is twice the number of possible nucleophiles in the dinuclear complex; in the absence of other effects this would only double the rate of reaction of the mononuclear complex. In addition to the two effects already mentioned, the difference in charge between the two complexes must effect the $pK_a$ of the ammine ligands, which are required to be deprotonated to act as nucleophiles, but this is spread over the two cobalt centers so the effect is not large. The lower $pK_a$ of the ammines in the dinuclear complex means that at a given hydroxide concentration there is a higher concentration of the active species. This will be offset to some degree by the expectation that as usual for the $S_N2(P)$ reactions of phosphate esters, the rate constant for the reaction will be dependant on the basicity of the nucleophile.[13,22] Thus, the lower basicity of the ammines in the complex $[(NH_3)_5CoOP(O)(OC_6H_4NO_2)OCo(NH_3)_5]^{4+}$ ($pK_a$ estimated to be $\sim 15$)[17] will mean a lowering of the rate constant for attack of the amido ion.

Attack of the amido ion on the phosphorus center of this dinuclear complex occurs some 80-fold slower than the corresponding reaction for $[(NH_3)_5CoOP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$. This implies that further esterification of a phosphate ester has a greater effect on the electrophilic character of the phosphorus atom than coordination of even a relatively small trivalent metal ion (effective ionic radius for Co(III) is 0.55 Å).[23] Even so, the effect of the additional metal ion leads to a useful increase in the rate of ester hydrolysis, and the effect is similar to that observed in a previous example[24] where two metal ions were coordinated to the same phosphate ester residue, where the intramolecular nucleophile was $OH^-$.

The chemistry detailed here is typified by the attack of a coordinated amido ion at the phosphorus center, almost certainly as the rate-determining step. The rate enhancement for the intramolecular reaction is of the order of $10^8$–$10^{10}$-fold compared with that of the free ester under the same conditions. Much of this effect comes from the intramolecularity of the nucleophilic attack, but a factor of $\sim 10^2$ can be ascribed to the effect of each metal ion on the P center in promoting the process. These factors are in spite of the strain engendered by the formation of a four-membered chelate ring. They do point to even larger factors for intramolecular paths involving coordinated nucleophiles, which are ideally oriented such as might be achieved in the enzyme cleft. They also point to the reason for the metal ions in the vicinity of substrate in such enzymic systems. The sum of such effects is well on the way to accounting for much of the rate increase observed in the enzymic reactions.

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# Intramolecular Attack of Amido Ion on Phosphate Esters Coordinated to the Pentaammineiridium(III) Moiety

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The phosphodiester metal ion complexes (ethyl 4-nitrophenyl phosphato)pentaammineiridium(III) and bis(4-nitrophenyl phosphato)pentaammineiridium(III) have been synthesized and their reactivities under basic conditions studied. Both complexes react predominantly via intramolecular attack of a deprotonated coordinated ammonia to liberate 4-nitrophenolate ion. The four-membered phosphoramidato chelate ring thus formed rapidly ring opens, probably via P–O and P–N rupture, to yield N-bonded phosphoramidate monoester and O-bonded phosphate ester complexes. The rate constant for intramolecular attack of amido ion is enhanced considerably relative to the reactivity of the uncoordinated substrate under the same conditions. However, the intramolecular reactions are slower in the Ir(III) complexes compared with analogous Co(III) complexes by $\sim 10^3$-fold. The strain induced by chelation of phosphate monoesters by metal ions in enzymes has been proposed as a possible explanation for the large increases observed in the rate of enzymic hydrolysis over the nonenzymic reactions. This study however raises doubt about the supposed reactivity of such strained phosphate ester chelates primarily because the rate of ring opening of the chelate appears to be much greater than that of exocyclic ester hydrolysis.

## Introduction

The work of Westheimer and others in the 1950s and 1960s showed that the five-membered-ring cyclic phosphate esters were hydrolyzed up to $10^8$-fold faster than the corresponding acyclic esters.[1] The rapid rate of hydrolysis of the cyclic esters was attributed to the strain in the ring, which destabilized the phosphate ester and stabilized the activated complex on the way to the phosphorane intermediate relative to the acyclic ester reactivity. Since that time, several groups of workers have proposed that the enzymic hydrolysis of phosphate monoesters (which require metal ion cofactors[2]) might occur via the intermediacy of the chelate phosphate ester;[3-5] i.e., the metal ion chelates the phosphate ester, forming a highly strained four-membered ring that reacts rapidly for reasons similar to those advanced for the rate of reaction of the organic cyclic phosphate esters.

Several groups of workers have tried to test this hypothesis by attempting the synthesis of chelate phosphate esters and studying the reactivity of such a species.[3,5,6] Several Co(III) complexes of phosphate ion are known,[7] and in instances where chelation is possible the chelate is quite stable in the pH region 4–9; beyond this region the monodentate and fully dissociated complexes are the most stable.[7] These observations encouraged workers to attempt the synthesis of Co(III) chelate phosphate esters. However, none of these attempts have been successful to date.

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The work described here was performed in an attempt to investigate the reactivity of an analogous system, i.e. a chelate phosphoramidate ester. It has been shown[8] that it is possible to produce, as an intermediate, chelate ethyl phosphoramidate, namely (ethyl phosphoramidato)tetraamminecobalt(1+) ion. However, in basic conditions, the ligand was slowly cleaved from cobalt to yield free ethyl phosphoramidate, most likely via metal–ligand bond cleavage. This paper is concerned with the reactions of iridium(III) phosphodiester complexes intended to yield chelates analogous to the Co(III) chelate described above but less susceptible to ligand–metal ion bond rupture. It has been shown in the general chemistry that the rate of Ir(III)–ligand bond rupture is much slower than that for the analogous Co(III) reaction. For example, the rate of aquation of $Cl^-$ ion for $[(NH_3)_5IrCl]^{2+}$ is $>10^4$-fold slower than that of the analogous Co(III) complex.[9] This reduced rate of metal–ligand bond rupture implies that if the chelate phosphoramidate ester is produced, reaction at the strained phosphorus center may become competitive with the metal-centered ring-opening and ligand-loss reactions.

## Experimental Section

Analytical grade reagents were used throughout except where otherwise stated. $^{31}P$ NMR spectra were recorded with either a JEOL JNM-60 or a Bruker CXP-200 spectrometer at 24.21 or 80.98 MHz, respectively. Chemical shifts (ppm) are quoted relative to 85% $H_3PO_4$ as an external standard; downfield shifts are positive. $^1H$ NMR spectra were recorded with a JEOL FX-200 spectrometer and DSS as an internal standard. All evaporations were carried out in a Buchi rotatory evaporator at ~20 Torr such that the solution temperature did not exceed 25 °C. Electronic spectra and kinetic traces were recorded with a Hewlett Packard HP8450A diode-array spectrophotometer equipped with a thermostated cell holder or with a Cary 118C spectrophotometer thermostated with recirculating water.

**$HOPO(OC_2H_5)(OC_6H_4NO_2)$** was synthesized as described previously.[13]

**$[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot 2H_2O$.** $[(NH_3)_5IrOSO_2CF_3](CF_3SO_3)_2$ (1.0 g), ethyl 4-nitrophenyl hydrogen phosphate (not recrystallized), and 2,4,6-collidine (0.1 mL) were dissolved in sulfolane (30 mL), and the mixture was heated to 45 °C for 24 h. The sulfolane and excess phosphate ester was then extracted with ether and the remaining solid dissolved in $H_2O$ (1 L) and absorbed on a Sephadex SP-C25 ($Na^+$ form) cation-exchange column. The column was eluted with 0.1 M $NaClO_4$, and the effluent was monitored at 285 nm. Two minor bands eluted first. These were collected separately and retained. A third band, eluted with 0.2 M $NaClO_4$, contained the desired product; it was collected, evaporated to ~70 mL, and cooled at 4 °C for 16 h. The white solid formed was collected, washed twice with ethanol and thrice with ether, and dried in vacuo. Yield: 0.32 g. Anal. Calcd for $C_8H_{28}N_6O_{20}PCl_3IrNa$: C, 10.90; H, 3.20; N, 9.54; Cl, 12.08; Na, 2.61. Found: C, 10.8; H, 3.2; N, 9.4; Cl, 11.9; Na, 3.0. $^1H$ NMR ($D_2O$): $\delta$ 1.28 (tr, $J_{H-H}$ = 7 Hz; 3 H), 4.12 (d of quart; $J_{P-H} \sim J_{H-H} \sim 7$ Hz; 2 H), 7.39 (d; $J_{H-H}$ = 9 Hz; 2 H), 8.29 (d; $J_{H-H}$ = 9 Hz). $^{31}P\{H\}$ NMR ($H_2O/D_2O$): $\delta$ +1.3 (s). $\epsilon^{max}_{216} = 6.5 \times 10^3\ M^{-1}\ cm^{-1}$; $\epsilon^{max}_{282} = 8.7 \times 10^3\ M^{-1}\ cm^{-1}$.

**$[(NH_3)_5IrOPO(OH)(OC_6H_4NO_2)](ClO_4)_2$.** The second of the two bands from the preparation of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ to be eluted with 0.1 M $NaClO_4$ was evaporated to ~15 mL and cooled to 4 °C for 16 h. The microcrystalline white solid that had precipitated was collected, washed with ethanol (2 × 2 mL) and ether (2 × 2 mL), and dried in vacuo for 8 h. Yield: 95 mg. Anal. Calcd for $C_6H_{20}N_6Cl_2IrO_{14}P$: C, 10.38; H, 2.90; N, 12.10; Cl, 10.21. Found: C, 10.8; H, 3.0; N, 11.9; Cl, 10.2. $^1H$ NMR ($D_2O$, 0.1 M DCl): $\delta$ 8.30 (d; $J$ = 9 Hz; 2 H), 7.39 (d; $J$ = 9 Hz; 2 H), 4.64 (br; 12 H; cis $NH_3$ probably obscured by HOD peak (4.9 ppm). $^{31}P\{H\}$ NMR: $H_2O/D_2O$, 0.1 M HCl, $\delta$ +2.9 (s); $H_2O/D_2O$, 1.0 M NaOH, $\delta$ +7.1 (s). $\epsilon^{max}_{220} = 6.04 \times 10^3\ M^{-1}\ cm^{-1}$; $\epsilon^{max}_{300} = 8.88 \times 10^3\ M^{-1}\ cm^{-1}$.

**4-Nitrophenyl (−)-Menthyl Phosphate.** 4-Nitrophenyl phosphorodichloridate (5.0 g) was dissolved in dry ether (20 mL) and pyridine (1.54 g) added. The suspension was stirred while (−)-menthol (3.05 g) in ether (10 mL) was added. The stirring was continued for 80 min, and then water (20 mL) and pyridine (2 g) were added, and the aqueous solution was extracted with ether (3 × 100 mL). The extract was dried ($Na_2SO_4$) and evaporated to dryness. The crude product was redissolved in ether (20 mL) and poured into water (1.5 L). On prolonged standing (3 weeks), white needles of the desired product separated, which were collected and dried in vacuo. Yield: 1.05 g. Anal. Calcd for $C_{16}H_{24}NO_6P$: C, 53.78; H, 6.77; N, 3.92. Found: C, 55.6; H, 7.0, N, 4.12. $^1H$ NMR; ($CDCl_3$): $\delta$ 8.20 (d; $J$ = 9 Hz; 2 H), 7.34 (d; $J$ = 9 Hz; 2 H), 4.25 (m; 1 H), 2.3–1.0 (complex series of multiplets; 8 H), 0.89 (tr; $J$ = 6 Hz; 7 H), 0.73 (d; $J$ = 7 Hz; 3 H). $^{31}P$ NMR ($H_2O/D_2O$): $\delta$ −5.0 (d; $J$ = 7 Hz).

**$[(NH_3)_5IrOPO(OC_{10}H_{19})(OC_6H_4NO_2)]Cl_2$.** 4-Nitrophenyl (−)-menthyl hydrogen phosphate (0.5 g), $[(NH_3)_5IrOSO_2CF_3](CF_3SO_3)_2$ (0.5 g), and 2,4,6-collidine (0.1 g) were dissolved in dry sulfolane, and the mixture stirred at 65 °C for 8 h. The solution was then extracted with ether (3 × 250 mL); the residue from the extraction was a white powder insoluble in water. The powder (0.25 g) was dissolved in ethanol (10 mL) and a saturated solution of LiCl in ethanol added (0.5 mL). The resulting precipitate was extremely fine and was washed and collected by repeated centrifugation and decantation of the supernatant. The off-white solid was dried in vacuo. Yield: 105 mg. $^1H$ NMR ($D_2O$, DSS): $\delta$ 8.30 (d; $J$ = 8 Hz; 2 H), 7.40 (d; $J$ = 8 Hz; 2 H), 2.0–0.5 (complex multiples; ~15 H). $^{31}P$ NMR ($H_2O/D_2O$): $\delta$ +0.70 (d; $J$ = 7 Hz; 1 P), +0.56 (d; $J$ = 7 Hz; 1 P).

**$[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot H_2O$.** $[(NH_3)_5IrOSO_2CF_3](CF_3SO_3)_2$ (1.35 g), $HOP(O)(OC_6H_4NO_2)_2$ (3.0 g), and 2,4,6-collidine (0.5 mL) were dissolved in sulfolane, and the mixture was heated to 50 °C for 20 h. The complex was precipitated as an oil by the addition of $H_2O$ (150 mL) and cooling in an ice bath. The water was decanted and the oil dissolved in $H_2O$ (2 L) by stirring the oil with a suspension of Dowex AG-1X8 ($Cl^-$ form) anion-exchange resin for 4 h. The resin was removed and the dissolved complex absorbed on a Sephadex SP-C25 ($Na^+$ form) cation-exchange column. The column was eluted with NaCl (0.1–0.3 M) and the effluent monitored at 285 nm. Two minor bands eluted before the major band, which contained the desired product. The solution containing this band was evaporated to ~150 mL and cooled in ice. The white precipitate that formed was collected, washed with ice-cold $H_2O$ (2 mL), and dried in vacuo. Yield: 0.25 g. Anal. Calcd for $C_{12}H_{27}N_7Cl_2IrO_{10}P$: C, 19.92; H, 3.76; N, 13.55; Cl, 9.80. Found: C, 19.9; H, 3.5; N, 13.3; Cl, 10.0. $^1H$ NMR: $D_2O$, $\delta$ 8.26 (d; $J_{H-H}$ = 9 Hz), 7.38 (d; $J_{H-H}$ = 9 Hz); $(CD_3)_2SO$, $\delta$ 8.24 (d; $J_{H-H}$ = 9 Hz; 4 H), 7.50 (d; $J_{H-H}$ = 9 Hz; 4 H), 5.12 (br; 3 H), 4.85 (br; 12 H). $^{31}P\{H\}$ NMR ($H_2O/D_2O$, pH 7, 1.0 M NaOH): $\delta$ −5.2 (s). $\epsilon^{max}_{214} = 1.6 \times 10^4\ M^{-1}\ cm^{-1}$; $\epsilon^{max}_{297} = 2.0 \times 10^4\ M^{-1}\ cm^{-1}$.

**UV/Vis Kinetics.** The kinetics of hydrolysis of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ were followed by observing the rate of release of 4-nitrophenolate at 400 nm. Equal volumes of solutions of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ (~$5 \times 10^{-5}$ M) and NaOH/$NaClO_4$ (total concentration 2.00 M) were mixed in a cuvette at 25 °C, and the increase in absorbance at 400 nm was recorded. The data sets were processed by using a nonlinear least-squares curve-fitting program, and all fitted well to single exponential functions. Each rate constant quoted is the mean ± standard deviation of at least three determinations.

A known weight of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot 2H_2O$ (~8 mg) was dissolved in $H_2O$ (1 mL). A solution of NaOH (2.00 mL, $\mu$ = 1.0 M $NaClO_4$) of the required concentration was pipetted into a cuvette and equilibrated at 25.0 °C. A 5-$\mu$L volume of the solution of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ was syringed into the cuvette and the absorbance at 400 nm recorded with time. The data showed biphasic kinetics, i.e. two 4-nitrophenolate-releasing reactions. The rates of the two reactions in the $[OH^-]$ range studied, 0.1–1.0 M, were different enough to be able to treat the two reactions independently.

A known weight of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot 2H_2O$ (3–5 mg) was dissolved in a solution of NaOH (500 $\mu$L, 1.0 M), allowed to react at 25 °C for 10 min, and then stored as a frozen solution at −10 °C. This solution was used within 24 h of its preparation. A small volume of this stock solution (5.0 $\mu$L) was added to a buffer solution (2.00 mL) at 25 °C and the required pH ($\mu$ = 1.0 M, $NaClO_4$). The increase in absorbance at 400 nm was recorded. The data from this reaction followed a single exponential decay curve, and its pseudo-first-order rate constant was evaluated as above.

A known weight of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot H_2O$ (3.5 mg) was dissolved in a solution of NaOH (500 $\mu$L, 1.00 M) and allowed to react at 25 °C for 10 min. To this solution was added glacial acetic acid (100 $\mu$L), and the solution was stored at −10 °C. This solution was used within 12 h of its preparation. A small volume of this stock solution (5.0 $\mu$L) was added to a buffer solution (2.00 mL) at 25 °C at the required pH or hydroxide concentration ($\mu$ = 1.0 M, $NaClO_4$). The data from

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this reaction followed a single exponential decay.

The hydrolysis rates of $^{-}O(O)P(OC_2H_5)(OC_6H_4NO_2)$ and $^{-}O(O)P(OC_6H_4NO_2)_2$ were determined spectrophotometrically by release of 4-nitrophenolate. The initial rate method was used, and the concentration of hydroxide was varied between runs. A stock solution of ester was prepared by dissolving a known weight of the free acid in $H_2O$ (25.0 mL). Stock solution (1.00 mL) and hydroxide solution (1.0 mL, 1.0 and 2.0 M, $\mu$ = 2.00 ($NaClO_4$)) were pipetted into a cuvette and placed in a thermostated cell holder (25 °C); after temperature equilibration the increase in absorbance at 400 nm was recorded. Only data from the first 0.5% of the reaction were used to determine the initial rates.

**$^{31}$P NMR and $^{1}$H NMR Experiments.** $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot H_2O$ (25 mg) and NaCl (58 mg) were dissolved in $H_2O$ (1.35 mL, containing 0.02 M $PO_4^{3-}$) and $D_2O$ (0.40 mL), and a $^{31}$P NMR spectrum was recorded. To this solution was added a solution of NaOH (0.25 mL, 4.0 M). After mixing of the solution, further spectra were recorded over a period of time. The signal intensities were plotted versus time after the integrated signals were normalized with respect to that of the standard, $PO_4^{3-}$. (Acquisition parameters: acquisition frequency 80.98 MHz, spectral width 9 kHz, record 8192 data points, zero fill to 16 384 data points, pulse repetition time 0.5 s, 2400 scans per spectrum.) When the reaction was complete, $NH_4Cl$ (112 mg) was added to the solution and a $^{31}P\{H\}$ NMR spectrum was recorded within 3 min of the addition. Then a $^{1}$H-coupled $^{31}$P NMR spectrum of the products was recorded.

$[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot 2H_2O$ (2 × 20 mg) was dissolved in NaOH solutions (1.5 mL, 1.0 M and 0.1 M, $\mu$ = 1.0 M ($NaClO_4$)) and the reaction allowed to proceed at 25 °C for several half-lives. $D_2O$ (0.25 mL) was added to the solutions, and then integrated $^{31}$P NMR spectra of the two solutions were recorded. The solutions were stored at 25 °C in a thermostated water bath over a period of 49 days and $^{31}$P NMR spectra recorded periodically. (Acquisition parameters: acquisition frequency 24.21 MHz, spectral width 5 kHz, pulse repetition time 1.0 s, pulse angle 90°.)

$[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot 2H_2O$ (15 mg) was dissolved in NaOH (1.5 mL, 0.2 M NaOH, 20% $D_2O$), and the reaction was maintained at ~25 °C for ~30 min. A $^{31}$P NMR spectrum was then recorded, and to this solution was added a known weight of acid to produce a buffer of known pH. Buffers used were MES (pH 6.1), CAPS (pH 10.4), and $NH_4Cl$ (pH 9.5). After addition of the acid, integrated spectra were recorded at intervals. (Acquisition parameters for all $^{31}$P NMR experiments: acquisition frequency 80.98 MHz, spectral width 9 kHz, accumulate 8192 data points, zero fill to 16 384 data points, pulse repetition time 0.5 s.)

$[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot 2H_2O$ (8 mg) was dissolved in a $D_2O$ solution of NaOD (0.5 mL, 1.0 M) with a trace of DSS as standard. The solution was filtered into a 5 mm diameter NMR tube, and consecutive $^{1}$H NMR spectra were recorded at approximately 15-min intervals. When the reaction was complete, ethanol (~1 $\mu$L) was added and a further spectrum recorded. (Acquisition parameters: acquisition frequency 199.5 MHz, spectral width 2 kHz, acquisition time 2.0 s, pulse delay 2.0 s, temp 27 °C.)

$[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot 2H_2O$ (5–10 mg) was hydrolyzed in NaOH solution (~25% $D_2O$), and a known weight of acid was added to the solution to produce a buffer of the required pH. Trimethyl phosphate (2 $\mu$L) was added as a standard. Buffers used were MES, HEPES, CAPS, and guanidinium, tetramethylguanidinium, and *n*-butylammonium chloride salts. The pH of the solutions was estimated from the acid/base ratio. $^{31}$P NMR spectra of the solutions were recorded.

$[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)](ClO_4)_2 \cdot NaClO_4 \cdot 2H_2O$ (14 mg) was dissolved in NaOH solution (250 $\mu$L, 1.0 M) and allowed to react at 25 °C for 2 h. The solution was then diluted to 500 $\mu$L with water and absorbed on a Dowex 50W-X2 ($Na^+$) cation-exchange column (0.5 × 2 cm) preequilibrated with 0.5 M NaOH (75% $D_2O$). The column was washed with 0.5 M NaOH (75% $D_2O$) until most of the 4-nitrophenolate was eluted (1 mL). The washings were collected, and a $^{31}$P NMR spectrum was recorded. (Acquisition parameters: acquisition frequency 80.98 MHz, spectral width 9 kHz, record 8192 data points, zero fill to 16 384 data points, pulse repetition time 0.5 s.)

$[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]Cl_2 \cdot 2H_2O$ (8 mg) was dissolved in NaOH (1.5 mL, 0.2 M NaOH, 20% $D_2O$), and after ~50 min a $^{31}$P NMR spectrum was recorded. Glacial acetic acid (34 $\mu$L) was added to this solution and another $^{31}$P NMR spectrum accumulated; to this solution was added NaOH (100 $\mu$L, 8 M) and a final spectrum recorded.

## Results

**Synthesis.** The complex ions $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$, $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$, and $[(NH_3)_5IrOPO(OC_{10}H_{19})(OC_6H_4NO_2)]^{2+}$ ($C_{10}H_{19}$ = (−)-menthyl) were synthesized by heating $[(NH_3)_5IrOSO_2CF_3](CF_3SO_3)_2$ and the appropriate phosphoric acid ester in sulfolane. Separation and purification of the products was by cation-exchange chromatography and crystallization. $[(NH_3)_5IrOPO_2(OC_6H_4NO_2]^{+}$ was produced as a byproduct of the synthesis of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ as a result of some $(HO)_2PO(OC_6H_4NO_2)$ impurity in the sample of $HOPO(OC_2H_5)(OC_6H_4NO_2)$. The product salts were characterized by elemental analysis and NMR and electronic spectroscopy. The $^{1}$H and $^{31}$P NMR spectra were in agreement with the proposed structures; the $^{31}$P NMR chemical shifts of the complexes showed the expected downfield shifts for coordination of the phosphate esters to the trivalent metal center.

**Table I.** Observed Rates of Production of 4-Nitrophenolate from $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ at 25 °C ($\mu$ = 1.0 M ($NaClO_4$))

| [NaOH], M | $10^4 k_{obs}$, $s^{-1}$ | [NaOH], M | $10^4 k_{obs}$, $s^{-1}$ |
|---|---|---|---|
| 0.10 | 0.319 ± 0.002 | 0.75 | 3.31 ± 0.07 |
| 0.25 | 0.85 ± 0.01 | 0.90 | 4.44 ± 0.02 |
| 0.50 | 1.90 ± 0.02 | 1.00 | 5.3 ± 0.2 |
| 0.60 | 2.46 ± 0.01 | | |

**Hydrolysis of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$.** The reaction of this ion in NaOH solution was studied by following the release of 4-nitrophenolate ion from the complex spectrophotometrically at 400 nm. The reaction was conducted at 25 °C ($\mu$ = 1.0 M ($NaClO_4$)) and obeyed the rate law

$$v = k_1[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)^{2+}][OH^-] + k_2[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)^{2+}][OH^-]^2$$

The rate constants $k_1$ and $k_2$ were determined by fitting the data in Table I to an equation of the above form. The rate constants $k_1$ and $k_2$ have the values (2.4 ± 0.2) × $10^{-4}$ L $mol^{-1}$ $s^{-1}$ and (2.9 ± 0.2) × $10^{-4}$ $L^2$ $mol^{-2}$ $s^{-1}$, respectively. $^{1}$H NMR spectra of the reaction solution on completion of the reaction showed that the only 4-nitrophenol-containing product was the 4-nitrophenolate ion.

The reaction was followed also by $^{31}$P NMR spectroscopy, with $[OH^-]$ = 0.5 M, temperature 25 °C, and $\mu$ = 1.0 M ($NaClO_4$); the rate constant for disappearance of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ was (1.7 ± 0.4) × $10^{-4}$ $s^{-1}$, almost identical with the rate of appearance of 4-nitrophenolate. The reaction yielded two phosphorus-containing products, one with a chemical shift of ~25 ppm and another with a chemical shift of 12.5 ppm. The chemical shift of the low-field signal (12.5 ppm) was independent of $OH^-$ concentration. The two compounds were produced in constant relative yields irrespective of hydroxide concentration, 81 ± 2% ($\delta$ ~25) and 19 ± 2%, ($\delta$ 12.5). They were stable in hydroxide ion solution; no change in the $^{31}$P NMR spectrum of the products was observed over a period of 49 days in either 1.0 or 0.1 M NaOH solution at 25 °C.

Identification of the products of this reaction was made from their $^{31}$P NMR chemical shifts and coupling patterns, the charge on the compounds, and their reactivity. Numerous unsuccessful attempts were made to crystallize the products of the reaction. The minor product ($\delta$ 12.5) appears to be the monodentate ethyl phosphate complex. The observed $^{31}$P NMR chemical shift is in the region expected for this complex, and the $^{1}$H-coupled $^{31}$P NMR spectrum of the complex displays a triplet with a P–H coupling constant of ~6 Hz. The stability of the complex in both acid and base also supports this assignment.

The major product also displays a triplet in its $^{31}$P NMR spectrum in the absence of proton decoupling, which implies that the phosphate still has the ethyl group bound. $^{1}$H NMR spectra of the products of the reaction conducted in $D_2O$ also indicate only a phosphate-bound ethyl group and that no ethanol was produced. By analogy with the reactivity of similar pentaamminecobalt(III) phosphate ester complexes[8,10] a substantial proportion of the reaction was expected to proceed via attack of deprotonated ammonia on the phosphorus atom. The first stable product expected from this reaction path was the chelate ethyl phosphoramidate ester. However, the effect of pH on the chemical

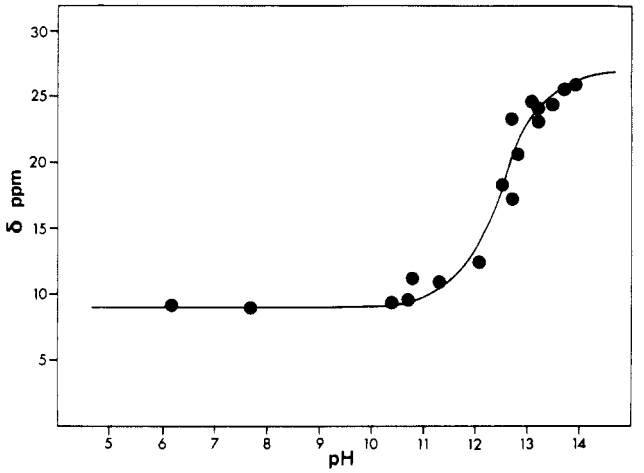



**Figure 1.** $^{31}P$ NMR chemical shift versus pH for the major product of the hydrolysis of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$. The solid line was calculated for $pK_a$ = 12.5, and the chemical shifts for the fully protonated and fully deprotonated species are 9.0 and 27.0 ppm, respectively.

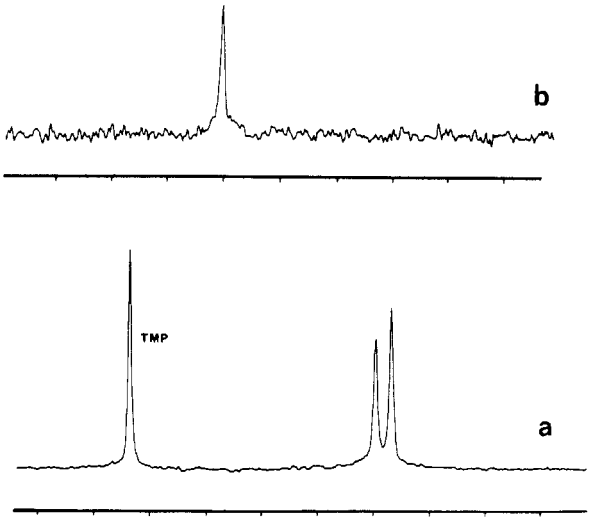



**Figure 2.** $^{31}P$ NMR spectra of the 4-nitrophenyl (−)-menthyl phosphate complex: (a) $[(NH_3)_5IrOP(O)(OC_{10}H_{19})(OC_6H_4NO_2)]^{2+}$ and standard (TMP); (b) major hydrolytic product, 24.2 ppm, hydrolyzed in 1.0 M $OH^-$ at 30 °C. The scale for both spectra is 0.5 ppm/division.

**Table II.** Pseudo-First-Order Rate Constants for the First Step in the Hydrolysis of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ Followed at 25.0 °C Spectrophotometrically at 400 nm

| [NaOH], M | $10^2 k_{obs}$, $s^{-1}$ | yield of 4-NP, % | [NaOH], M | $10^2 k_{obs}$, $s^{-1}$ | yield of 4-NP, % |
|---|---|---|---|---|---|
| 0.10 | 0.085 ± 0.005 | | 0.60 | 0.71 ± 0.02 | |
| 0.25 | 0.24 ± 0.01 | | 0.75 | 1.01 ± 0.02 | |
| 0.50 | 0.530 ± 0.01 | 97 | 1.00 | 1.7 ± 0.05 | 99 |

shift of the signal made this assignment doubtful. The chemical shift of the species in question was dependant on a protonation with a $pK_a$ of ~12.5 (Figure 1). The titration was fully reversible, and the chemical shifts of the limiting species were 9.0 ppm (fully protonated) and ~27 ppm (fully deprotonated). These observations are more consistant with the major reaction product being the monodentate N-bonded ethyl phosphoramidate complex rather than the N,O chelate.

Several other experiments were performed to try to verify the structural assignment of the major product. A 0.5 M NaOH solution containing the two products from the reaction of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ was applied to a Dowex 50W-X2 column preequilibrated with 0.5 M NaOH. Washing with 0.5 M NaOH (1.5 mL) eluted a complex displaying a 25 ppm signal but not that showing the 12.5 ppm signal. Under the conditions of this experiment the N,O chelate ethyl phosphoramidate would be a monocation whereas the hydroxo N-bonded ethyl phosphoramidate complex should be zero charged, if the bridging nitrogen was fully deprotonated in both cases. This experiment indicated that the species responsible for the 25 ppm signal was neutral or negatively charged, while the complex with the 12.5 ppm signal was cationic as expected.

An analogous complex possessing a chiral ester group was also synthesized, viz. the (4-nitrophenyl (−)-menthyl phosphato)-pentaammineiridium(2+) ion. This ion displays a pair of doublets in its $^{31}P$ NMR spectrum as a result of the diastereoisomers in the molecule; both the phosphorus atom and the menthyl group are stereogenic centers. The hydrolysis of this molecule occurred at about the same rate as that of the corresponding ethyl 4-nitrophenyl phosphato complex and yielded analogous products. The products displayed only singlets in their $^{31}P$ NMR spectra (Figure 2), suggesting that one chiral center had been lost.

**Hydrolysis of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$.** The reaction of this complex ion in basic solution was followed spectrophotometrically at 400 nm. At hydroxide concentrations above ~0.05 M, the reaction proceeds in two distinct 4-nitrophenolate-releasing steps. The first step of the reaction was followed at $[OH^-]$ between 0.1 and 1.0 M; at these concentrations the second step is slow enough to be separated graphically. All sets of data fitted well to single exponential functions. The observed pseudo-first-order rate constants are shown in Table II. The yield of 4-nitrophenol from the first step of the reaction was 98 ± 2%/mol of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$.

**Table III.** Observed Rate Constants for the Second Step in the Hydrolysis of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ [a]

| [NaOH], M/pH | $10^3 k_{obs}$, $s^{-1}$ | yield of NP, % | [NaOH], M/pH | $10^3 k_{obs}$, $s^{-1}$ | yield of NP, % |
|---|---|---|---|---|---|
| 1.00 | 2.03 ± 0.00 | 69 | 8.72[b] | 315 ± 1 | 57 |
| 1.00[b] | 2.13 ± 0.01 | | 8.26 | 310 ± 1 | |
| 0.50 | 1.99 ± 0.01 | 69 | 7.73 | 320 ± 1 | |
| 0.20 | 2.19 ± 0.02 | 66 | 7.72 | 322 ± 2 | 57 |
| 0.05 | 2.77 ± 0.03 | | 7.24 | 295 ± 1 | 63 |
| 10.85 | 23.2 ± 0.03 | 63 | 6.90 | 240 ± 1 | 57 |
| 10.85[b] | 28.5 ± 0.3 | 61 | 6.66 | 188 ± 1 | |
| 10.44 | 60.0 ± 0.1 | 63 | 6.45 | 176 ± 3 | |
| 10.44[b] | 64.5 ± 0.3 | 62 | 6.29 | 138 ± 1 | |
| 9.99 | 128 ± 0.2 | 63 | 6.10 | 108 ± 3 | |
| 9.38 | 244 ± 1 | 65 | 5.69 | 53 ± 3 | 56 |
| 8.72 | 297 ± 1 | | | | |

[a] Same conditions as those in Table II. [b] These runs were initiated with the complex at pH ~3 (see text).

The hydrolysis of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ in $OH^-$ solution obeyed the rate law

$$v = k_3[(NH_3)_5IrOPO(OC_6H_4NO_2)_2^{2+}][OH^-] + k_4[(NH_3)_5IrOPO(OC_6H_4NO_2)_2^{2+}][OH^-]^2$$

The rate constants $k_3$ and $k_4$ were determined by fitting the data in Table II to an equation of the above form. The values for $k_3$ and $k_4$ were (4.8 ± 0.7) × $10^{-3}$ L $mol^{-1}$ $s^{-1}$ and (1.2 ± 0.09) × $10^{-2}$ $L^2$ $mol^{-2}$ $s^{-1}$, respectively.

At and below an $OH^-$ concentration of 0.01 M, the reaction was monophasic; i.e., only one 4-nitrophenolate-releasing step was observed. However, under these conditions more than 1 mol of 4-nitrophenolate was released per mole of reactant; i.e., the intermediate apparently reacted faster than it was produced. Therefore, at any pH below this point, it was necessary first to produce the intermediate at a high $[OH^-]$ concentration and then reduce the pH and follow the second step of the reaction. The second step of the reaction was thereby followed between pH ~6 and $[OH^-]$ = 1.0 M.

The rate of hydrolysis of the intermediate displayed a bell-like dependence on pH, with a maximum in the rate occurring at pH ~8.0 (Figure 3). The second step of the reaction released about 65 ± 4% of the amount of NP (nitrophenolate) obtained from

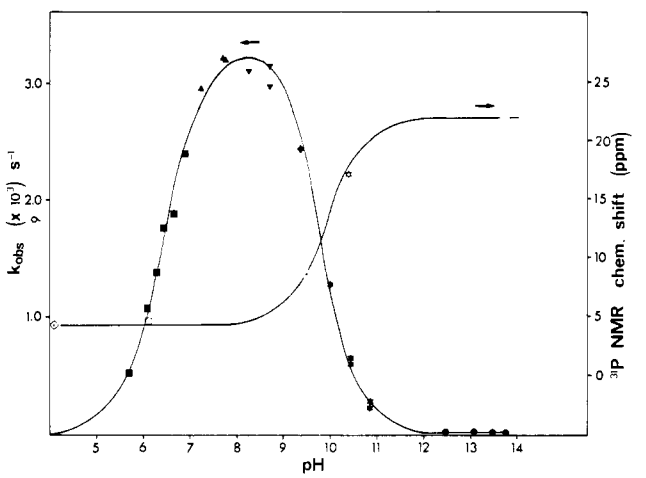
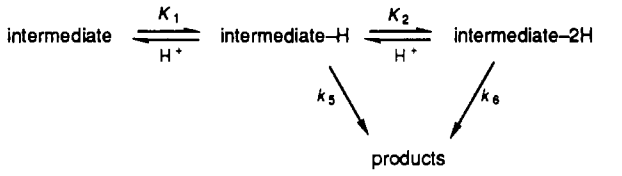



**Figure 3.** pH versus rate of the second step in the reaction of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ (filled symbols) and versus chemical shift of the intermediate (open symbols). Conditions: $\mu$ = 1.0 M ($NaClO_4$), $T$ = 25 °C. Buffers: □, Mes; ▲, Hepes; ▼, Tris; ♦, Ches; ☆, Caps; ○, $OH^-$; ⊙, $NH_4^+$; ⊡, acetate.

the initial step. The reactivity of the intermediae can be characterized by the following scheme:




The rate constants and p$K_a$'s for this system are p$K_1$ = 6.39 ± 0.02, p$K_2$ = 9.76 ± 0.05, $k_5$ = 3.2 × $10^{-3}$ $s^{-1}$, and $k_6$ = 2.0 × $10^{-5}$ $s^{-1}$, all at 25 °C and $\mu$ = 1.0 M ($NaClO_4$).

The reaction of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ in hydroxide ion solution was also followed by $^{31}$P NMR spectroscopy. In 1.0 M NaOH solution the disappearance of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ was too fast to follow; the initial products of the reaction however were compounds with chemical shifts of 6.9 ppm (30%) and 21.9 ppm (70%) (Figure 4). The signal at 6.9 ppm is coincident with the signal due to added $[(NH_3)_5IrOPO_2(OC_6H_4NO_2)]^+$, synthesized independently, and the compound does not react further in the time scale of this experiment. The major product ($\delta$ 21.9) decayed further in 1.0 M $OH^-$ to yield two products. One had a chemical shift of 15.1 ppm, while the other had a chemical shift of 10.1 ppm. The rate of appearance of these products in 1.0 M NaOH, (1.6 ± 0.1) × $10^{-5}$ $s^{-1}$ at 25 °C, was almost identical with the rate for the second 4-nitrophenolate-releasing step at that hydroxide concentration. The yield of NP produced in the second step at 1.0 M $OH^-$ was 69% of the initial concentration of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$, identical with the yield of the major product ($\delta$ 21.9) in the initial step.

The compounds produced in the initial step of the reaction were assigned as $[(NH_3)_5IrOPO_2(OC_6H_4NO_2)]^+$ (30%) and the *cis*-hydroxo(*N*-4-nitrophenyl phosphoramidato)iridium(III) complex (~70%) by their $^{31}$P NMR chemical shifts and by analogy with the previous complex.

When the pH of a solution of the initial products is reduced by the addition of CAPS to produce a buffer in the region of pH 10.4, the $^{31}$P NMR signal at ~22 ppm shifts to 17.1 ppm, which is replaced slowly by a signal at 30.7 ppm with a rate constant of (8.5 ± 2.0) × $10^{-4}$ $s^{-1}$ at 25 °C. While this signal at 30.7 ppm is the predominant product, a signal at 9.3 ppm also appears in the spectrum.

When the pH of a solution of the initial products is reduced by the addition of MES to produce a buffer in the region of pH 6.1, the $^{31}$P NMR signal at ~22 ppm is replaced by a signal at 4.6 ppm, which decays to form a signal at 30.7 ppm with a rate constant of (7.2 ± 0.5) × $10^{-4}$ $s^{-1}$ at 25 °C. Slowly the molecule

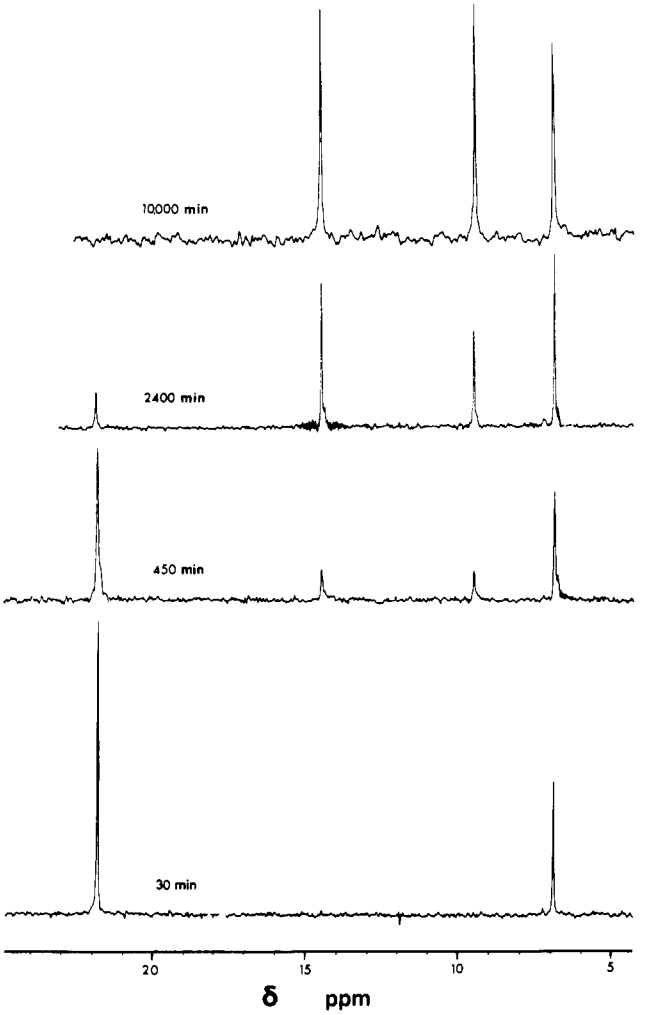



**Figure 4.** $^{31}$P NMR spectra showing the second step in the reaction of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$. Conditions: NaOH = 1.0 M, T = 25 °C, parameters as per text.

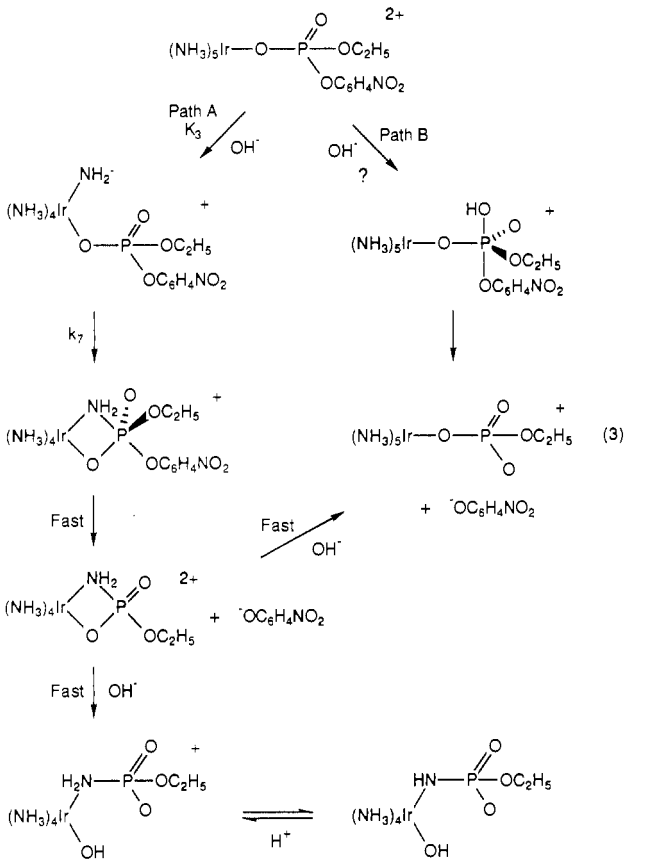
responsible for the signal at 30.7 ppm yields a product with a chemical shift of 11.4 ppm.

When the pH of a solution of the initial products is reduced by the addition of $NH_4Cl$ to produce a buffer in the region of pH 9.5, the $^{31}$P NMR signal of the intermediate is seen only fleetingly at ~8.5 ppm and yields a product with a chemical shift of 30.8 ppm, which in a subsequent reaction yielded a complex with a $^{31}$P NMR chemical shift of 9.6 ppm. In a similar experiment in acetate buffer (pH ~4) the chemical shift of the major intermediate was shifted to 4.3 ppm. The intermediate was stable in this condition and did not react further.

Further argument is desirable to sustain the structural assignments of the products. For example a $^{31}$P chemical shift of 9.0 ppm was thought to be incompatible with a four-membered-ring chelate phosphoramidate but was in the region predicted for the N-protonated N-bound ethyl phosphoramidate. This is consistent with the observation that N-coordination of phosphoramidate ion to a Co(III) metal center resulted in an upfield shift of 1.5 ppm[10] in the $^{31}$P NMR spectrum of the phosphoramidate and a chemical shift of free ethyl phosphoramidate of 9.9 ppm.[8] The large downfield shift on deprotonation at the nitrogen site is in agreement with the result obtained previously where deprotonation at the nitrogen site of the N,O chelate phosphoramidate on Co(III) resulted in a reversible downfield shift of ~16 ppm.[11]

At first sight, there appeared to be an alternative explanation for the chemical shift variation with pH, other than deprotonation, namely that there was a pH dependent equilibrium between the N,O chelate phosphoramidate ester and the N-bonded phosphoramidate ester. The equilibrium would involve rapid ring-opening and -closing reactions. Since only one signal was observed in the

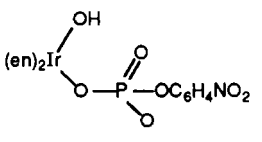
**Scheme I.** Possible Second-Order Reaction Paths for $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ in Hydroxide Solution




$^{31}P$ NMR spectra, it is only possible to calculate a lower limit for the rate constants for the ring-opening and -closing reactions. For two equally populated states, the lifetime of the individual states at the coalescence temperature is given approximately by the equation[12]

$$\tau_c = \sqrt{2}/\pi(\nu_A - \nu_B)$$

where $\tau_c$ is the lifetime at the coalescence temperature and $\nu_A$ and $\nu_B$ (Hz) are the chemical shifts of the two species. The equation can be readily applied to the spectra of the product of the $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ reaction, assuming that the system consists of two rapidly interconverting species. When the signal appears halfway between the two extreme resonances (i.e. at 18 ppm), the lifetimes of the two species involved must be equal and be shorter than $3 \times 10^{-4}$ s. This means that the rate constants involved must be greater than $3 \times 10^3$ $s^{-1}$. By comparison, the estimated rate constant for intramolecular attack of hydroxide ion on the phosphorus center of cis-coordinated 4-nitrophenyl phosphate bound to the Ir(III) center in the complex **1** is $\sim 10^{-6}$ $s^{-1}$ at 25 °C.[13] The magnitude of the rate constant



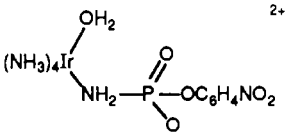
**1**

required to produce coalescence in the $^{31}P$ NMR spectra therefore precludes the possibility that there are two rapidly interconverting species in solution.

In the ion-exchange experiment with the products of the reaction of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ in 0.5 M NaOH, the complex displaying the ~25 ppm signal elutes from the column faster than the monocationic monodentate monoester complex ($\delta$ 12.5). If this were chelate ethylphosphoramidate, the species should either be a mono- or a dication; if however the species was the N-deprotonated N-bound monodentate ethyl phosphoramidate complex, the complex would be zero charged and would therefore elute from the cation-exchange column faster than the monocationic product.

Moreover, the (−)-menthyl-containing complex ion, $[(NH_3)_5IrOPO(OC_{10}H_{19})(OC_6H_4NO_2)]^{2+}$, hydrolyzed at a rate similar to that of the $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ complex and yielded a similar product ratio with similar $^{31}P$ NMR chemical shifts. The $^{31}P$ NMR spectrum of the reactant displayed a well-separated doublet, due to the diastereomers arising from the (−)-menthyl group and the phosphorus chiral centers. The products however both retain the (−)-menthyl group bound to the phosphorus atom and yet display only singlets in the $^{31}P$ NMR spectrum. This is expected for the high-field signal arising from $[(NH_3)_5IrOPO_2(OC_{10}H_{19})]^+$, since the phosphorus center is now achiral. The low-field signal however, if it were due to a chelate, should reflect the chirality, and a doublet would have been expected in the $^{31}P$ NMR spectrum especially since the doublet is observed with the parent diastereoisomeric diester complexes. Admittedly, this experiment cannot be conclusive unless both diastereoisomers are observed; however, the negative result is consistent with the argument that the phosphorus center is not a stereogenic center, i.e. it is not chelated.

The reactivity pattern of the major intermediate product of the $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ reaction is also consistent with its assignment as the monodentate N-bound phosphoramidate ester. The rate of hydrolysis of this intermediate is dependent on two deprotonations. One site ($pK_a$ 6.4) must be deprotonated for reaction to occur. The other, with a $pK_a$ of 9.8, reduces the rate of reaction by $10^2$-fold. These $pK_a$'s may be assigned to the cis-aqua ligand and the phosphoramidate $NH_2$ group in the cis-aqua *N*-4-nitrophenyl phosphoramidato complex depicted (**2**).



**2**

The products of the hydrolysis of these complexes are therefore assigned as the monodentate N-bound phosphoramidate esters and the monodentate phosphate monoesters.

**Hydrolysis of the Uncoordinated Phosphate Esters.** The hydrolysis of $^-O_2P(OC_2H_5)(OC_6H_4NO_2)$ in NaOH solution was first order in both phosphate ester and hydroxide with a second-order rate constant at 25 °C of $(3.3 \pm 0.3) \times 10^{-7}$ L $mol^{-1}$ $s^{-1}$.

The hydrolysis of $^-O_2P(OC_6H_4NO_2)_2$ in hydroxide solution was determined by the initial rate method, and the reaction was first order in both reagents. The second-order rate constant for the reaction was $(1.3 \pm 0.1) \times 10^{-5}$ L $mol^{-1}$ $s^{-1}$ at 25 °C and $\mu$ = 1.0 M ($NaClO_4$).

## Discussion

In alkaline solution the two reactants $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ and $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ each yielded two products in constant ratio over the pH range studied. The minor products (~20–30%) were the monodentate monester complex ions $[(NH_3)_5IrOPO_2(OC_2H_5)]^+$ and $[(NH_3)_5IrOPO_2(OC_6H_4NO_2)]^+$, respectively. The predominant products (~70–80%) however were phosphoramidate monoesters that must result from intramolecular attack of a coordinated amido ion at the phosphorus center (Scheme I), since that is the only source of ammonia.

By analogy with the reactions described previously, intramolecular attack of amido ion should produce an aminophosphorane that decays to yield the N,O ethyl phosphoramidate chelate. This chelate apparently rapidly opens to yield the N-bonded ethyl phosphoramidate. The ring-opening reaction most likely proceeds largely with P–O cleavage, as observed for the analogous reaction of the chelate ethyl phosphate complex $[(en)_2IrO_2P(O)OC_2H_5]$.[13]

At first glance, the production of the monodentate phosphate monoesters could arise via intermolecular attack of $OH^-$ on the initial reactants, (Scheme I, path B). This mechanism is consistent

with the observation that the apparent rate constant for the reaction is 200–400-fold larger than that for the analogous reaction for the uncoordinated phosphate esters. This rate enhancement is of the order observed for the intermolecular reactions of monodentate esters coordinated to Ir(III) and Rh(III) metal centers.[14] However, the kinetics of hydrolysis of $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ and $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ show two term rate laws, one term first order in complex and $OH^-$ and another first order in complex and second order in $OH^-$, i.e. overall third order. The products and their relative yields, however, do not vary over the hydroxide concentration range 0.1–1.0 M despite the considerable difference in the relative contributions of the two paths to the observed rate. This implies that either there is an accidental coincidence and the two paths produce the same products in the same ratio or there is some common intermediate after the rate-determining step from which both products are formed.

This second explanation seems to be the most likely given the constant product ratio from both sources over a wide range of conditions. The common intermediates would be the N,O chelate esters. Rupture of the P–N bond would yield the monodentate phosphate ester, and rupture of the P–O bond would yield the monodentate N-bound phosphoramidate ester. There are several possibilities for the nature of the reaction that displays the second-order term in $[OH^-]$. One is that it proceeds via a hexacoordinate intermediate; such paths are implicated in the hydrolysis of a Co(III)-coordinated phosphate ester.[15] In addition, hexacoordinate species have been postulated as intermediates in the hydrolysis of oxyphosphoranes in acetonitrile.[16] Another possibility is that the term reflects a deprotonation of the intermediate phosphorane. However, these possibilities cannot be distinguished on the information available at present.

The intramolecular attack of coordinated amido ion on the phosphorus center dominates the reactivity of both $[(NH_3)_5IrOPO(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ and $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ in hydroxide solution, accounting for at least 70% and probably all the products. If the reaction proceeds as shown in Scheme I, i.e. the third-order term is ignored for the moment and the preequilibrium $K_3$ is assumed, the rate of loss of reactant by path A is

$$-d[(NH_3)_5Ir(ester)^{2+}]/dt = k_7[(NH_3)_4(NH_2^-)Ir(ester)^{2+}] \quad (1)$$

This assumption is well grounded, since it is known that exchange of ammine protons for $[(NH_3)_6Ir]^{3+}$ is rapid in hydroxide solution, with a bimolecular rate constant of $1.5 \times 10^4$ L mol$^{-1}$ s$^{-1}$ at 25 °C.[17] Equation 1 yields

$$k_{obs} = \frac{k_7K_3[OH^-]}{K_3[OH^-] + K_w} \quad (2)$$

Since $K_3[OH^-] \ll K_w$, eq 2 reduces to

$$k_{obs} = k_7\frac{K_3}{K_w}[OH^-] \quad (3)$$

which is the form of the observed rate law with

$$k = k_7\frac{K_3}{K_w} \quad (4)$$

If the p$K_a$ of the cis-ammine ligands is ~17, the rate constant for the unimolecular attack of amido ion on the phosphorus center in the complex $[(NH_3)_4(NH_2^-)IrOPO(OC_2H_5)(OC_6H_4NO_2)]^+$ is $\sim 10^{-1}$ s$^{-1}$ at 25 °C. The p$K_a$ of the iridium(III)-bound ammines is estimated to be ~17 because generally the p$K_a$ of Ir(III) complexes is ~1 p$K_a$ unit greater than that of the corresponding Co(III) complex[17,18] and the p$K_a$ for dicationic cobalt(III) ammine complexes has been estimated at ~16.[19] The rate constant so calculated for the analogous Co(III) reaction was ~10 s$^{-1}$.[8] The rate of intramolecular attack of iridium(III)-bound amido ion at the phosphorus center proceeds $\sim 10^6$-fold faster than the rate of intermolecular attack of hydroxide ion (1 M) on the free ligand. This rate difference is due in large part to the intramolecularity of the reaction ($\sim 10^4$) and in small part to the effect of the metal ion on the electrophilicity of the phosphorus atom ($\sim 10^2$).

An analogous assessment for the rate of attack of coordinated amido ion on the phosphorus center of $[(NH_3)_5IrOPO(OC_6H_4NO_2)_2]^{2+}$ yields a rate constant of 1 s$^{-1}$ at 25 °C.

The *cis*-aqua(*N*-4-nitrophenyl phosphoramidato)tetraammineiridium(III) ion generated from the initial diester reacts in a subsequent step to yield 4-nitrophenolate ion and other complex ion products. The bell-shaped pH–rate profile can be accommodated by two deprotonations. In the pH region 5–8, the rate is controlled by a deprotonation of the cis-aqua ligand (p$K_a$ 6.39 ± 0.02). In the region pH 8–11, the rate is controlled by a p$K_a$ of 9.76 ± 0.05, which is most likely the deprotonation at the phosphoramidate nitrogen center. The chemical shift of the N-bound 4-nitrophenyl phosphoramidato intermediate complex was dependent on pH, following a titration curve with a p$K_a$ ~9.9 (Figure 3), in agreement with the kinetically determined p$K_a$.

There is a difference in the p$K_a$ of the phosphoramidate group between the two types of complexes of more than 2 units, the difference arises from the esterifying group, ethyl in one case and 4-nitrophenyl in the other. Overall, the rate diminution upon deprotonation at the phosphoramidate nitrogen is expected, since deprotonation must reduce the electrophilic character of the phosphorus atom. Attack of the cis-hydroxo ion on the N-bound phosphoramidate ester should yield initially the N,O chelate phosphoramidate and 4-nitrophenolate. $^{31}$P NMR observations show that, at both pH 10.4 and 6.1, the initial product of the reaction had a chemical shift of 30.7 ppm, ascribed to the N,O chelate phosphoramidate. In addition to the product at 30.7 ppm, a signal at ~10 ppm appeared in the spectrum, which is probably the N-bound ring-opened species.

The reactions demonstrate the efficacy of the intramolecular attack of cis-coordinated amino ion on coordinated phosphate esters when coordinated to the relatively large Ir(III) ion. The larger central ion does appear to inhibit ring closure however in forming the strained four-membered ring relative to that in analogous Co(III) complexes by $\sim 10^3$-fold.[8,15]

This work also indicates that the N,O-chelated 4-nitrophenyl phosphoramidate ester undergoes chelate ring opening readily without loss of the ester group even when the ester is a good leaving group. Also, the only observed reaction of the chelate is the ring-opening reaction. However, the product, the cis-hydroxo N-bound 4-nitrophenyl phosphoramidato complex subsequently loses the ester group by intramolecular attack of the cis-hydroxo ligand at the phosphorus center. Moreover, the ring-opening reaction of the chelate phosphoramidate intermediate appears to occur via phosphorus–oxygen cleavage like the ring-opening reaction of the chelate ester $[(en)_2IrO_2PO(OC_2H_5)]^+$ ion under similar conditions.[13]

It is generally accepted that a nucleophile attacking a four-coordinate phosphorus atom will occupy an axial position in the resulting phosphorane.[20,21] In the present systems the resulting four-membered ring will span axial–equatorial positions, since the strain required for the ring to span equatorial–equatorial positions (120°) is much larger.[1,20] These conditions imply that the ester group should occupy an equatorial position in the aminophosphorane as it is initially formed (Scheme II). Moreover, an extension of the principle of microscopic reversibility[1] requires

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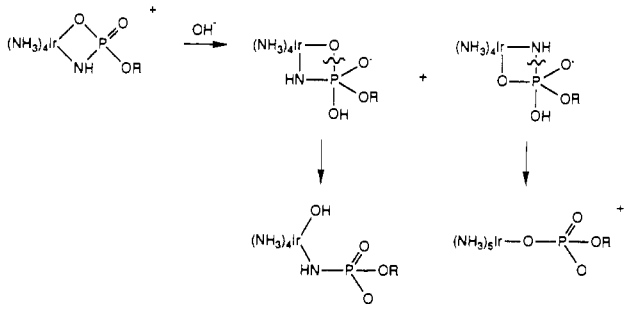
**Scheme II.** Proposed Reaction Scheme for the Ring Opening of the Iridium(III) Chelated Phosphoramidate Esters



that the leaving group, if it is of a nature similar to that of the nucleophile,[22] depart from an axial position in the phosphorane. In this instance therefore, since the ester group is located equatorially in the initially formed aminophosphorane, some form of ligand reorganization, such as pseudorotation[23] or the turnstile mechanism,[21] is required to place the ester group in an axial position. The fact that the products detected in the reaction are an N-bound phosphoramidate ester and O-bound phosphate ester implies that the required pseudorotation occurs much less readily than chelate ring opening at either the O-P or N-P bonds.

The ring-opened molecules, however, are not subject to the same constraints; they can ring close to form an aminophosphorane, that conforms to the requirements described above. The entering nucleophile occupies an axial position in the phosphorane that is formed, the ring substituents span axial-equatorial positions, and the ester group can readily be axially located in the resulting phosphorane. In this manner, the 4-nitrophenolate group is readily cleaved from the complex.

Unfortunately, this system has not allowed an estimation of the effect of chelation on the rate of exocyclic cleavage. It has shown however that the putative N,O-chelate phosphoramidate ester is not a long-lived species in hydroxide ion solution. The aminophosphorane formed by $OH^-$ attack on the N,O chelate decomposes with ring opening too fast to allow pseudorotation to realize ester hydrolysis. The study therefore raises some doubt as to whether the chelation of phosphate monoesters could be responsible for their extremely rapid rates of hydrolysis in certain enzymes.

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# Coordination of Aquated Cis-Platinum(II) Diamines to Purine Nucleosides. Kinetics of Complex Formation

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Kinetics for the formation of 1:1 and 1:2 complexes between various aquated cis-Pt(II) diamines and the purine nucleosides adenosine, guanosine, 1-methylguanosine, inosine, 1-methylinosine, and 9-(β-D-ribofuranosyl)purine have been studied by LC in aqueous solution (pH 4) at 298.2 K. Substitution of the N-H protons in *cis*-$Pt^{II}(NH_3)_2$ with methyl groups gives the order $CH_3NH_2$ > $NH_3$ > $(CH_3)_2NH$ > tetramethylethylenediamine for the complexation rate of Pt compounds. Apart from steric hindrances exerted by the methyl groups, the reactivity of these Pt(II) ions can be influenced by other factors. The H-bonding ability of the amine ligands does not, however, significantly contribute to the kinetics under these conditions. The complexation rate of purine nucleosides follows the order Guo ≈ 1-MeGuo > Ino ≈ 1-MeIno > Puo > Ado with each Pt(II) compound. The minor reactivity difference between guanine and hypoxanthine derivatives is attributed to greater basicity of the N7 site of the former compounds. In contrast, the complexation rate is drastically influenced by the substituent at C6 of the purine ring. Formation of an H-bond from the coordinated water molecule to C(6)O plays an important role in the enhanced reactivity of 6-oxo-substituted purines, whereas the C(6)$NH_2$ group sterically prevents the attack of Pt(II).

## Introduction

Coordination of platinum(II) compounds to nucleic acids and their fragments has been the subject of numerous studies in the last two decades owing to the anticancer activity of *cis*-Pt-$(NH_3)_2Cl_2$ and related compounds.[1] At present, a considerable agreement exists that DNA is the main target of these drugs in tumor cells. Binding studies with mono- and oligonucleotides, nucleosides, and model compounds by X-ray crystallography and NMR spectroscopy have given valuable information about the available coordination sites. Among the wide variety of different binding modes thus far observed, the most preferred one appears to be the coordination to the guanine N7 site, both mono- and bifunctionally.[1a,2] Especially important is the formation of a bis(guanosine) complex as an intrastrand cross-link between two adjacent guanine bases in DNA, which has been suggested to play a vital role in the biological activity of these compounds.[3]

Both thermodynamic stability and kinetics of complexation have been employed to explain the strong preference of Pt(II) binding to guanine N7. Although almost equal formation constants were reported for the 1:1 complexes of aquated *cis*-$Pt^{II}(NH_3)_2$ with the ribonucleosides adenosine, cytidine, and guanosine,[4] this lack of thermodynamic selectivity was subsequently questioned.[5] On the other hand, recent theoretical studies have revealed the thermodynamic preference of mono- and bifunctional Pt(II) for guanine

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