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Ammine Ligand Exchange in Tetraammineplatinum(II) in Aqueous Solution

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The rate of exchange of ammonia between tetraammineplatinum(II) and solution ammonia in aqueous ammonia/ammonium perchlorate buffers of unit ionic strength has been determined in the temperature range 81–100 °C using nitrogen-15 labeling and optical emission isotopic distribution analysis. The rate of exchange increases with increasing ammonia concentration ($0.050 < [\mathrm{NH_3}] < 0.50$ M), and the observed first-order rate constant is linearly dependent on the ammonia concentration $k_{\mathrm{obs}} = k_{\mathrm{H_2O}} + k_{\mathrm{NH_3}}[\mathrm{NH_3}]$, corresponding to two parallel reactions: (i) a direct exchange between $\mathrm{Pt(NH_3)_4}^{2+}$ and $\mathrm{NH_3}$ ($\Delta H^* = 125$ (4) kJ mol^{-1}, $\Delta S^* = 4$ (10) J mol^{-1} K^{-1}, $k_{\mathrm{NH_3}} = 9.5$ (8) $\times$ 10^{-10} L mol^{-1} s^{-1}, statistically corrected rate constant extrapolated to 25 °C); (ii) an indirect exchange which most likely involves rate-determining formation of $\mathrm{Pt(NH_3)_3H_2O^{2+}}$ ($\Delta H^* = 103$ (6) kJ mol^{-1}, $\Delta S^* = -78$ (15) J mol^{-1} K^{-1}, $k_{\mathrm{H_2O}} = 3.9$ (5) $\times 10^{-10}$ s^{-1}, statistically corrected rate constant extrapolated to 25 °C). The direct exchange is many orders of magnitude slower (an extrapolated half-life of 23 years in 1 M $\mathrm{NH_3}$ at 25 °C) than the ammonia exchange in the isoelectronic tetraamminepalladium(II) and tetraamminegold(III) complexes as the result of a larger enthalpy of activation.

Introduction

The interaction of platinum(II) amine compounds with nucleic acids, which is the primary event in the antitumor activity of platinum amine compounds, is possible in cells through the large difference between the rate of substitution of amine and halide ligands in the active complexes.[3,4] While halide ligand substitution rates, including exchange and hydrolysis rates, have been the subject of numereous studies,[5–8] the extreme inertness of amine ligands in platinum(II) complexes has hampered kinetic studies of substitution reactions of amine ligands. Such information is, however, of relevance for better understanding of the behavior of platinum(II) complexes in biological fluids and for design of new antitumor platinum(II) drugs. We felt we had the required patience to study the very slow ammine ligand exchange in tetraammineplatinum(II) in aqueous solution using nitrogen-15 labeling and report the activation parameters for the exchange process, which is demonstrated to occur by parallel direct exchange and transient formation of aquatriammineplatinum(II). Together with the activation parameters previously obtained for the ammine ligand exchange in the isoelectronic tetraamminegold(III) and tetraamminepalladium(II) complexes,[9,10] the present results provide the basis for a direct comparison of the activation for a simple exchange process at three different metal centers belonging to the important class of low-spin d^8 complexes.

Experimental Section

Chemicals. $[\mathrm{Pt(NH_3)_4}]\mathrm{Cl_2{\cdot}H_2O}$ was prepared from $\mathrm{K_2[PtCl_6]{\cdot}6H_2O}$ (H. Drijfhout & Zoon's, Amsterdam) and recrystallized, according to the procedure of Keller.[11] Analysis (Microanalytical Laboratory at the H. C. Ørsted Institute, Copenhagen: H, 3.76; N, 15.80; Cl, 20.33) agreed with the hydrate (calcd: H, 4.02; N, 15.92; Cl, 20.13). The UV spectrum ($\lambda_{\max} = 287$ nm, $\epsilon_{\max} = 38.5$ L mol^{-1} cm^{-1}) agreed with that reported by Chatt et al.[12] (287 nm, 36 L mol^{-1} cm^{-1}). The ^{195}Pt NMR spectrum in $\mathrm{D_2O}$ at 300 K revealed a single resonance line at 1935 ppm (Bruker AC 250, at 53.5 MHz, spectral with of 167 000 Hz and pulse repetition rate of 0.05 s). Labeled $^{15}\mathrm{NH_4ClO_4}$ stock solution was made from gaseous $^{15}\mathrm{NH_3}$ (99%, Amersham Int.) by neutralization to pH = 4.0 with $\mathrm{HClO_4}$ (2.22 M) and dilution with unlabeled $\mathrm{NH_4ClO_4}$ (1.11 M) to a calculated ^{15}N enrichment of 12.7%, and analyzed for total ammonium (1.105 M $\mathrm{NH_4}^+$; ion exchange followed by titration with HCl) and isotopic distribution (12.29 ± 0.13% ^{15}N; four independent determinations by optical emission spectroscopy). Other chemicals were of analytical grade.

Isotopic Analysis. The ^{15}N isotopic abundance in the reaction medium and in the precipitated compounds in the exchange experiments were determined by optical emission spectroscopy. The analytical procedure (a detailed description may be found in ref 13) involved a Dumas destruction at 400 °C of the material (copper plus copper(II) oxide).

Exchange Experiments. An aqueous 1.0 M $\mathrm{(Na,NH_4)ClO_4}$ reaction medium, made from labeled $\mathrm{NH_4ClO_4}$ stock solution, standardized NaOH solution, and standardized $\mathrm{NaClO_4}$ solution, was used throughout. Ammonia concentration was calculated from the amount of NaOH added; cf. footnote to Table I. $[\mathrm{Pt(NH_3)_4}]\mathrm{Cl_2{\cdot}H_2O}$ (weighed amount corresponding to a concentration of 0.018 or 0.036 M) was dissolved in the actual reaction medium, the resulting solution was sealed in ampules with 0.5 mL in each, and the ampules were transferred to a water thermostat (or a boiling water bath). The alkaline solution did not react with the ampules during the experiment as tested by titration with HCl and by UV spectroscopy (0.500 M $\mathrm{NH_3}$ at 100 °C for 2 days). Ampules were removed at known times, and the exchange reaction was stopped by cooling the ampules in an ice bath. A 300-μL portion of the reaction mixture was poured into 100 μL of an ice cold 2.3 M sodium *p*-toluenesulfonate solution. A white precipitate was immediately formed ($[\mathrm{Pt(NH_3)_4}](\mathrm{tos})_2{\cdot}0.5\mathrm{NH_4ClO_4}$, as found by analysis of N, H, C, S, and Cl and by ^{15}N analysis). The mixture was cooled in ice for 2 min, and the precipitate was filtered off in a G-3 sintered glass funnel, washed twice with 0.3 mL of ice-cold water, and subsequently dissolved in 0.1 mL of 1 M HBr (ca. 50 °C), and ca. 10 μL of the resulting solution was transferred to a 1 cm long glass capillary by capillary attraction. The solution was evaporated to dryness in the capillary (ca. 50 °C in vacuum), and the residue was subjected to Dumas destruction and subsequent isotopic analysis.

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(1) Chemistry Department.
(2) Department of Mathematics and Physics.
(3) Reedijk, J.; Fichtinger-Schepman, A. M. J.; van Oosterom, A. T.; van de Putte, P. *Struct. Bonding* **1987**, *67*, 53.
(4) Lippard, S. J., Ed. *Platinum, Gold and Other Metal Chemotherapeutic Agents*; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983.
(5) Coe, J. S. *MTP Int. Rev. Sci.: Inorg. Chem. Ser. Two* **1974**, *9*, 45.
(6) Jolley, W. H.; Smith, E. D.; Martin, D. S.; Clardy, J. C.; Woods, J. D. *Inorg. Chem.* **1972**, *11*, 2866.
(7) Grantham, L. F.; Elleman, T. S.; Martin, D. S. *J. Am. Chem. Soc.* **1955**, *77*, 2965.
(8) Tucker, M. A.; Colvin, C. B.; Martin, D. S. *Inorg. Chem.* **1964**, *3*, 1373.
(9) Brønnum, B.; Johansen, H. S.; Skibsted, L. H. *Inorg. Chem.* **1988**, *27*, 1859.
(10) Brønnum, B.; Johansen, H. S.; Skibsted, L. H. *Acta. Chem. Scand.* **1989**, 975.
(11) Keller, R. N. *Inorg. Synth.* **1946**, *2*, 250.
(12) Chatt, J.; Gamlen, G. A.; Orgel, L. E. *J. Chem. Soc.* **1958**, 486.
(13) Johansen, H. S.; Middelboe, V. *Appl. Spectrosc.* **1982**, *32*, 221.

0020-1669/92/1331-3023$03.00/0

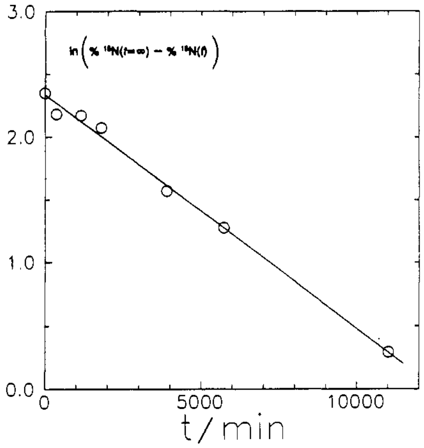

Figure 1. Increasing 15-nitrogen enrichment in $Pt(NH_3)_4^{2+}$ plotted according to the McKay equation. The enrichment of the initially unlabeled tetraammineplatinum(II) increases to % $^{15}N(t=\infty)$ = 11.5. Experimental conditions: 94.1 °C, $c_{Pt} = 0.018$ M, 0.10 M NH_3 in 0.10 M $NaClO_4$, 0.90 M NH_4ClO_4 (initial ^{15}N enrichment of ammonia/ammonium medium, 12.3%). The exchange has a half-life of 62 h under these experimental conditions, and the reaction was followed for 3 half-lifes.

Results

Tetraammineplatinum(II) dissolved in nitrogen-15 labeled aqueous ammonia/ammonium buffer solution was found to be enriched in a very slow process

$$Pt(NH_3)_4^{2+} + {}^{15}NH_3 \rightleftharpoons Pt(NH_3)_3({}^{15}NH_3)^{2+} + NH_3 \qquad (1)$$

The fast and almost quantitative precipitation of the *p*-toluenesulfonate salt of the tetraammineplatinum(II) complex provides a convenient method for removing $Pt(NH_3)_4^{2+}$ from the reaction mixture and thereby quenching the exchange reaction.

The exchange reaction was studied at elevated temperatures (81.0, 87.1, 94.1, and 100.0 °C) in a 1.0 M $(Na,NH_4)ClO_4$ medium with large excess of ammonia/ammonium relative to platinum(II). For conditions of fixed temperature and fixed ammonia concentration, the increase in ^{15}N enrichment (% $^{15}N(t)$) in precipitated tetraammineplatinum(II) salt was found to follow first-order kinetics according to eq 2 as shown in Figure 1. The

$$\ln(\%\,{}^{15}N(t=\infty) - \%\,{}^{15}N(t)) = -k_{obs}t + \ln(\%\,{}^{15}N(t=\infty) - \%\,{}^{15}N(t=0)) \qquad (2)$$

value of $^{15}N(t=\infty)$ calculated from the initial enrichment of the reaction medium agreed with the enrichment determined by optical emission spectroscopy for the precipitated complex at the end of experiments followed "to completion" (i.e. for more than 4 half-lifes). The first-order rate constant is based on ligand concentration and is inherently statistically corrected (factor of 4) and is, according to the McKay equation,[14] related to the exchange rate R_{ex} by

$$k_{obs} = R_{ex}(c_{Pt} + c_{NH_4})/(4c_{Pt}c_{NH_4}) \qquad (3)$$

in which c_{NH_4} and c_{Pt} denote total ammonia/ammonium concentration and total complex concentration, respectively. For the experimental conditions employed in the present study (i.e. large excess of ammonia/ammonium; and exchange at ammonia concentrations for which the tetraammineplatinum(II) complex is thermodynamically stable, as confirmed by comparison of UV spectra prior to exchange with UV spectra after completion of exchange experiment), eq 3 is approximated by

$$R_{ex} = 4k_{obs}[Pt(NH_3)_4^{2+}] \qquad (4)$$

The observed first-order rate constant was found to be linearly dependent on $[NH_3]$ at each of the four temperatures investigated, as shown in Table I and Figure 2 for the lowest and the highest of the temperatures used in the study, respectively

$$k_{obs} = k_{H_2O} + k_{NH_3}[NH_3] \qquad (5)$$

The observed rate constant for the exchange process was not influenced by c_{Pt} (0.018 or 0.036 M, excluding participation of dimeric compounds in the exchange), by the presence of chloride (0.05 M, see Figure 2), or by the exposure to light (irradiation of a 0.018 M $Pt(NH_3)_4^{2+}$ solution with 313-nm monochromatic light with an intensity of 8 × 10^{15} quanta min^{-1} mL^{-1} (ferrioxalate actinometry) for 4 h at 25 °C did not induce any detectable exchange).

Observation of two parallel exchange processes for tetraammineplatinum(II) is not unexpected and agrees with the kinetics generally found for ligand substitution processes in platinum(II) complexes, i.e. a direct substitution reaction and a substitution with transient formation of reactive aqua complexes.[15] It should be noted that the tetraammineplatinum(II) ion is *thermodynamically stable* in all of the reaction media used for exchange experiments and that aqua complexes and hydroxy complexes formed at higher pH only are transients of fleeting existence on the time scale of exchange and are not accumulating, as previously discussed for tetraamminepalladium(II).[10] The temperature dependence of the rate constant for the two exchange reactions is well described by the Arrhenius equation (Figure 3) leading to the activation parameters given in Table II.

Table I. Observed[a] Rate Constant for Ammonia Exchange in Tetraammineplatinum(II) in 1.0 M (Na, NH_4)ClO_4 at 81.0 °C with Different Ammonia Concentrations

$[NH_3]$/M[b]	$[NH_4^+]$/M	$[Na^+]$/M	k_{obs}/s^{-1}	k_{calc}/s^{-1}
0.050	0.95	0.050	4.84×10^{-7}	4.83×10^{-7}
0.100	0.90	0.100	6.48×10^{-7}	6.49×10^{-7}
0.50	0.50	0.50	1.98×10^{-6}	1.98×10^{-6}

[a] Calculated rate constants are based on the assumption of the linear relationship of eq 5. [b] Reaction mixture was made by adding standardized NaOH solution to labeled 1.11 M NH_4ClO_4, and $[NH_3]$ was equated to OH^- added.

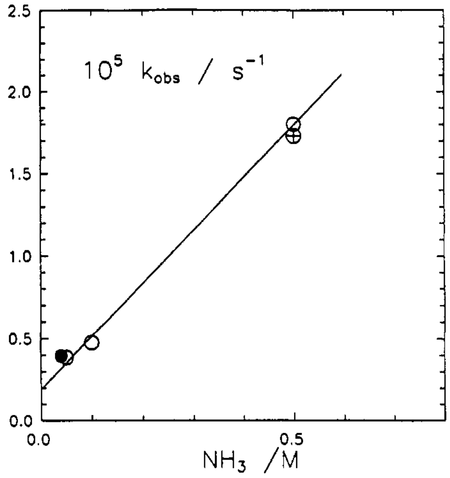

Figure 2. Observed first-order rate constant for ammine ligand exchange in $Pt(NH_3)_4^{2+}$ at 100.0 °C as a function of ammonia concentration. Experimental points were determined for solutions with $c_{Pt} = 0.018$ M (except $c_{Pt} = 0.036$ M for ⊕) in a 1.0 M perchlorate medium (0.050 M chloride present for ●) as outlined in Figure 1. The solid line was calculated by linear regression according to eq 5; cf. Table I.

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[14] Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1981.

[15] Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*, 2nd ed.; John Wiley and Sons, Inc.: New York, 1967.

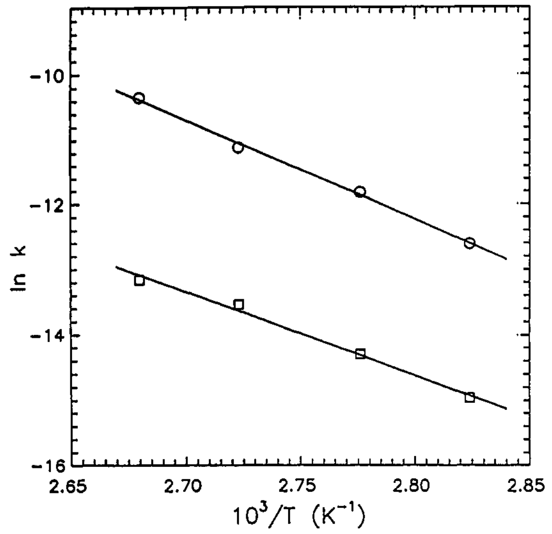

Figure 3. Temperature dependence of the rate constant for the two parallel reaction paths for ammine exchange in tetraammineplatinum(II) plotted according to the Arrhenius equation: ○, direct exchange, k in L mol^{-1} s^{-1}; □, indirect exchange, k in s^{-1}. For each temperature, the two rate constants were determined as outlined in Figure 2.

Table II. Activation Parameters and Rate Constants at 25.0 °C for Hydrolysis and Exchange of Ammonia Coordinated in Square-Planar Tetraammine Metal Complexes in 1.0 M Ammonium Perchlorate Solution

	$Pd(NH_3)_4^{2+}$	$Pt(NH_3)_4^{2+}$	$Au(NH_3)_4^{3+}$
hydrolysis			
k_{H_2O}/s^{-1}	$3.0 (2) \times 10^{-4}$	$3.9 (5) \times 10^{-10}$	$\sim 3 \times 10^{-6}$
$\Delta H^*/kJ \cdot mol^{-1}$	80 (2)	103 (6)	~109
$\Delta S^*/J \cdot mol^{-1} \cdot K^{-1}$	–38 (6)	–78 (15)	~20
NH_3 exchange			
$k_{NH_3}/L \cdot mol^{-1} \cdot s^{-1}$	$1.6 (2) \times 10^{-2}$	$9.5 (8) \times 10^{-10}$	$1.69 (6) \times 10^{-1}$
$\Delta H^*/kJ \cdot mol^{-1}$	67 (3)	125 (4)	61 (2)
$\Delta S^*/J \cdot mol^{-1} \cdot K^{-1}$	–54 (12)	4 (10)	–55 (6)
ref	10	this work	9, 16

Discussion

Ammine ligand exchange rates and activation parameters for the exchange process provide the most fundamental characterization of the intrinsic reactivity of metal–ammine complexes. Tetraammineplatinum(II) was found to be very inert and robust, and by exchange experiments at elevated temperatures, it was shown that the ammine exchange in aqueous solution can be accounted for in terms of two parallel reactions: (i) a direct exchange with an extrapolated half-life of 23 years in 1 M NH_3 at 25 °C (as calculated from the data in Table II); (ii) an indirect exchange most likely with transient formation of $Pt(NH_3)_3(H_2O)^{2+}$. The latter process is tentatively identified with the hydrolysis of tetraammineplatinum(II)

$$Pt(NH_3)_4^{2+} + H_2O \rightarrow Pt(NH_3)_3(H_2O)^{2+} + NH_3 \quad (6)$$

with a half-life of 56 years in aqueous solution at 25 °C. The hydrolysis of tetraammineplatinum(II) has apparently not been subjected to kinetic studies, and rate data are not available for a direct comparison between the indirect exchange and aquation, as for the isoelectronic tetraamminepalladium(II).[10] Until such data are provided, the indirectly determined rate data and derived activation parameters may serve as tentative estimates.

The activation parameters for the ammine ligand exchange and the hydrolysis of the tetraammineplatinum(II) are given in Table 2 compared with the activation parameters for exchange and hydrolysis of the isoelectronic and likewise square-planar tetraamminegold(III) and tetraamminepalladium(II). With respect to ammine exchange, tetraamminegold(III) and tetraamminepalladium(II) have comparable activation parameters, whereas tetraaammineplatinum(II) has an impressive high enthalpy of activation.[5] This is in contrast to the hydrolysis reaction, for which tetraammineplatinum(II) and tetraamminegold(III) have comparable values for the enthalpy of activation. This indication of a less significant discrimination power of platinum(II), when compared to Au(III),[16] can be further quantified when expressed as the k_{NH_3}/k_{H_2O} ratio, which have the following values: Pt(II), 2; Pd(II), 50; Au(III), 6×10^4.

In conclusion, the 15-nitrogen labeling study has provided quantitative data for two reactions in tetraammineplatinum(II) of fundamental interest for platinum(II) chemistry and confirmed that the Pt–NH_3 bond is difficult to break and that the nature of the incoming ligand is of less importance for Pt(II) than for Pd(II) and in particular Au(III).

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Registry No. $Pt(NH_3)_4^{2+}$, 16455-68-8; NH_3, 7664-41-7.

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(16) Skibsted, L. H. *Adv. Inorg. Bioinorg. Mech.* **1986**, *4*, 137.