designates the protonated bis(L-glutamate) complex, etc. The observed rate constant for exchange, k_{ex}, was

Scheme I



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[14] Spectra were fit on the basis of data in "Tables of Exchange Broadened NMR Multiplets," Weizmann Institute of Science, Rehovoth, Israel.

[15] However, it should be noted that similar substitution in dimethylammonium ion, which is perhaps more similar to the complexes being considered, decreases pK_a from 10.77 to 9.80. See R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 65. However, glycine itself (pK_2 = 9.78) is more acidic than sarcosine (pK_2 = 10.11).

[16] Work in progress in our laboratory.

[17] G. W. Watt and D. G. Upchurch, *J. Am. Chem. Soc.*, 90, 914 (1968).

determined from the decrease in the total area of the CH signal. This area is proportional to [2(H_2complex) + (HDcomplex)]. Assuming that the over-all rate of H_2 complex → HDcomplex is twice the rate of HDcomplex → D_2complex, it can be shown that $k_{ex} = k_1/2$. Thus, $k_1 = 2k_{ex}$ is somewhat *greater than* k_r. Since deprotonation in D_2O invariably leads to racemization, k_1 so calculated corresponds to k_1 in the above scheme. The only condition under which k_r could be *as great as* k_1 would be if $k_{in} \gg k_{in}'$, so that inversion would *invariably* accompany removal of the first proton. If H–L–Pt–L$^-$ ever captures a deuteron, exchange occurs without inversion. The fact that $k_1/k_r = 0.7$, rather than 0.5, suggests that inversion of H–L–Pt–L$^-$ probably occurs more than half of the time before a proton is recaptured. This requires some preference for H–L–Pt–D$^-$ over H–L–Pt–L$^-$, which does not seem unreasonable in view of the higher symmetry of H–L–Pt–D$^-$ with its bulky, negatively charged $CH_2CH_2CO_2^-$ groups on opposite sides of the coordination plane. Unfortunately, the complexity of the system precludes a more complete analysis, which could lead to relative values of k_{in} and to the equilibrium constant for the reaction

$$2\text{D–Pt–L} \rightleftarrows \text{D–Pt–D} + \text{L–Pt–L}$$

Attempts to study this equilibrium by observing the relative areas under peaks of diastereoisomers in the proton nmr spectrum[9] were also unsuccessful, since both species had essentially identical spectra, even at 100 MHz.[11]

Measurably fast C–H proton exchange was also observed in several other complexes at high pH, but difficulties associated with maintaining constant pH made it impossible to obtain data of comparable accuracy. Nevertheless, the rate of exchange is comparable to that of **3** and to other α-carbon protons of chelated amino acids[6-9] for **1** and **2** as well as for Pt(L-Glu)Cl_2^{2-}, Pt(L-Asp)$_2^{2-}$, and Pt(L-Asp)Cl_2^{2-}.

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Proton Magnetic Resonance Studies of Amino Acid Complexes of Platinum(II). III. Isomerism, Proton Exchange, and Inversion at Asymmetric Coordinated Nitrogens[1]

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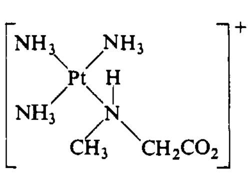
Abstract: Rates of N–H proton exchange of **1** and **2** were determined (a) by analysis of line-shape changes of H_2O solutions at high pH and (b) by analysis of slow spectral changes of D_2O solutions at mid pH. The exchange reactions are OH^- catalyzed. However, intramolecular catalysis by acetate fragments is also important in the mid-pH range. Rates of inversion were determined by line-shape analysis of the acetate methylene AB quartet at high pH. Inversion rates were found to be less than N–H proton exchange rates by a factor of 70. The rate of inversion of the deprotonated nitrogen of $Pt(NH_3)_2$(EDDA) was determined to be 10^5–10^6 sec^{-1} at 39° on the basis of an nmr-determined N–H acid dissociation constant, $K_a \cong 0.01K_w$. Activation energies for inversion of **1** and **2** are 14–16 kcal. Conformational implications of nmr parameters, including J_{Pt-H}, are also considered.

In an accompanying paper[4] we have discussed the nmr determination of N–H exchange rates of Pt(Gly)Cl_2^- and Pt(Sar)Cl_2^-. This paper reports similar studies of two other amino acid complexes, **1** and **2**. For these complexes, asymmetry at the coordinated nitrogen also permitted evaluation of rates of inversion and, therefore, a comparison of the rates of N–H exchange and inversion as reported by Buckingham, Sargeson, and coworkers for Co(III) complexes[5] and by Haake and Turley for Pt(II) complexes of N,N′-dimethylethylenediamine.[6,7]



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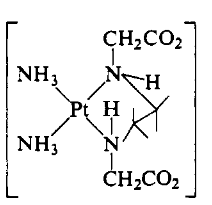

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Compounds **1** and **2** differ from the glycine and sarcosine complexes in another important respect. Both have free acetate fragments which might be expected to participate in intramolecular catalysis of N–H proton exchange.

Since the EDDA complex has two asymmetric centers, both *meso* and *d,l* forms are possible. The two isomers would be expected to have somewhat different spectra, so as to permit evaluation of the isomer ratio. Signif-

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[1] A portion of this work was reported at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

[2] National Science Foundation Undergraduate Research Participant, summer, 1967.

[3] National Science Foundation Undergraduate Research Participant, summer, 1968.

[4] L. E. Erickson, A. J. Dappen, and J. C. Uhlenhopp, *J. Am. Chem. Soc.*, **91**, 2510 (1969).

[5] References 1–4 of ref 4.

[6] P. Haake and P. C. Turley, *J. Am. Chem. Soc.*, 90, 2293 (1968).

[7] It should be noted that a similar study of $KPt(Sar)Cl_2$ was unsuccessful because of rapid hydrolysis of the ligand in the critical pH range.