Metal Ion Promoted Phosphate Ester Hydrolysis. Intramolecular Attack of Coordinated Hydroxide Ion

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Abstract: The phosphate diesters, ethyl 4-nitrophenyl phosphate, and bis(4-nitrophenyl) phosphate in *cis*-$[(en)_2Ir(OH)O_2P(OR)_2]^+$ (en = 1,2-diaminoethane) react with the *cis*-hydroxo group at pH 8 to liberate nitrophenolate ion $\sim 10^6$-fold faster than for the free ligand under the same conditions. The expected products of these reactions, the chelate phosphate esters, were not observed; only the ring-opened monodentate monoester products were obtained as a result of P–O bond cleavage. The *cis*-hydroxo ligand is a good nucleophile toward bound phosphate esters; however, the reactions of Ir(III) complexes described here proceed about 10^3-fold slower than the reactions of the analogous Co(III) complexes despite the more basic coordinated OH^- on the iridium(III) ion. The reduction in rate is ascribed to the larger size of the Ir(III) ion compared to Co(III), which makes ring closure more difficult. While it is clear that coordinated OH^- can be an effective nucleophile especially in an intramolecular reaction, it appears unlikely that reactions forming four-membered chelate phosphate esters will be relevant in biological systems because the biologically relevant ions Mg^{2+} and Zn^{2+} are relatively large ions (>Ir(III)). Also, the observation that the chelated ester prefers to undergo ring opening rather than lose the alcohol group implies that such chelate esters are unlikely to be effective in the enzymic systems.

The cleavage of P–O bonds in phosphate derivatives provides the energy required by organisms for many tasks, e.g. muscular movement, synthesis of complex biological molecules, and transport of solutes against concentration gradients. Biological phosphoryl-transfer reactions are mediated by enzymes, many of which require metal ion cofactors.[1] This observation has prompted research into the role of metal ions in both the enzymic and nonenzymic reactions of phosphate derivatives.

The work of Westheimer[2] and others[3] in the 1950s and 1960s demonstrated that organic phosphates possessing five-membered rings including the P atom hydrolyze up to 10^7-fold faster than their acyclic analogues.[2] The reason proffered for this enhanced reactivity is that ring strain destabilizes the phosphate ester and is relieved on the way to the phosphorane intermediate relative to the noncyclic ester. Since that work, several groups of researchers[4-6] have suggested that the origin of the rate enhancement in the enzymic hydrolysis of phosphate monoesters may, in part, be due to chelation of the substrate by a metal ion. The presence of this strained four-membered ring may induce rapid exocyclic hydrolysis of the ester group by a mechanism similar to that described by Westheimer.

Cobalt(III) amine complexes of orthophosphate are quite stable, and in some instances[7,8] the chelate phosphate is thermodynamically preferred over the monodentate species at neutral pH. Despite this stability, attempts[4,6,8] to synthesize chelate phosphate esters have proven fruitless although interesting dimeric species have arisen from such attempts.[9] The difficulties encountered, in part, implied that such chelates might be particularly reactive and therefore worth pursuing further.

The strategy used in the current attempt to synthesize a chelated phosphate ester was indicated by the results obtained[10] for an intramolecular attack of an amido ion on a coordinated diester. The precursor complex should therefore possess a phosphodiester coordinated cis to a water molecule. After deprotonation of the water ligand, the resulting coordinated hydroxide ion may attack the phosphorus center to yield an oxyphosphorane, which should then decay to the desired chelated phosphate monoester.

Ir(III) was the metal ion chosen as the locus in order to limit complications arising from metal–ligand bond rupture and cis–trans isomerization. Iridium(III) amine complexes in general are relatively inert to dissociation of their ligands and also resist rearrangement.[11]

Experimental Section

All chemicals used were of analytical grade unless otherwise stated. Electronic spectra were recorded on a Hewlett Packard 8450A spectrophotometer. Kinetic traces were recorded on either the spectrophotometer above equipped with a 89100A temperature-controlled cell holder or a Cary 118C instrument thermostated with a recirculating water bath. ^1H NMR spectra were recorded with a JEOL FX-200 spectrometer ($\sim$22 °C). ^{31}P NMR spectra were recorded with either a JEOL FX-60 (25–27 °C) or a Bruker CXP-200 spectrometer operating at 24.21 and 80.98 MHz, respectively.

Buffers were made up from standardized $HClO_4$ or NaOH (Volucon) in CO_2-free glass-distilled water. The buffer components were used as supplied by the manufacturers: Tris, Caps (Sigma Chemical Co.), Hepes, Mes (BDH Chemicals). The ionic strength of the buffers was maintained at 1.0 M ($NaClO_4$). The pH of the deaerated buffers was measured at 25 °C with a Radiometer PHM 26 pH meter fitted with G202C glass and K4122 calomel electrodes, which were calibrated with standard buffers. Abbreviations for buffers used are as follows: Caps, (cyclohexylamino)propanesulfonic acid; Ches, 2-(cyclohexylamino)ethane sulfonic acid; Hepes, *N*-(2-hydroxyethyl)piperazine-*N'*-ethanesulfonic acid; Mes, 2-(*N*-morpholino)ethanesulfonic acid; Tris, tris(hydroxymethyl)aminomethane.

All evaporations were carried out at $\sim$20 Torr in a Buchi rotatory evaporator such that the solution temperature did not exceed 25 °C.

$HOP(O)(OC_2H_5)(OC_6H_4NO_2)$. To 4-nitrophenyl phosphorodichloridate (5.12 g) in dry ether (30 mL) was added dry pyridine (1.58 g) in ether (10 mL). Nitrogen was passed over the surface of the resulting suspension, and ethanol (0.92 g) in ether (15 mL) was added dropwise over 15 min. When the addition was complete, pyridine (1.58 g) in water (30 mL) was added and the mixture stirred for a further 10 min. An excess of 5 M HCl solution was added to the biphasic mixture, which was then extracted three times with ether. The ethereal solution was dried with sodium sulfate and evaporated to yield the product as a white solid, yield 3.8 g. The crude product was recrystallized from hot ether/pentane; mp 102–103 °C. Anal. Calcd for $C_8H_{10}NO_6P$: C, 38.88; H, 4.08; N, 5.67; P, 12.54. Found: C, 38.9; H, 4.1; N, 5.7; P, 12.4. ^1H

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NMR (D_2O; ~pH 7): 1.33 (tr, J = 7.2 Hz, 3 H), 4.12 (dq, $J_{H-H} \sim J_{P-H}$ ~ 7.2 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 8.20 (d, J = 8.1 Hz, 2 H). $^{13}C\{H\}$ NMR (D_2O, ~pH 7): −51.1 (d, J = 7.5 Hz), −2.95 (d, J = 6.0 Hz), 53.89 (d, J = 4.5 Hz), 59.15 (s), 76.78 (s), 90.69 (d, J = 5.9 Hz). $^{31}P\{H\}$ NMR (H_2O/D_2O, pH 7): −5.0 (s).

***cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$S_2O_6 \cdot {}^1/_2H_2O$.** To *cis*-[(en)$_2$Ir(OSO_2CF_3)$_2$]CF_3SO_3 (4.0 g) dissolved in dry sulfolane (40 mL) was added HOP(O)(OC_2H_5)($OC_6H_4NO_2$) (1.35 g) and the solution heated to 50 °C for 22 h. To this solution was added water (10 mL), acidified with concentrated $HClO_4$ (0.5 mL), and the solution stirred for a further 3 h. The solution was extracted twice with ether, and the residue, dissolved in water (1 L), acidified to ~pH 1 with $HClO_4$. The crude mixture was sorbed on a Dowex 50W-X2 (H^+) column, the column was washed with water and eluted with 2 M HCl. The eluate was monitored at 285 nm, and the major band, containing the desired product, was collected after several minor bands had eluted. The solution was evaporated to dryness and the resulting oil dissolved in warm methanol (20 mL); a warm solution of $Li_2S_2O_6$ (1.0 g in 10 mL of methanol) was added dropwise until no more precipitation occurred (excess dithionate redissolves the precipitate). The solution was cooled, and the solid was collected, washed twice with methanol and twice with ether, and dried in vacuo for 18 h; yield 0.53 g. Anal. Calcd for $C_{12}H_{29}N_5IrO_{14}PS_2$: C, 19.1; H, 3.9; N, 9.3; P, 4.1. Found: C, 19.2; H, 3.7; N, 9.2; P, 4.0. ^1H NMR (downfield from DSS, D_2O, 0.05 M $DClO_4$): δ 1.28 (tr, J_{H-H} = 7.1 Hz, 3 H), 2.59 (br), 2.75 (br, 8 H total), 4.14 (dq, $J_{P-H,H-H} \sim 7$ Hz, 2 H, 5.70 (br), 6.00 (br), 6.27 (br, 8 H total), 7.41 (d, J = 9.3 Hz, 2 H), 8.30 (d, J = 9.3 Hz, 2 H). $^{31}P\{H\}$ NMR (H_3PO (85%), H_2O/D_2O, pH 2): δ 1.600 (1 P), 1.624 (1 P).

***cis*-[(en)$_2$Ir(OH_2)OP(O)($OC_6H_4NO_2$)$_2$](ClO_4)$_2$.** *cis*-[(en)$_2$Ir(OSO_2CF_3)$_2$](CF_3SO_3) (1.0 g) and HOP(O)($OC_6H_4NO_2$)$_2$ (0.45 g) were dissolved in sulfolane (20 mL); with the addition of 2,4,6-collidine (0.2 g), the solution was heated to 40 °C for 19 h. After this time, dilute triflic acid (CF_3SO_3H) (1 mL, 0.2 M) was added and the solution stirred for a further 3 h. The solution was then extracted with ether (2 × 300 mL), and the residue, dissolved in H_2O (2000 mL). After the pH was adjusted to ~2 with HCl, the mixture was sorbed on a Sephadex SP-C25 column (Na^+ form). The column was washed with water (pH ~2) and then eluted with NaCl (0.1–0.2 M, pH ~2). The eluate was monitored at 285 nm. Several unidentified minor bands eluted before the major band containing the desired product came off the column with 0.2 M NaCl. This eluate was evaporated to 150 mL, and $LiClO_4$ (10 g in 20 mL of H_2O) was added. The solution was kept at 4 °C for 16 h. The fine precipitate that formed was collected, washed with cold water (2 mL), and dried in vacuo (0.25 g). Anal. Calcd for $C_{16}H_{26}N_6Cl_2IrO_{16}P$: C, 22.13; H, 3.02; N, 9.68. Found: C, 22.5; H, 3.1; N, 9.4.

The perchlorate salt of *cis*-[(en)$_2$Ir(OH_2)OP(O)($OC_6H_4NO_2$)$_2$]$^{2+}$ was very insoluble in water and was not useful for experiments requiring a reasonable concentration of complex, e.g. NMR experiments. The chloride salt was used for these experiments, and it was obtained by evaporation of the eluate from the ion-exchange column to ~50 mL and by cooling it at 4 °C for 16 h. The chloride salt that deposited was collected and dried in vacuo for 18 h. Elemental analysis indicated that 3 mol of NaCl coprecipitated with the monohydrate complex. Anal. Calcd for $C_{16}H_{28}N_6Cl_5IrNa_3O_{10}P$: C, 20.6; H, 3.0; N, 9.0; Cl, 19.9. Found: C, 20.6; H, 3.0; N, 9.0; Cl, 18.5. ^1H NMR (D_2O, 0.01 M DCl): δ 2.59 (br, 4 H), 2.77 (br, 4 H), 5.7, 5.9, 6.2, 6.45, 6.63 (all br, 8 H), 7.40 (d, J = 9 Hz, 4 H), 8.28 (d, J = 9 Hz, 4 H). ^{31}P NMR (H_2O/D_2O, pH 10): δ −6.0 (s).

Spectrophotometric Kinetics. A solution of *cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$S_2O_6 \cdot {}^1/_2H_2O$ (10 μL, ~10^{-2} M) was syringed into a thermostated cell containing the required hydroxide or buffer solution (2.0 mL). The solution was rapidly mixed, and the increase in absorbance at 400 nm was recorded with time. The data sets were processed by a non-linear least-squares iterative program (LSTSQR)[12] and fitted well to single-exponential decays. At pH 6.29 the rate constant was determined by the initial rate method with a range of complex concentrations to confirm the expected reaction order. The molar absorbtivity of nitrophenolate at this pH was 2610 mol L^{-1} cm^{-1}. Only the first 1–2% of the reaction was used to determine the rate of nitrophenolate production.

A small buffer effect was observed with Hepes at pH 8.22. Rate constants of 4.53 × 10^{-5}, 4.80 × 10^{-5}, and 5.23 × 10^{-5} s^{-1} were obtained for 0.1, 0.2, and 0.3 M Hepes at μ = 1.0 M ($NaClO_4$) and 25 °C, and only with this buffer and at this pH were deviations with the buffer concentration detected above the experimental error. The activation parameters for the reaction were determined in 0.01 M NaOH at five temperatures varying between 15 and 35 °C.

The kinetics of hydrolysis of *cis*-[(en)$_2$Ir(OH_2)OP(O)($OC_6H_4NO_2$)$_2$]$^{2+}$ were followed by observing the rate of release of nitrophenolate from the complex spectrophotometrically at 400 nm. A stock solution of *cis*-[(en)$_2$Ir(OH_2)OP(O)($OC_6H_4NO_2$)$_2$]$Cl_2 \cdot 3NaCl$ (~1 mg in 20 mL of H_2O) was prepared, and equal volumes of this solution and buffer or hydroxide solution at twice the required final concentration and ionic strength were mixed at 25 °C. The increase in absorbance at 400 nm was followed with time. The data sets obtained normally encompassed consecutive reactions, and the rate constants for the two reactions were extracted from the data by established procedures. When the initial reaction was complete, the subsequent reaction fitted well to a single-exponential decay and rate constants were obtained by curve fitting with the LSTSQR program. The rate constant for the initial reaction was extracted from the data in a variety of ways depending on the ratio of the two rate constants. When the ratio of the rate constants was more than 100, the following reaction was ignored and the data sets processed by the LSTSQR program fitted well to single-exponential functions. When the difference was between 10- and 100-fold, the rate constants were obtained graphically as described by Jackson et al.[13]

^{31}P NMR Kinetics. The complex *cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$S_2O_6 \cdot {}^1/_2H_2O$ (30 mg) was dissolved in a solution of Tris/$HClO_4$ buffer (pH 8.6, μ = 1.0 M, $NaClO_4$), D_2O (20%) was added, and consecutive ^{31}P NMR spectra were recorded at 25 °C.

The complex *cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$S_2O_6 \cdot {}^1/_2H_2O$ (20 mg) and NaCl (105 mg) were dissolved in H_2O (1.5 mL) containing Na_3PO_4 (0.01 M), NaOH (0.1 mL, 2 M) was added, and consecutive spectra were recorded at 25 °C. (Acquisition parameters are the following: acquisition frequency, 80.98 MHz; sweep frequency, 9 kHz; acquire 8 K data points, zero fill to 16 K points; pulse repetition time, 0.5 s, number of scans per spectra, 7200–14400.)

Known weights of *cis*-[(en)$_2$Ir(OH_2)OP(O)($OC_6H_4NO_2$)$_2$]$Cl_2 \cdot 3NaCl$ and NaCl (to make final ionic strength 1.0 M) were dissolved in a mixture of D_2O and H_2O (final D_2O concentration, 25%), and concentrated NaOH or buffer solutions were added to make the solution up to the required volume and NaOH concentration or pH. Trimethyl phosphate (2 μL) was added to the solution as an internal standard (^{31}P NMR acquisition parameters as above; number of scans per spectra, 600–14400). Rate constants were extracted from the integrated spectra by plotting log ($I_\infty - I_t$) vs time where I is the integral of the product signal normalized with respect to the standard.

Tracer Study. *cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$S_2O_6 \cdot {}^1/_2H_2O$ (40 mg), Tris (109 mg), and NaCl (70 mg) were dissolved in $H_2{}^{18}O$ (1.8 mL, 9.84% ^{18}O), and HCl(50 μL, 9.0 M) was added to make a buffered solution of pH ~8.2, 9.5% $H_2{}^{18}O$, μ = 1.0 M (NaCl). The solution was maintained at ~20 °C for 16 h, and then several ^{31}P NMR spectra of the solution were recorded after the addition of D_2O (250 μL) and trimethyl phosphate (4 μL). (Acquisition parameters are the following: acquisition frequency, 80.98 MHz; sweep frequency, 2000 Hz; pulse angle, 90°; pulse repetition time, 4.5 s.)

Results

The complexes studied in this work were synthesized by heating equal amounts of *cis*-[(en)$_2$Ir(OSO_2CF_3)$_2$](CF_3SO_3) and HOP(O)(OC_2H_5)($OC_6H_4NO_2$) or HOP(O)($OC_6H_4NO_2$)$_2$ in sulfolane and then quenching with water to hydrolyze the second triflato ligand. The complexes were purified by cation-exchange chromatography and characterized by elemental analysis, ^1H and ^{31}P NMR spectroscopy, and electronic spectroscopy. The $^{31}P\{H\}$ NMR spectrum of *cis*-[(en)$_2$Ir(OH_2)OP(O)(OC_2H_5)($OC_6H_4NO_2$)]$^{2+}$ consisted of two signals of equal intensity separated by 0.024 ppm. This indicated the presence of the two diastereomers expected since both the Ir and P centers are stereogenic. The ^{31}P chemical shift of the complex was shifted ~7 ppm downfield from the ionized free ligand as expected.[14] The ^{31}P NMR chemical shift variation of the $^-OP(O)(OC_6H_4NO_2)_2$ moiety upon coordination was slightly less than usual, at 5 ppm downfield.[14]

(12) LSTSQR is a fitting program written initially for an IBM computer and has been modified to run on a Vax 11/750. The program, using a generalized weighted least-squares fitting procedure, allows the use to describe the functions to be fit in terms of a number of constants and variables. The program uses an iterative procedure minimizing the value of the weighted least squares. A program listing is available on request.

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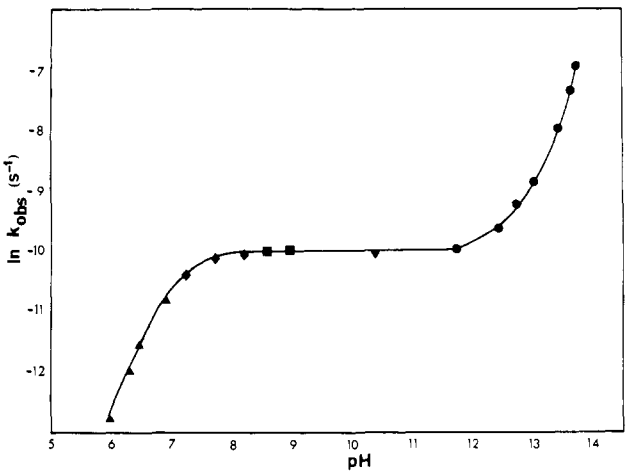

Figure 1. pH versus ln rate constant profile for the hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ (μ = 1.0 M $NaClO_4$, 25 °C). The solid line was calculated with the rate constants given in the text.

Hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$. Loss of 4-nitrophenolate from *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ was followed spectrophotometrically at 400 nm in a series of buffers from pH 5.94–10.43 and in hydroxide solutions from 0.01–1.0 M (Figure 1). In the range pH 6–11 the reaction follows the rate law in (1) where k_1 is

$$k_{obs} = k_1K_1/(K_1 + [H^+]) \quad (1)$$

assigned as the rate constant for the reaction of the deprotonated complex and K_1 is the dissociation constant for the proton of the H_2O ligand. Nonlinear least-squares fitting by computer of the data in the range pH 6–10.5 to the above equation resulted in values for these two constants of $k_1 = (4.6 \pm 0.1) \times 10^{-5}$ s^{-1} and $K_1 = (1.02 \pm 0.08) \times 10^{-7}$ ($pK_1 = 6.99 \pm 0.04$). This pH dependence was expected for a reaction requiring deprotonation of a coordinated water ligand. The pK_a of the coordinated H_2O is also in the expected area for a dicationic Ir(III) species.[15]

At higher pH values, the rate of hydrolysis increased. The reaction above pH ~12 was dependent on $[OH^-]$ with a two-term rate law as observed for 4-nitrophenolate hydrolysis from the corresponding pentaammine complex, $[(NH_3)_5IrOP(OC_2H_5)(OC_6NO_2)]^{2+}$.[10] The rate of hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ over the entire pH range studied is described by the rate law in (2). Nonlinear least-squares fitting of the data (avilable as supplementary material) gave values for k_2 and k_3 of $(2.7 \pm 0.5) \times 10^{-4}$ L mol^{-1} s^{-1} and $(6.6 \pm 0.06) \times 10^{-4}$ L^2 mol^{-2} s^{-1}, respectively.

$$k_{obs} = k_1K_1/(K_1 + [H^+]) + k_2[OH^-] + k_3[OH^-]^- \quad (2)$$

In neither, the kinetics followed by ^{31}P spectroscopy nor by visible spectroscopy, was there any evidence that the two diastereoisomers of the complex ion reacted at significantly different rates. Also, a small buffer effect (≤14%) was observed for a 3-fold change in buffer concentration (0.1–0.3 M Hepes). This effect is so small it could be ascribed to one or more sources. It was therefore ignored in the analysis of the mechanism.

The activation parameters for the intramolecular reaction were determined in 0.01 M NaOH over 15–35 °C. In this plateau region of the pH-rate profile, the rate constant for the reaction is equal to k_1. The plot of ln k_{obs} vs $1/T$ was linear, yielding $\Delta H^* = 69 \pm 2$ kJ mol^{-1} and $\Delta S^* = -93 \pm 5$ J K^{-1} mol^{-1}.

The reaction of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ was also followed by ^{31}P NMR; at pH 8.6 the signal due to the starting material was observed to decay to a triplet (J_{P-H} = 6 Hz) at 13.8 ppm in its ^{31}P NMR spectrum. The rate constant for loss of starting material and concomitant production of the 13.8 ppm signals was $(4.7 \pm 0.5) \times 10^{-5}$ s^{-1} at 25 °C, μ = 1.0 M (NaCl), i.e. identical with the rate constant for nitrophenolate production. The reaction product was a net zero charged compound at pH 9; the product in dilute NH_4^+/NH_3 buffer passed through both Dowex 50W-X2 cation-exchange and Dowex AG-1X8 anion-exchange columns unchanged. Its ^{31}P NMR chemical shift, ^1H coupling, and lack of charge at pH 9 all implied that the product was the *cis*-[bis(ethylenediamine)(ethyl phosphato)hydroxoiridium(III)] complex.

The reaction of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ in 1 M OH^- ion solution also yielded a single product, which displayed a triplet at 12.5 ppm in its ^{31}P NMR spectrum. The product was stable to further hydrolysis over several days. The difference between the chemical shifts of the reaction products at pH 8.6 and 1.0 M OH^- is due solely to the pH difference. Under identical conditions the products display identical NMR spectra. Therefore, both in 1.0 M NaOH and at pH 8.6, *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ yields only one P-containing product, *cis*-$[(en)_2Ir(OH)OP(O)_2(OC_2H_5)]$, via ring opening of the chelate ester intermediate.

A tracer experiment was designed to test if the chelate ester ring opened with Ir–O or P–O cleavage. *cis*-$[(en)_2Ir(OH)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ was hydrolyzed in Tris buffer at pH 8.2 in a solution containing 9.6% $H_2{}^{18}O$. This tracer experiment relies on the fact that ^{31}P NMR signals show a significant ^{18}O isotope shift upfield relative to ^{16}O provided the oxygen atom is bonded to the phosphorus center.[16] The result of the experiment, as shown in Figure 2 implies that the label has been largely incorporated during the reaction, which gives rise to the isotope shift for the ^{31}P NMR signal. The quantitation of the result was made difficult by the broadness of the product peak at 13.7 ppm. The half-height width of the standard trimethyl phosphate was in the region of 0.5–0.9 Hz depending on the resolution-enhancement technique employed. The product peak had a half-height width of ~3 Hz, which is of the order of the shift expected for the ^{18}O-substituted product. The shoulder on the high-field side of the product peak was reproducible by a number of resolution-enhancement techniques including trapezoidal multiplication, Gaussian multiplication,and convolution difference. In addition, the shoulder was clearly evident in standard spectra, i.e. exponential multiplication of the free-induction decay. Spectra recorded under identical conditions in the absence of $H_2{}^{18}O$ did not show the satellite peak on the high-field side for the product (peak a, Figure 2). The measured isotopic shift of 0.048 ± 0.01 ppm was in the region expected for ^{18}O isotope shifts on phosphate esters.[17] The large error associated with the shift is due to the broadness of the peaks and the noise in the spectrum, which conceals the true peak position. The spectra could not be usefully integrated; however, inspection of Figure 2 shows that the intensity and position of the shoulder on the product peak are in the region expected for near complete incorporation of label. Oxygen exchange in the product and the reactant is assumed to be very slow at pH 8.2 in keeping with observations on free phosphate,[18] phosphate esters,[19] and Co(III)-coordinated phosphate.[20] If solvent $^{18}OH_2$ exchanges with Ir-bound OH^- and the reaction occurred by an intramolecular path followed by ring opening at the P–O bond, then only 50% incorporation of label would be evident in the ^{31}P signal. This possibility appears to be voided by the results, and furthermore the prospect of exchange of OH^- at the Ir(III) site is unlikely in the extreme given the very slow exchange rates even for coordinated H_2O.[21] Therefore, it was

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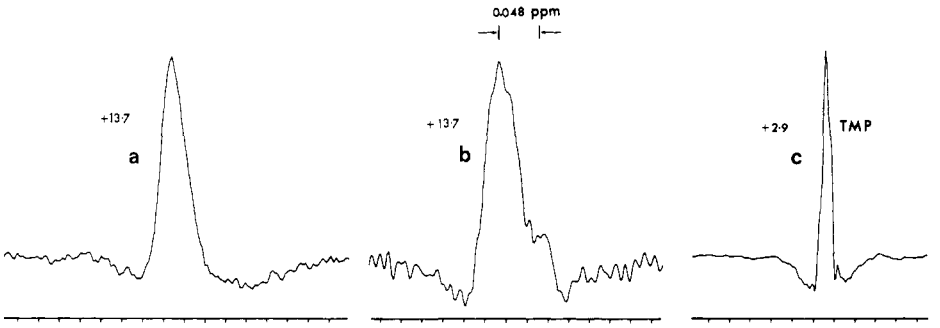


Figure 2. $^{31}P\{H\}$ NMR spectrum of the products of hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$, at pH 8.2 (Tris buffer, μ = 1.0 M NaCl): (a) product of hydrolysis in the absence of $H_2{}^{18}O$; (b) product of hydrolysis in 9.6% $H_2{}^{18}O$; (c) standard, trimethyl phosphate same spectrum as b. The vertical scale for signal b is 4 times that of a. Acquisition parameters as per text; resolution enhancement by trapezoidal multiplication; TM1 = 500, TM2 = 3000.

Table I. Rate Constants for the Initial Step in the Hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$ (25 °C, μ = 1.0 M $NaClO_4$) Determined Spectrophotometrically at 400 nm

pH or $[OH^-]$	buffer (0.2 M) or NaOH	k_{obs}, $\times 10^4$ s^{-1}
5.83	Mes	0.34 ± 0.01
6.35	Mes	0.764 ± 0.002
6.72	Hepes	1.21 ± 0.01
7.12	Tris	2.09 ± 0.02
7.29	Tris	2.51 ± 0.01
7.68	Tris	3.19 ± 0.04
8.18	Tris	3.60 ± 0.03
8.67	Tris	3.84 ± 0.05
10.98	Caps	3.95 ± 0.1
0.01	NaOH	6.14 ± 0.05
0.03	NaOH	12.9 ± 0.1
0.05	NaOH	20.5 ± 0.1
0.10	NaOH	39 ± 1
0.25	NaOH	105 ± 2
0.50	NaOH	241 ± 3
1.00	NaOH	809 ± 3

Table II. Rate Constants for the Second Step in the Hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$ (μ = 1.0 M $NaClO_4$, 25 °C)

$pH/[OH^-]$	buffer	k_{obs}, $\times 10^6$ s^{-1}
8.67	Tris	7.4 ± 0.1
0.01	NaOH	8.3 ± 0.1
0.10	NaOH	7.5 ± 0.04

concluded that the ring-opening reaction proceeded with P–O cleavage.

Hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$. This was followed by observing the release of nitrophenolate from the complex. Biphasic kinetics indicated that there were two consecutive reactions occurring. The rate constants for the two reactions were extracted from the data by established procedures described in the Experimental Section. The rate constant for the fast step refers to reaction of *cis*-$[(en)_2Ir(OH)OP(O)(OC_6H_4NO_2)_2]^+$ to yield an intermediate complex and nitrophenol, and that for the slower step refers to the subsequent reaction of the intermediate, also to produce nitrophenol. The assignment of the rate constants was established by two procedures. First, ^{31}P NMR spectroscopy of the reaction mixture showed that, in the time scale of the fast reaction, the starting material had disappeared. Second, the yield of nitrophenolate from the two steps of the reaction was equal. Table I and Figure 3 show the variation of the rate of the initial reaction with pH.

The overall reaction of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$ in the range pH 5–14 was described by the rate law in (3). At low pH, the reaction was dependent on pH and

$$k_{obs} = k_4K_2/(K_2 + [H^+]) + k_5[OH^-] + k_6[OH^-]^2 \quad (3)$$

(21) Borghi, E.; Monacelli, F. *Inorg. Chim. Acta* **1971**, *5*, 211.

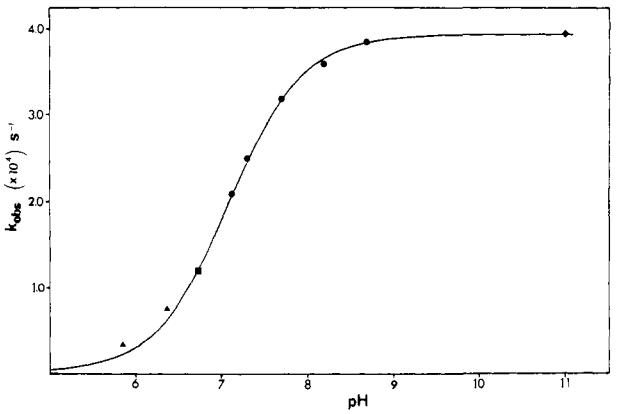


Figure 3. pH versus rate constant profile for the initial step of the reaction of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$ at 25 °C (μ = 1.0 M $NaClO_4$). The solid line was calculated with a pK_a of 7.06 and a k_4 value of 3.95×10^{-4} s^{-1}.

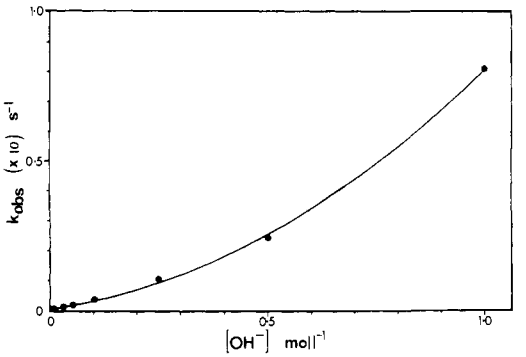


Figure 4. k_{obs} versus $[OH^-]$ for the initial step in the reaction of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$, at 25 °C ($\mu$ = 1.0 M $NaClO_4$). The solid line is calculated for the equation: k_{obs} (s^{-1}) = 4.95×10^{-4} + $2.0 \times 10^{-2}[OH^-] + 6.0 \times 10^{-2}[OH^-]^2$.

consistent with a deprotonation (pK_2 = 7.06 ± 0.02). The rate constant k_4 = (3.95 ± 0.05) × 10^{-4} s^{-1} is ascribed to attack of coordinated OH^- at the phosphorus center. At higher pH, the rate increases with both a first- and second-order dependence on $[OH^-]$ (Figure 4). The rate constants k_5 and k_6 were calculated to be (2.0 ± 0.3) × 10^{-2} L mol^{-1} s^{-1} and (6.0 ± 0.3) × 10^{-2} L^2 mol^{-2} s^{-1}, respectively.

The hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$ was also followed by ^{31}P NMR spectroscopy. At pH 9.5 in Ches/OH^- buffer, the starting material reacted to yield a product with a chemical shift of +7.2 ppm. The rate constant for its production was (6 ± 1) × 10^{-4} s^{-1}, at 25 °C, similar to the rate constants for release of nitrophenolate ion at that pH. This is the chemical shift expected for a monodentate 4-nitrophenyl phosphate species, and the logical assignment of this signal is to the *cis*-[bis(ethylenediamine)hydroxo(4-nitrophenyl phosphato)-

iridium(III)] complex. ^{31}P NMR spectra recorded throughout the reaction at higher pH, $[OH^-] = 0.025$, 0.1, and 1.0 M, 25 °C, $\mu = 1.0$ M (NaCl), revealed that in the initial step a single phosphorus containing product was formed from the starting material at −6.0 ppm. The product had a chemical shift of +7.1 ppm and was identical with the product of the reaction at pH 9.5.

The rate of production of nitrophenolate in the second step of the reaction was independent of pH in the region 9–13, and the yield of nitrophenolate in this step was identical with that of the first step. These observations are what could be expected for an intramolecular reaction of *cis*-$[(en)_2Ir(OH)OP(O)_2(OC_6H_4NO_2)]$. The reaction again presumably occurs via attack of coordinated OH^- at the phosphorus center ($\sim 8 \times 10^{-6}$ s^{-1} at 40 °C) to yield the chelated phosphorane, which rapidly decays to the chelate phosphate. If the activation parameters for the intramolecular reaction are similar to those for *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$, the rate constant for the reaction at 25 °C would be $\sim 2 \times 10^{-6}$ s^{-1}.

^{31}P NMR spectra recorded during the second step of the reaction at pH 9.5 show that the intermediate at +7.2 ppm reacts to yield a single product with a chemical shift of ~15 ppm. This product has the chemical shift expected for coordinated monodentate phosphate. Thus, even at pH 9.5 the chelate $[(en)_2IrO_2PO_2]$ complex is not stable and the ring opens. In contrast, the corresponding Co(III) complex at this pH is predominantly in the form of the chelate.[7]

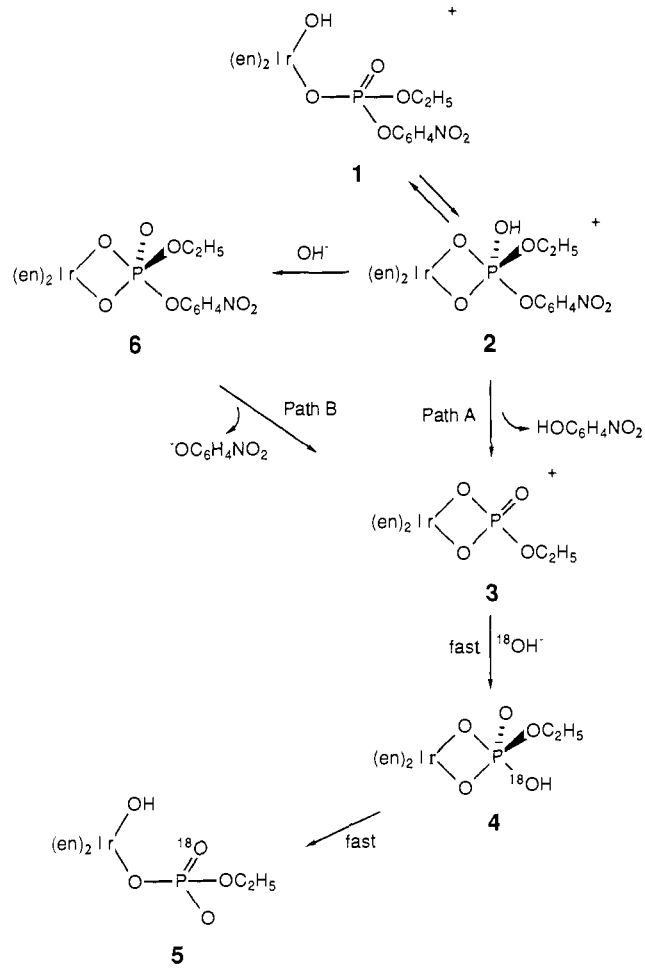
Discussion

The results described in this paper are relevant to the biological phosphate chemistry involving metal ions for several reasons. First, they demonstrate the efficacy of coordinated OH^- ion as a nucleophile in an intramolecular path for cleaving phosphate esters under near-neutral pH conditions. Second, the reactivity of a chelated phosphate ester has been evaluated for the first time. Third, the rate of the intramolecular attack by coordinated OH^- on the bound phosphate ester is shown to be dependent on the size of the metal ion. Each of these features deserves further elaboration.

The phosphate diester complexes described in this study, *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ and *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_6H_4NO_2)_2]^{2+}$, are largely unreactive in acidic conditions, but after the coordinated water molecule is deprotonated ester hydrolysis ensues. This was expected from analogous studies with cobalt(III) phosphate ester complexes,[20,22,23] and hydrolysis arises from intramolecular attack of coordinated OH^- at the phosphorus centers, liberating 4-nitrophenolate ion quantitatively (Scheme I, path A). The process should yield, after decay of the intermediate five-coordinated phosphorane, the chelated phosphate monoester, but these products were not observed. Instead, monoester complexes of the type *cis*-$[(en)_2Ir(OH)OPO_2(OR)]$ were produced. There are two possible routes to such a product via Ir–O or P–O cleavage, and the ^{18}O tracer study indicates that ring opening occurs at least predominantly by P–O rupture. This result is reminiscent of the methyl ethylene phosphate hydrolysis in basic conditions where endocyclic hydrolysis also dominated the chemistry (≥90%). In the present study, there is no exocyclic hydrolysis of the ester (±2%) in the conditions pH 6–1.0 M OH^-, and a major conclusion is that the chelate esters are comparatively unreactive species in terms of promoting ester hydrolysis.

Above pH 12, the rate of hydrolysis increases by paths both first and second order in $[OH^-]$, and the obvious mechanism for the first-order path would appear to be an intermolecular attack of OH^- at the phosphorus center. However, the corresponding pentaammineiridium(III) complexes of these phosphodiesters also display a rate law with both first- and second-order terms in [OH]. In that case, the results overall implied that intermolecular attack of OH^- did not contribute significantly to the rate of reaction, rather the reaction appeared to proceed via an intramolecular

Scheme I



attack of amido ion on the P center followed by chelate ring opening.[10] A similar path could be exercised in this instance, and the term first order in OH^- would arise from either deprotonation of the coordinated OH^- to give the coordinated O^{2-} ion as a more potent intramolecular nucleophile or deprotonation of the protonated oxyphosphorane **2** formed as the intermediate species. This leads to chelate monoester **3**, which then undergoes rapid P–O rupture to give the monodentate ester complex **5** (path B, Scheme I). The attack of coordinated O^{2-} ion on the P center seems a feasible route.[24] From the Co(III) chemistry the pK_a of coordinated hydroxide ion has been estimated as ~20.[25] Analogous iridium(III) amine complexes are generally ~10-fold more basic,[15] and therefore in 1 M OH^- the proportion of the complex in the $Ir^{3+}O^{2-}$ form would be $\sim 10^{-7}$. To achieve a pseudo-first-order rate constant of $\sim 10^{-3}$ s^{-1}, the rate constant for attack of IrO^{2-} needs to be $\sim 10^4$ s^{-1}. This is $\sim 10^4$-fold greater than that estimated for $IrNH_2^-$ acting in a similar manner,[10] and the coordinated amido ion is about 10^4-fold less basic than the analogous oxide ion. On the basis of this analysis, the pathway is feasible but a route involving deprotonation of the oxyphosphorane **2** is thought more likely (path B, Scheme I).

The pathway second order in OH^- is probably due to intermolecular addition of OH^- to a deprotonated form of the oxyphosphorane **6**, thereby increasing its coordination number to 6. Such species have been invoked previously and six-coordinate P^v is reasonably commonplace in any event, e.g. PF_6^-. So, there is no novelty in such a proposal.

There are other interpretations of the rate laws, but on balance we feel the weight of evidence and consistency in all the chemistry

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is with the paths outlined. Also, from the point of view of possible routes for enzymic catalysis, the reactions in high base concentrations are much less relevant than the route independent of OH^-.

In general, the uncoordinated phosphodiesters are relatively unreactive in mild aqueous conditions, i.e. pH 2–10.[26] There has been no study on the hydrolysis of $^-OP(O)(OC_2H_5)(OC_6H_4NO_2)$ or similar compound, e.g. methyl-4-nitrophenyl phosphate, under these conditions. The reason for this is readily apparent; the reaction is prohibitively slow even at elevated temperatures. It is safe to assume, however, that the rate of hydrolysis of ethyl-4-nitrophenyl phosphate ion at pH 8 will be at least 1 order of magnitude slower than that of bis(4-nitrophenyl) phosphate ion at that pH. A study of the hydrolysis of $^-OP(O)(OC_6H_4NO_2)_2$ in the region pH 1–10 has been carried out by Kirby and Younas.[26] The reaction rate goes through a minimum at ~pH 4; at pH 8 the rate constant for loss of nitrophenolate was $\sim 8 \times 10^{-7}$ s^{-1}, at 100 °C, and μ = 1.0 M (KCl). The activation parameters for the reaction are not readily assessed, but if they are similar to those for the reaction of bis(2,4-dinitrophenyl) phosphate,[26] the rate constant at 25 °C would be $\sim 10^{-9}$ s^{-1}. Therefore, at pH 8, the hydrolysis of $^-OP(O)(OC_2H_5)(OC_6H_4NO_2)$ should not proceed with a rate constant greater than $\sim 10^{-10}$ s^{-1}. At pH 8, *cis*-$[(en)_2Ir(OH)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^+$ hydrolyzes the ester at a rate of $\sim 5 \times 10^{-5}$ s^{-1}, at least 10^5-fold faster than the free ligand hydrolyzes at this pH. Similarly, at pH 8, nitrophenolate release from $^-OP(O)(OC_6H_4NO_2)_2$ is enhanced $\sim 10^6$-fold by coordination to Ir(III) in the complex *cis*-$[(en)_2Ir(OH)OP(O)(OC_6H_4NO_2)_2]^+$. Coordination of the ions $^-OP(O)(OC_2H_5)(OC_6H_4NO_2)$ and $^-OP(O)(OC_6H_4NO_2)_2$ to the Ir(III) center cis to a hydroxo ligand therefore results in an enhanced rate of cleavage of these esters near neutral pH, which is attributed largely to the intramolecular nature of the reaction (vide supra).

The chelate ester ring-opening process presumably occurs via the $S_N2(P)$ mechanism, i.e. via the phosphorance intermediate. Arguments similar to those used by Westheimer[2] imply that the phosphorane 4 formed by attack of hydroxide ion or H_2O on the chelate phosphate ester **3** must have one Ir–O ligand axial and the other equatorial so that the four-membered ring spans axial–equatorial positions in the phosphorane. The other axial position is presumably occupied by the entering nucleophile leaving two equatorial positions, which must be occupied by the ester function and the oxygen ion (Scheme I). The phosphorane 4 that is formed apparently does not have a lifetime long enough to pseudorotate or is in some manner inhibited from pseudorotating to put the ester group into a labile apical position.

In this respect, the reaction is a close analogy to the methyl ethylene phosphate hydrolysis in basic conditions where largely ring opening and little loss of the methoxy group occurred (~5% at pH 8).[2]

The lack of pseudorotation in **4** to put –OR in an apical position could be accommodated if the electronegative oxygen ion was preferred in an apical position. However, this is contrary to accepted dogma.[2,27] Neither does there appear to be any intrinsic property in a four-ring system, which limits pseudorotation.[28] The exclusive ring opening can be accommodated, however, if the reaction from **3** → **5** approaches a concerted process. Even though intermediate phosphoranes of this type have been detected in analogous Co(III) systems,[23] the slower intramolecular hydrolysis and the greater strain induced by the larger Ir(III) ion for the four-ring intermediate would both push the reaction path toward a more concerted process in the current system. Moreover, the methyl ethylene phosphate hydrolysis in base involves a competition balanced between paths involving ring opening and pseudorotation of the intermediate phosphorane.[2] The presence of a four-membered ring in the current system might be expected to tip the balance in favor of ring opening of the phosphorane.

It is of interest to note that the intramolecular reactions described in this communication appear to proceed much more slowly than would have been predicted by comparison with the rate of hydrolysis of *cis*-$[(en)_2Co(OH)OP(O)_2(OC_6H_4NO_2)]$.[23] In the region pH 9–12, the cleavage of 4-nitrophenol is independent of pH and proceeds by attack of the cis-coordinated hydroxide ion at a rate of $\sim 8 \times 10^{-4}$ s^{-1} at 25 °C. In contrast, the complex *cis*-$[(en)_2Ir(OH)OP(O)_2(OC_6H_4NO_2)]$, produced as an intermediate in the hydrolysis of *cis*-$[(en)_2Ir(OH)OP(O)(OC_6H_4NO_2)_2]^+$, reacted via the intramolecular pathway with an estimated rate constant of $\sim 2 \times 10^{-6}$ s^{-1} at 25 °C. This is a decrease of ~500-fold upon going from Co(III) to Ir(III). Similarly, the rate of hydrolysis of *cis*-$[en_2Ir(OH)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^+$ was some 10^3-fold slower than predicted for the analogous cobalt(III) complex, $\sim 10^{-1}$ s^{-1}. This estimate of the rate constant for the Co(III) complex was obtained by adjusting the observed rate constant for the hydrolysis of the monoester, *cis*-$[en_2Co(OH)OP(O)_2(OC_6H_4NO_2)]$,[23] $\sim 10^{-3}$ s^{-1}, for the increased susceptibility of the diester to nucleophilic attack.

These observations are even more surprising when it is realized that OH^- and NH_2^- bound to Ir(III)-bound species are expected to be somewhat more nucleophilic than the corresponding Co(III) complexes, because the Co(III) complexes are more acidic than the analogous Ir(III) complexes. The reason for the decrease cannot lie in a difference in the degree of electrophilic activation of the phosphate ester by the different metal ions since such effects have been shown to be insignificant in the series Co(III), Rh(III), and Ir(III) for trimethyl phosphate,[29] dimethylformamide, and some nitriles.[30] The reason for the observation, most likely, lies in the fact that the two metal ions are quite different in size. The effective ionic radii of the two ions are 0.545 and 0.68 Å for Co(III) and Ir(III), respectively.[31] This difference in size must have an effect on the energy required to form the necessary four-membered ring. X-ray crystallographic analyses of the complexes $[(en)_2CoO_2PO_2]$[6] and $[(NH_3)_4CoO_2PO_2]$[32] have shown that the in-ring bond angles and lengths were almost identical for both complexes and the four-membered ring was strained. The strain is evident in the in-ring O–Co–O angle of 76°, the reduction of the O–P–O angle to 99°, and the proximity of the cobalt and the phosphorus atoms.[6] In the case of the bis(ethylenediamine) complex, the nonbonded interatomic distance between the Co and P is only 2.55 Å, which is close to the sum of the covalent radii of the two atoms involved. The larger Ir(III) ion must cause further strain in this ring. Simple geometric considerations dictate that if the metal–O bond lengths were increased to 2.1 Å, a reasonable estimate for the Ir–O bond,[33] and the bond angles and lengths about the phosphorus center were invariant, the O–M–O bond angle would be decreased to 69°, even more strained than the angle subtended at the Co(III) center. If these critical bond angles, O–M–O and O–P–O, were increased to relieve the strain the metal–phosphorus nonbonded interaction would increase.

Vibrational analysis for the metal(III) hexaammine complexes (metal is Co and Ir) implies that the intrinsic resistance to compression of the N–M–N bond angle should also be greater for Ir than Co.[34] This conclusion also carries over to related systems having the O–M–O bond angle. From an inspection of molecular geometries involved it would seem that the O–Ir–O bond angle may need to compress to nearly 70° to achieve a reasonable

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(32) Haromy, T. P.; Knight, W. B.; Dunaway-Mariano, D.; Sundaralingam, M. *Biochemistry* **1982**, *21*, 6950.
(33) Ir–N bond lengths have been estimated to be ~2.1 Å. Borch, G.; Klaeboe, P.; Nielsen, P. H. *Acta Chem. Scand., Ser. A* **1979**, *A33*, 19. The Co–O and Co–N bond lengths in the complex $[(en)_2CoO_2PO_2]$ are very similar; therefore, the bond length for the Ir(III)–O bond was estimated to be 2.1 Å.
(34) See: *Infrared Spectra of Inorganic and Coordination Compounds*, 2nd ed.; Nakamoto, K., Ed.; Wiley-Interscience: New York, 1970.

transition-state geometry for the reaction involving the intramolecular attack of hydroxide ion on a coordinated phosphate derivative (vide supra). In contrast to this expectation, a suitable transition-state geometry for the corresponding Co(III) complex would be closer to 78–80°, based on the geometry in the product ground state.[6,32] Large energy increases per unit angle compression are expected when the O–M–O bond is required to achieve such a configuration. The greater compression required in the case of the Ir(III) complex is therefore expected to markedly increase the energy required to reach the transition state in this reaction.

In conclusion, this work attests the efficiency of OH^- bound to the metal ion as an intramolecular nucleophile for phosphate ester hydrolysis via the four-membered ring metal ion–phosphorane chelate. However, the rate is apparently modulated by the size of the metal ion and the ease of formation of the four-membered chelate ring. Given that Mg^{2+}, Zn^{2+}, and Mn^{2+} are the ions likely to be involved in biological systems and that they are larger than Ir^{3+},[31] it does not seem likely that these ions will act efficiently in this way. They can, of course, still function as both a source of nucleophiles ($M-OH^-$) and as electrophilic activators of the phosphate ester, although these functions may be carried out by different metal ions. The enzyme cleft can, of course, arrange the intramolecularity of the reaction. Presumptions of this kind are supported by the proximity of the metal ions in the refined alkaline phosphatase structure[35] and the frequency with which multiple metal ions appear to be required in phosphate-utilizing enzymes.[1]

Finally, this study has shown conclusively that a four-membered ring chelate phosphate ester will not hydrolyze with loss of the exocyclic esterifying group even when the metal ion ligand bonds are inert.

Acknowledgment. We thank the ANU NMR service for their help and the Analytical Service Unit for the microanalyses.

Supplementary Material Available: Table of rate constants for the hydrolysis of *cis*-$[(en)_2Ir(OH_2)OP(O)(OC_2H_5)(OC_6H_4NO_2)]^{2+}$ (1 page). Ordering information is given on any current masthead page.

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Homogeneous Catalysis of Silane Alcoholysis via Nucleophilic Attack by the Alcohol on an Ir(η^2-$HSiR_3$) Intermediate Catalyzed by $[IrH_2S_2(PPh_3)_2]SbF_6$ (S = Solvent)

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Abstract: $[IrH_2S_2L_2]SbF_6$ (**1**, L = PPh_3; S = THF, **a**; CH_3OH, **b**; H_2O, **c**; Me_2CO, **d**) is found to be a very active and highly selective catalyst for silane alcoholysis. A hydroxyl group can be selectively silylated even in the presence of another potentially reactive C=C or C=O group. The homogeneity of the catalytic system has been established by DCT (dibenzo[*a*,*e*]cyclooctatetraene) and Hg tests. Rather than the "oxidative addition" mechanism commonly postulated, the results of kinetic and mechanistic studies are more consistent with a mechanism in which the silane is activated through binding to the metal via the Si–H bond in an η^2 fashion without oxidative addition and then undergoes nucleophilic attack by the alcohol. The order of relative reactivities of different alcohol isomers is secondary alcohol > primary alcohol > tertiary alcohol. The origin of this anomalous reactivity pattern is discussed with reference to the proposed mechanism. Some silane adducts (e.g., with Et_3SiH and $Et_2HSiSiHEt_2$) related to the intermediate species proposed in the catalytic cycle can be detected spectroscopically at low temperatures, but they are too reactive for isolation. In particular, they react rapidly with nucleophiles such as water and alcohols. The proposed "adduct formation" mechanism cannot apply to simple alkenes, which are insufficiently nucleophilic to attack even an activated η^2-bound silane. Consistent with this picture, alkene hydrosilation is not catalyzed by **1**.

The alcoholysis of hydrosilanes, or the O-silylation of alcohols (eq 1), has important applications in the synthesis of silyl ethers and in the protection of reactive OH groups in organic syntheses.[1]

$$R'_3SiH + ROH \rightarrow R'_3SiOR + H_2 \qquad (1)$$

Since alcohols are normally insufficiently nucleophilic to attack silanes in the absence of a catalyst, most silanes undergo alcoholysis only in the presence of either strongly nucleophilic or electrophilic catalysts. These are often unsuitable for use in organic substrates with sensitive functional groups. Only a very limited number of homogeneous transition-metal complexes have been reported as catalysts for the reaction. At room temperature the majority of these catalysts fail to catalyze the alcoholysis of trialkylsilanes such as triethylsilane. For example, $CoH_3(PPh_3)_3$,[2] $CoH(N_2)(PPh_3)_3$,[2] $FeH_2(PMePh_2)_4$, and $FeH_2(N_2)(PEtPh_2)_3$[3] are active for $(EtO)_3SiH$ but inactive for Et_3SiH. $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) is active for Et_3SiH only in refluxing benzene.[4] $Co_2(CO)_8$,[5] $IrX(CO)L_2$ and $[IrCl(C_8H_{14})_2]_2$,[6] and $Ru(PMe_3)_2(CO)_2Cl_2$[7] are the most active catalysts reported to date. They

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