

the amine NH protons and bound CO₂ have been considered^{7,10} as the origin of the high discrimination observed between *N-rac*-CoL⁺ and *N-meso*-CoL⁺. Of course, an additional factor for the six-coordinate complexes is the nature of the sixth ligand; water and acetonitrile are compact and electronically equivalent ligands (for this metal center), but other solvents or other potential ligands might increase or diminish the relative stability of the prim-*N-rac* isomer of the CO₂ complex by destabilizing or stabilizing, respectively, the six-coordinate *N-meso*-CO₂ complex. More difficult to assess, but possibly of considerable importance, is stabilization due to selective solvation of the macrocycle in the various isomers.

The stability order found for the hydride complexes (*N-meso* >> prim-*N-rac* ≈ sec-*N-rac*) is exceptional and surprising.⁴⁰ The *N-meso* hydride complex is evidently favored over the other two isomers by at least 3 kcal mol⁻¹. Consideration of steric interactions of the axial ligands with the macrocycle would seem to favor locating the hydride in the secondary position of the *N-rac* form of the complex. The latter would also maximize solvation of the axial water molecule bound on the primary face. The fact that the *N-meso* isomer is favored at equilibrium would then seem to require specific solvational requirements for the hydride ligand itself. At this point, any further discussion of this rather remarkable result does not seem worthwhile. However, the result

(40) Mechanistic studies of the conversion of the hydroxymethyl complex *N-meso*-CoL(CH₂OH)²⁺ to formaldehyde, dihydrogen and *N-meso*-CoL²⁺ confirm the high pK_a of *N-meso*-CoL(H)²⁺ (Chou, M. H.; Creutz, C. Work in progress).

does serve to teach us how subtle the effects on the binding of the axial ligands can be.⁴¹

Concluding Remarks. CO rapidly adds to both *N-meso*- and *N-rac*-CoL⁺ to form a highly stable five-coordinate complex whose stability is relatively independent of isomer and solvent. Very rapid addition of CO₂ to *N-rac*-CoL⁺ yields a strongly bound five-coordinate species at higher temperatures, but the dominant form of the complex at lower temperatures is six-coordinate. Evidently, the other two CO₂ adduct isomers and all three of the hydride complexes are six-coordinate over the accessible temperature range. These are usefully regarded as six-coordinate cobalt(III) complexes of the very high field ligands CO₂²⁻ and H⁻, respectively. Despite the high affinity of CoL⁺ for both CO₂ and CO, hydrides are favored below pH 3-7 (depending upon the isomer and the ligand); equilibration among CO₂, CO, and hydride complexes of a given isomer proceeds exclusively via formation of the free cobalt(I) complex. The *N-meso* hydride (pK_a ≥ 13.9) is the thermodynamic sink of these systems, but pathways for its formation from the *N-rac* isomers are not readily accessible in acid solutions.

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(41) Actually, the fact that the *N-rac* form is favored for CoL²⁺, NiL²⁺, and CoL⁺ is equally inexplicable.

Homogeneous Catalysts for Selective Molecular Oxygen Driven Oxidative Decarboxylations

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Abstract: Cobalt(II) ion has been found to catalyze the molecular oxygen driven oxidation of *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) to *N*-(phosphonomethyl)glycine (PMG) in aqueous solution.¹ This homogeneous catalytic conversion is novel and represents, in effect, an oxidative dealkylation of one carboxymethyl moiety yielding the *N*-substituted glycine. The reaction is selective to the desired product PMG when carried out at the natural pH of the free acid substrate (~1-2) and when carried out at substrate loadings less than 5% by weight. In addition, the catalytic system is selective for the PMIDA substrate; i.e., other closely related ligands show no reactivity, e.g., NTA, EDTA, etc. The results of kinetic and mechanistic studies on dilute systems are presented and discussed with special emphasis on how an understanding of the mechanism can make it possible to generate a catalyst system that gives high yields even with high substrate loadings. The reactions are first-order in substrate and [Co]₁. The oxygen pressure dependence exhibits saturation kinetics, while the selectivity increases as oxygen pressure increases. The rate is also inversely proportional to [H⁺]. The high selectivity of the oxidation and the unique selectivity of the cobalt catalytic system for the PMIDA substrate are discussed in terms of the magnitude of the metal ligand binding constant at the low pH of the reaction.

Introduction

The ability to utilize molecular oxygen as a selective oxidizing agent has many obvious advantages owing to its abundance and low cost. An area that is of considerable continuing interest has been the oxidative dealkylation of tertiary amines to yield secondary amines.²⁻⁷ This is of interest both for the synthetic

utility²⁻⁷ and for understanding the mechanism of biological oxidative dealkylations catalyzed by cytochrome P450 monooxygenases.⁸ While there have been many reports of such studies in the literature with a variety of stoichiometric reagents, only two examples utilizing molecular oxygen in a catalyzed reaction have been described,^{9,10} and these reports are for simple unfunctionalized trialkyl-substituted amines.

(1) a) Presented in part by Riley, D. P. Symposium on Atom Transfer Chemistry. 197th National Meeting of the American Chemical Society, Dallas, TX, April 10, 1989. b) Riley, D. P.; Rivers, W. U.S. Patent 4853159.

(2) Galliani, G.; Rindove, G. B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 828.

(3) Burrows, E. P.; Rosenblatt, D. H. *J. Org. Chem.* **1983**, *48*, 992.

(4) Smith, J. R. L.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206.

(5) Hull, L. A.; Davis, G. T.; Rosenblatt, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 6247.

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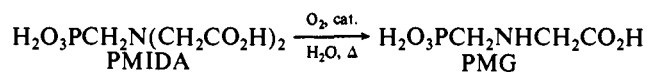
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The utilization of oxygen as an oxidant for the synthesis of the commercially significant amino acid *N*-(phosphonomethyl)glycine (PMG), the active agent in the herbicide Roundup, has been studied extensively at the Monsanto Co. A catalytic route (below) to PMG that uses a heterogeneous catalyst for the conversion of the tertiary amine *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) is commercially practiced and has been described in



the patent literature.¹¹ A key aspect of this oxidation is the need for an active catalyst affording high selectivity at high substrate conversions (>99%), since the product and starting material are very similar in their solubility properties and hence difficult to separate. Water is the solvent of choice for the process since it is stable to the oxidation conditions and since the PMIDA and the product PMG are virtually insoluble in all organic solvents. Another important consideration in the drive to minimize process costs and to maximize the efficiency of this conversion is that the reaction should be run with a minimum volume of solvent, i.e., as high a payload of substrate as possible. Additionally, to minimize reagent costs and process operations, it is desirable to run with the free acid form of the substrate at its natural unbuffered pH (1–2). This presents the added problem that both PMIDA and the product PMG are only sparingly soluble in water at pH ~ 1, even at elevated temperatures. As a consequence, the heterogeneous catalyst presents a problem; namely, it must be separated from the product by filtration of a dilute aqueous PMG solution. To crystallize the product PMG requires subsequent removal of water—an energy-intensive step and an additional process step.

An obvious way to simplify the process for this conversion would be the use of a *homogeneous* catalyst for this oxidation. This would, in principal, make it possible to carry out this catalytic step with use of a high payload of the substrate (slurries would be most desirable) and to generate in a high conversion step a slurry of the product. Filtration of the cooled solution would effect the separation of the product from the catalyst, which would remain in the filtrate and be recycled back to the oxidation reactor. Such a scheme would offer many process savings and be much easier to operate. This scenario represents a clear example of the advantage of a homogeneous catalyst over a heterogeneous catalyst.

In this paper, we show that cobalt(II) ion in aqueous solutions at the unbuffered pH of the PMIDA substrate (pH ~ 1–2) is a competent homogeneous catalyst for the oxygen-driven oxidative dealkylation of PMIDA. We also present kinetic and mechanistic studies devoted to gaining an understanding of this catalysis so that a homogeneous catalyst system that can satisfy all of the process requirements cited above can be developed for this conversion.

Experimental Section

Materials. All inorganic salts were purchased from Alfa Inorganics and used as received. The PMIDA substrate was synthesized according to the procedure of Moedritzer *et al.*¹² Analytical standards for organic products such as PMG and AMPA were obtained from Aldrich.

Procedure. The reactor system utilized for the studies described here employed a 300-mL Hastalloy C Autoclave Engineer's autoclave with all internal parts constructed of Hastalloy C. To minimize mass-transfer effects, dual baffles were added to the side walls and a Hastalloy C fritted gas-inlet tube was installed with the exit directly below the center of a standard six-blade impeller stirrer. Pure oxygen gas was used, and the flow rates (both inlet and exit) were monitored and controlled by Brooks Model No. 5850TR mass flow controllers calibrated in the 0–55 cm³/min range on the inlet side. The flow rate utilized was 350 cm³/min in the dilute systems studied here for kinetic runs. On the outlet side of the reactor, a Brooks Model No. 5850 flow indicator was employed. Oxygen pressure regulators used were Tescom Model No. 26-1000 for 0–5000 psig. A Tescom Model No. 26-1700 back pressure regulator was used.

Pressure transducers used for monitoring and controlling pressure in an external O₂ reservoir and in the reactor were Validyne Model No. DP360-66. The heat control was provided by a standard Autoclave Engineer heater system that uses a Love Model No. 1513-7188 proportional temperature controller with a solenoid for cooling water. An in-line Wilks Miran infrared CO₂ gas analyzer was employed on the exit side of the reactor to aid in monitoring the extent of reaction as percent CO₂ evolved, with the output going to a calibrated chart recorder. All gas lines and sample lines were constructed of Hastalloy C.

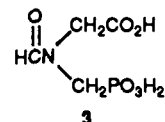
Analytical Procedure. All analyses were performed with HPLC with a Varian Model No. 2050 variable wavelength detector with the wavelength set at 200 nm and with a Varian Model No. 2010 HPLC solvent pump. A Rheodyne Model No. 2082 injector valve with a 5-μL sample loop was employed with use of an injection volume of 5 μL from a 10-μL Hamilton HPLC syringe. All phosphorus-containing materials were monitored by ligand-exchange HPLC with a 25-cm Hamilton PRP-X100 anion exchange column. The mobile phase for the PMIDA analysis was water adjusted to pH 2.2 with acetic acid. The mobile phase of all the other phosphorus-containing materials was water with the pH adjusted to 1.9 with trifluoroacetic acid. The aqueous mobile phase for monitoring aqueous Co(II) ion, H₂O₂, formamide, formic acid, glyoxylic acid, and DMF was made from phosphoric acid (1 mL/L).

Spectrophotometric Studies. The typical procedure used for generating solutions of a Co^{III}(PMIDA) complex *in situ* is described here. In a typical reaction, a solution that contains PMIDA at 0.025 M and Co(II) ion (added as the SO₄²⁻ salt) at 0.025 M is brought to the desired pH by the addition of NaOH or H₂SO₄. The electronic spectrum of the resultant solution was then recorded on a Beckman DU-70 model recording spectrophotometer. To generate a Co(III) complex, it was necessary to employ the heterogeneous oxidant PbO₂. Control experiments reveal that, over the pH range studied (1–6), PbO₂ does not react with either aquocobalt(II) ion or the PMIDA ligand when they are present individually. The procedure for generating the Co^{III}(PMIDA) complex involved stirring the PbO₂ with the solution of Co(II) and PMIDA at the desired pH for 10 min followed by filtration. At this point, a *t*₀ spectrophotometric reading is recorded. The resultant Co(III) solution is then placed in a thermostated water bath at the desired temperature, aliquots are taken periodically, which are chilled to ~10 °C, and then their electronic spectra are recorded. For kinetic analysis of reaction rates at any given temperature, the reactions are run in triplicate.

Results

From extensive screening studies, we have found that the metal ions Co(II) and Mn(II) are effective for catalyzing the molecular oxygen driven oxidative dealkylation of the PMIDA at the unbuffered PMIDA pH in water. While manganese catalysis is very good in this system in high dilution, it does suffer from the disadvantage that Mn(II) forms an insoluble complex with the substrate (stoichiometry Mn(PMIDA)₂), which causes a loss in reactivity in those reactions that have high initial substrate to catalyst concentrations. Since the Co system does not suffer from this insolubility problem, our process development and mechanistic studies were focused on the cobalt-catalyzed oxidations of PMIDA. Since the substrate is itself only somewhat soluble in water even at elevated temperatures (~0.30 M at 90 °C at pH ~ 1–2), all of the kinetic studies discussed here were carried out on dilute systems ([PMIDA]_i = 0.10 M). This made it possible to sample *homogeneous* reactions without precipitation of reactants or products.

In Figure 1 is shown a typical reaction profile for the catalytic oxidation of the PMIDA under 800 psig of O₂ and at 85 °C, where [PMIDA]_i = 0.10 M and [CoSO₄·7H₂O] = 0.005 M. As can be seen, the reaction proceeds at a reasonable rate to completion with a high selectivity to the desired product PMG and with a constant selectivity throughout the reaction. A coproduct *N*-formyl(PMG)(3) was found to easily hydrolyze, producing PMG and formic acid. As a consequence, the yield data in this profile refers to the total PMG + *N*-formyl(PMG) combined.



In all the reactions we have studied using Co catalysts, the yield of *N*-formyl(PMG) is relatively constant and in the range of 7–10%. In Table I are listed some of the other byproducts of this

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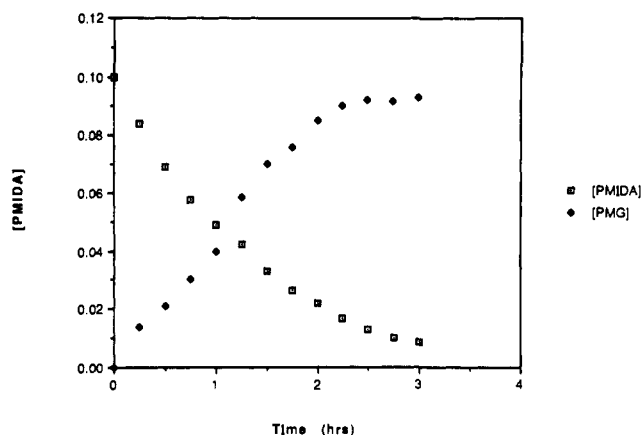


Figure 1. Molecular oxygen oxidation of PMIDA in H₂O at 85 °C under 800 psig of O₂ pressure with, as catalyst, a 0.005 M solution of CoSO₄·7H₂O where [PMIDA]_i = 0.10 M.

Table I. Additional Components Produced in the PMIDA Oxidation Depicted in Figure 1 at 100% PMIDA Conversion

product	yield ^a (%)
CO ₂	98
HCO ₂ H (formic acid)	97
HCOH (formaldehyde)	<2
Me ₂ NCOH (DMF)	2
PO ₄ ³⁻	2
H ₂ NCH ₂ PO ₃ H ₂ (AMPA)	1.1
MeHNCH ₂ PO ₃ H ₂ (MAMPA)	4.8
H ₂ O ₂	17
N-formyl(PMG)	10
PMG	83
PMIDA N-oxide	none detected
N-MePMG	<1

^a Based on moles of PMIDA.

oxidation. In general, good phosphorus mass balances are achieved in these reactions by the HPLC methods outlined in the Experimental Section. The products of this oxidation are representative of cobalt catalysis, although the levels of several of the components are sensitive to reaction variables such as O₂ pressure, temperature, and substrate loading. These effects will be discussed in detail below as each variable is considered.

The Co catalysis under all conditions does produce carbon dioxide in a 1:1 stoichiometry with the starting PMIDA. Hydrogen peroxide is also detected in these reactions. In the example shown, the H₂O₂ levels approached the 0.017 M level during the course of the reaction. In separate experiments, we found that aqueous solutions of Co(II) ion will slowly decompose H₂O₂ at pH ~1 at 90 °C, generating Co(III) ion during the process. Thus, it is conceivable that H₂O₂ is generated at higher levels in these systems. There are trace levels of dimethylformamide in these reactions as well as inorganic phosphate and (aminomethyl)phosphonic acid (AMPA). In these systems, the possibility of PMIDA N-oxide formation was closely monitored, but the failure to detect any N-oxide plus the results of coaddition experiments ruled out its possibility as an intermediate to PMG in these systems. N-methyl(PMG) is formed in low levels (<2%) at temperatures below 90 °C in these systems, but at higher temperatures increasing amounts of this product results. Its formation is due to the Eschenweiler-Clark reaction: secondary amine PMG is alkylated with formaldehyde and formic acid.¹³ Another undesired side product is the [(N-methylamino)methyl]phosphonic acid (MAMPA), a material whose formation is virtually independent of PMIDA loading and temperature but sensitive to the oxygen pressure (vide infra).

Another facet of the Co catalysis is that high PMIDA payloads are possible with cobalt. While the reactions proceed to completion in kinetically predictable rates, the reaction selectivities decrease as the amount of substrate charged to the reactor increases. For example, when a PMIDA reaction is carried out under the same

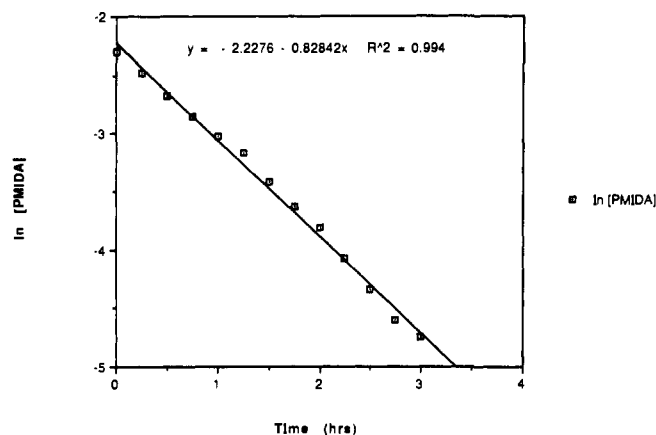
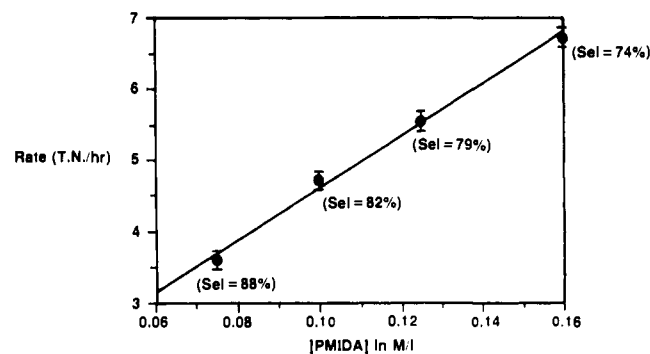


Figure 2. Plot of ln [PMIDA] versus time for the reaction profile in Figure 1.



where % Sel = % PMG + % N-Formyl PMG
% PMIDA converted

Figure 3. Effect of [PMIDA]_i on the initial rate profile as the turnover number versus [PMIDA]_i at 450 psig of O₂ pressure at 85 °C.

conditions, as noted in Figure 1 except that a reaction containing 8.8% PMIDA (by weight) is used instead of a 2.2% charge, the selectivity of the reaction is only 57% during the course of the reaction and at 100% conversion. When the PMIDA payload is increased to 25%, the selectivity to PMG is even lower at 43%. The selectivity loss in these higher payload trials is accompanied by an increase in the percent phosphate, AMPA, and DMF, as well as an increase in the level of H₂O₂ produced. For example, with an 8.8% PMIDA payload, the percent PO₄³⁻ was 17%, MAMPA was 5%, and AMPA was 14%.

Kinetic Studies. The cobalt-catalyzed oxygen oxidation of the PMIDA possesses an induction period at lower temperatures and pressures and at lower [Co]. This can be eliminated by adding trace amounts of a strong oxidant such as *m*-chloroperoxybenzoic acid. This makes it possible to obtain kinetic results over a wide range of reaction conditions. In Figure 2 is shown the plot of ln [PMIDA] vs time (h) for the reaction profile shown in Figure 1. As can be seen, the decay of substrate follows a first-order behavior over more than 3 half-lives. This behavior is characteristic for all of the Co-catalyzed reactions we have studied. In order to confirm the first-order dependence of the rate on [PMIDA], the reaction profile was monitored at several different initial concentrations of PMIDA. In Figure 3 is shown the effect of the [PMIDA]_i on the initial rate when the reaction was run under 450 psig of O₂ pressure at 85 °C with [CoSO₄·7H₂O] = 0.008 M. The initial rate is plotted as the turnover number, defined as moles of substrate converted divided by the moles of catalyst per unit of time (in this case, hours). This reaction is clearly first-order in PMIDA substrate. In addition, in Figure 3 are shown the selectivities for each [PMIDA]_i at >97% conversion. The selectivity shows a definite dependence on the initial concentration of PMIDA, with higher loadings resulting in lower selectivity as stated above. No effect of the PMIDA loading is

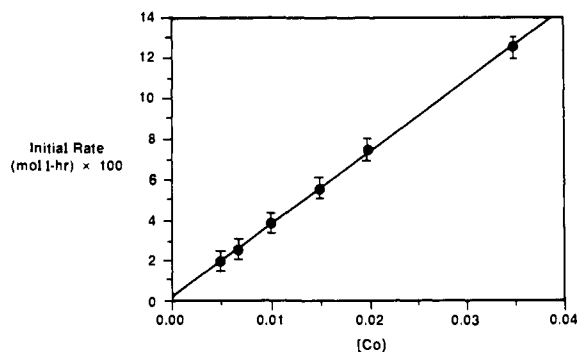


Figure 4. Effect of $[\text{CoSO}_4 \cdot 7\text{H}_2\text{O}]$ on the initial rate of PMIDA oxidation under 400 psig of O_2 pressure at 85 °C when $[\text{PMIDA}]_i = 0.10$ M.

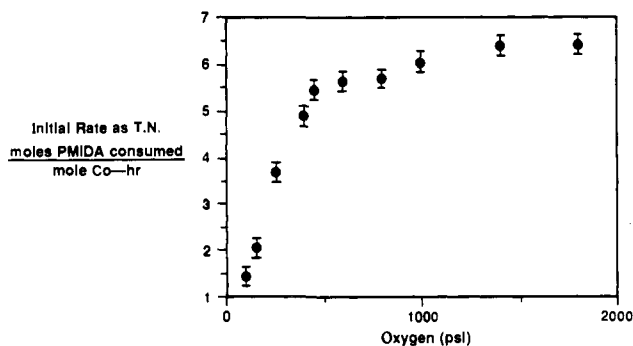


Figure 5. Initial rate of loss of PMIDA (0.10 M initial concentration) as a function of oxygen pressure at 85 °C with a 0.01 M solution of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ catalyst.

observed on the MAMPA or *N*-formyl(PMG) yields even at loadings as high as 30% PMIDA (by weight) of the total reactor charge.

The effect of $[\text{Co}]$, was studied in this system, and in Figure 4 is shown a representative plot of the effect of $[\text{CoSO}_4 \cdot 7\text{H}_2\text{O}]$ on the initial rate ($[\text{PMIDA}]_i = 0.10$ M) for a series of reactions at 85 °C and under 400 psig. The linear increase in the rate of the catalytic reaction indicates that the reaction is first-order in added Co(II). Importantly, the extrapolation of the linear fit to no added catalyst gives a zero rate of reaction. Also, the reaction selectivity at 95% conversion was independent of the Co concentration and found to be $87 \pm 2\%$.

Oxygen pressure was found to exhibit dramatic effects on the rate and the selectivity of the Co-catalyzed PMIDA oxidations. The effect of pressure was monitored (100–1800 psig) in a series of reactions at 85 °C and with $[\text{CoSO}_4 \cdot 7\text{H}_2\text{O}] = 0.0067$ M with use of 0.10 M PMIDA solutions. The results of the rate dependence are depicted graphically in Figure 5, as turnover number (initial rate of PMIDA loss divided by $[\text{Co}]$ per hour) versus pressure of O_2 . The reaction rate exhibits a linear increase in rate in the range 100–400 psig. At higher pressures, saturation kinetics are observed and the rate is independent of oxygen pressure. Figure 6 reveals the effect of O_2 pressure on the selectivity to PMG + *N*-formyl(PMG) for the trials of Figure 5. The selectivity to PMG (at >95% conversion) continues to increase as pressure increases, even at pressures as high as 1800 psig. The yields of byproducts are shown in Table II. All of the phosphorus-containing byproducts listed in Table II decrease as the oxygen pressure increases.

The effect of pH on this Co-catalyzed reaction was studied by adding either NaOH or H_2SO_4 to adjust the pH of a 0.10 M PMIDA solution. The reactions were run at varying pH (from 1.3 to 2.5) under 400 psig of O_2 pressure at 85 °C. A plot of the observed first-order rate constant versus $1/[\text{H}^+]$ yields a linear plot (Figure 7). The selectivity to PMG and *N*-formyl(PMG) is unfortunately deleteriously affected by increasing the pH. Thus, as the rate increases, the selectivity decreases. At the highest pH studied (2.5), the selectivity had dropped to ~59%, while the rate

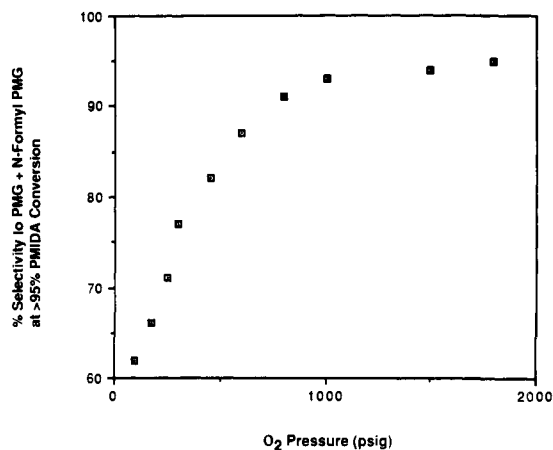


Figure 6. Selectivity to PMG (percent PMG + percent *N*-formyl(PMG)) at greater than 97% conversion for the reactions depicted in Figure 5.

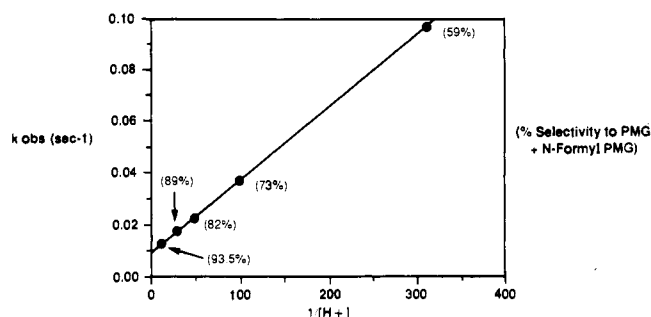


Figure 7. k_{obs} versus $1/[\text{H}^+]$ for the cobalt(II) sulfate catalyzed oxidation of PMIDA (0.10 M) at 85 °C under 400 psig of O_2 pressure with the selectivity to PMG + *N*-formyl(PMG) at >95% conversion shown in parentheses.

Table II. Effect of Oxygen Pressure on the Yields of Several Oxidation Products for a Series of Oxidations Carried Out at 85 °C with 0.10 M PMIDA and 0.0067 M CoSO_4

pressure (psig)	PMG (%)	phosphate (%)	AMPA (%)	MAMPA (%)	<i>N</i> -MePMG (%)
100	62.0	14.4	11.2	7.2	4.0
175	66.0	13.3	11.1	7.0	2.9
250	71.0	11.2	8.8	6.3	2.4
300	77.0	9.1	6.3	5.4	2.2
450	82.0	7.0	5.1	4.60	1.7
600	87.0	4.7	4.4	3.2	1.10
800	91.0	3.3	3.1	2.2	0.90
1000	93.0	2.2	2.70	2.0	0.60
1500	94.0	1.8	2.2	1.8	0.500
1800	94.9	1.1	2.1	1.7	0.400

was almost 6 times faster than at the natural PMIDA pH (~1.6). The amounts of phosphate and AMPA grew as the pH increased. Other side products were unaffected over this pH range.

Temperature Studies. The effect of temperature on the reaction rate of this Co-catalyzed oxidation was studied under two different oxygen pressures (200 and 1500 psig) and at four temperatures (80, 85, 90, and 95 °C) with 0.10 M PMIDA solutions containing 0.008 M $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$. Linear Arrhenius plots of $\ln k_{\text{obs}}$ versus $1/T_{\text{obs}}$ were obtained at both pressures. From the slopes of each plot, the activation energy (E_a), was found to be -29.8 and -25.6 kcal/mol at 200 and 1500 psig, respectively. Temperature also plays an important role in determining the selectivity to PMG. At 200 psig, the selectivity to PMG and *N*-formyl(PMG) combined was 85% at 80 °C, 82% at 85 °C, 79% at 90 °C, and 70% at 95 °C. The selectivity losses are due to increased levels of phosphate and AMPA (no change in MAMPA, ~7–8% by-products, with *N*-MePMG becoming a problem at 95 °C (~4.6%, ca. 1.3% at 90 °C).

Stability Constants. In an effort to elucidate the role of complexation in this catalytic chemistry, the stability constants for

Table III. Formation Constants for the Co(II) Complex Co(L) at 2.00 mmol L in 0.10 M NaClO₄ with Various Ligands L

ligand	log K_{ML}	log K_{ML_2}
PMIDA ^a	11.2	<14.8
PMG ^a	7.3	<11.1
NTA ^b	10.4	14.3
<i>N</i> -MeIDA ^c	7.71	

^aThis work. ^bNitrilotriacetic acid (ref 15). ^c*N*-Methyliminodiacetic acid (ref 15, p 125).

Table IV. Absolute Formation Constants and Acidity Constants for L = PMIDA^a

complex	log K
HL/H ₂ L	10.54
H ₂ L/H ₃ L	16.18
H ₃ L/H ₄ L	18.55
H ₄ L/H ₅ L	10.54
CoL/Co ₂ L	11.22
CoHL/Co ₂ HL	16.47

^aThis work.

the formation of cobalt(II) complexes with a number of ligands were measured by potentiometric methods.¹⁴ In Table III are listed binding constants for various ligands with Co(II). It should be noted that the PMIDA substrate is a competent ligand whose binding constant to Co(II) is better than the well-known sequestrant NTA. Additionally, the PMIDA substrate binds more tightly to Co(II) than the product PMG as reflected in the 10⁴ greater binding constant of PMIDA. The absolute formation constants and acidity constants for the PMIDA ligand are listed in Table IV. Use of these values makes it possible by standard methods¹⁶ to calculate the K_{eff} at any pH. As an example, at pH = 1 (the approximate pH of the PMIDA reaction), the K_{eff} value calculated for a 0.10 M PMIDA solution containing 0.010 M Co(II) ion is $8 \times 10^{-4} M^{-1}$. Consequently, at reaction temperature, the concentration of complexed Co(II) ion is very low. This conclusion is also supported by the experimental observation that the electronic spectrum of Co(II) solutions at pH = 1 in the presence of PMIDA shows no change from the simple aquocobalt(II) spectrum.

Isotope Effects. In order to probe the mechanism of this reaction, the CoSO₄ (0.007 M) catalyzed oxygen oxidation of a 0.14 M PMIDA solution was carried out at 95 °C under 200 psig of O₂ pressure in both H₂O and 99% D₂O. The rate constants for the two reactions are 4.94 (H₂O) and 1.19 h⁻¹ (D₂O); $k_H/k_D = 4.15$. The selectivity to PMG was monitored in the two reactions: in H₂O, the percent selectivity to PMG was 60% with 31% PO₄³⁻ and 7.1% MAMPA. For the D₂O reaction, the percent selectivity to PMG was 86.5% with 8.4% PO₄³⁻ and 4.2% MAMPA. The reaction mass from the D₂O reaction was eluted through a preparative LC column containing cation exchange resin and the pure MAMPA fraction collected and taken to dryness. Mass spectral analysis confirmed that this material was MAMPA but that one nonexchangeable deuterium atom had been incorporated into the molecule. Proton NMR at 80 Mhz of this material in D₂O (DDS internal standard) gave the same spectrum as authentic MAMPA: two nonwater resonances at δ 2.8 and 3.2 (d, $J_{PH} = 30$ Hz) corresponding to the *N*-Me and methylene resonances, respectively. The ¹H NMR integration shows that the intensities of the two resonances are 1:1, with the *N*-Me resonance somewhat broadened compared to authentic MAMPA. The conclusion is

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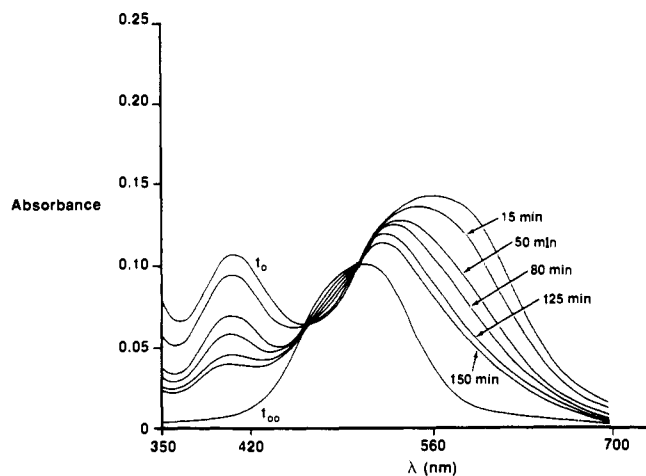


Figure 8. Electronic spectrum of a 0.025 M solution of a Co(III)(PMIDA) complex at pH 2.2 at 44 °C generated by the procedure described in text; $t_{1/2} \approx 94$ min under these conditions.

that the MAMPA byproduct in D₂O is the mono[d]methylated product DCH₂NCH₂PO₃H₂.

Counterion Effects. The effects of a counterion were studied in this chemistry in a series of reactions by using different Co(II) salts; e.g., CoSO₄, CoF₂, CoCl₂, CoBr₂, CoI₂, Co(ClO₄)₂, and Co(SCN)₂. These reactions were carried out for 3 h (>95% conversion obtained) under 450 psig of O₂ pressure at 85 °C with a PMIDA loading of 28 g/125 mL of H₂O and [Co] = 0.01 M. In all cases except for Br⁻ and I⁻, the reactions were identical in rate and yield of PMG (66.4%) and PO₄³⁻ (27.0%). The iodide system was completely inactive, and the bromide system was faster with a better selectivity: PMG = 76.4% and PO₄³⁻ = 18.2%. In contrast to all the other anions, the presence of Br⁻ eliminated the buildup of hydrogen peroxide so that its presence was virtually eliminated in the reaction. Optimization studies revealed that there exists at every temperature an optimum ratio of [Br⁻] to loading of the PMIDA substrate for maximum selectivity. At 85 °C, a 20% PMIDA slurry (31.3 g of PMIDA/125 mL of H₂O) was oxidized under 1800 psig of O₂ pressure with CoSO₄ (0.01 M) as the catalyst. At 95% conversion, a 57% selectivity to PMG was obtained after 3.5 h. When the same reaction was run with an optimum level of bromide ion ([Co]/[Br⁻] = 0.59; added as NaBr, 1.76 g), the reaction gave 91.7% selectivity at 96.7% conversion in 3 h. The byproduct overoxidation product yields were greatly diminished; PO₄³⁻ was only 2.7% and AMPA was only 0.66%, while the yield of MAMPA was relatively unchanged at 4.5%.

Spectrophotometric Studies. The heterogeneous oxidant PbO₂ is a competent oxidant for generating a Co(III) complex in situ. Alone, neither PMIDA or Co(II) will react with PbO₂, but solutions with equimolar concentrations of Co(II) and PMIDA react in minutes at room temperature to generate solutions containing Co(III), which are relatively stable at room temperature, decaying over a 24-h period to Co(II) and PMIDA and PMIDA oxidation products. In Figure 8 is shown a representative electronic spectrum of a 0.025 M Co(III)(PMIDA) complex (labeled as t_0) at pH 2.3 and 44 °C. The spectrum converts over a period of several hours to the t_∞ spectrum, which is identical with the spectrum of aquocobalt(II). By monitoring the absorbance change at 404 nm (as $A - A_\infty$) as a function of time, kinetic values for the decay of a putative Co(III)(PMIDA) complex at several temperatures could be computed. The decay process itself follows first-order kinetics rigorously over 3 half-lives in the pH range investigated (1–5) and at all the temperatures investigated (35–50 °C). The temperature dependence on the rate of oxidation of the bound PMIDA ligand by Co(III) was studied at pH 2.2 and 1.4 (approximate pH of the catalytic chemistry with 0.10 M PMIDA). The temperature dependence of the rate constants derived by monitoring the decline in the intensity of the 404-nm band with time obeyed the Arrhenius relationship (linear $\ln k$ vs $1/T$) at

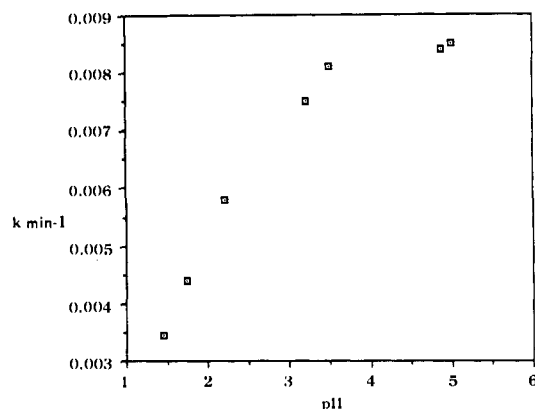


Figure 9. Effect of pH on the first-order rate constant for the decay of Co(III) as monitored at 404 nm at 40 °C.

Table V. Products Obtained from Co(III)(PMIDA) Oxidation at pH 2.4 after 6 h at 50 °C

product	yield ^a (%)	yield ^b (%)
PMIDA	45.1	45
PMG	35.5	36.7
formic acid	0	37
glyoxylic acid	0	0
<i>N</i> -MePMG	0	0
<i>N</i> -formyl(PMG)	0	16.3
formaldehyde	78.8	41.1
glycolic acid	16	2.2
phosphate(3-)	3.8	.9
AMPA	4	1.1
MAMPA	8	1.9

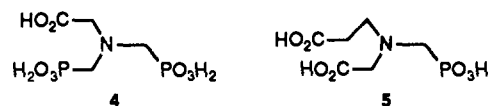
^aAnaerobic. ^bUnder 50 psig of oxygen.

both pH's and yielded an activation energy of -28.7 kcal/mol at pH 1.4 and -26.4 kcal/mol at pH 2.2. The effect of pH on the first-order rate constant for the decay process was also studied by monitoring the rate constant for the decline of the 404-nm band at 40 °C as a function of pH. The results of this study are depicted in the graph of Figure 9, which shows that the rate of decomposition of a 0.025 M solution of the Co(III)(PMIDA) complex at 40 °C increases as pH increases. In this study, it was observed that, at a pH of 5 or less, the position of the band maxima and the shape of the electronic spectra are independent of pH.

The products of the Co(III) oxidation of PMIDA were monitored for two reactions that were carried out at 50 °C at pH 2.4 for 6 h. One reaction was done anaerobically, while the other was carried out under 50 psig of O₂. Both reactions were monitored spectrophotometrically and followed until all Co(III) had disappeared. Additionally, it was observed that the presence of O₂ had no effect on the rate of decomposition of the Co(III) complex. In Table V, the analysis of products from the decay of the Co(III) oxidation of PMIDA are shown. The two sets of reactions both exhibit good phosphorus mass balances with nearly 100% P accountability. The conversion of the PMIDA in both cases was about 55%, corresponding to an approximate stoichiometry of 2 Co(III)/PMIDA. The yield of the PMG was virtually identical with the two reactions, but in the presence of O₂ there is a considerable amount of *N*-formyl(PMG) (16%) produced. In fact, if the amount of *N*-formyl(PMG) and PMG are considered together, then the selectivity to PMG approaches 95% for this oxidation. Also, the oxidation in the absence of O₂ produces no formic acid, while the oxygenated reaction produces the same number of moles of formic acid as PMG, suggesting that the formic acid is produced via the hydrolysis of *N*-formyl(PMG). Accordingly, the formaldehyde level is much reduced in the presence of O₂ as is the glycolic acid level. Also, the MAMPA level is reduced from ~ 8 to 1.9% with the introduction of O₂.

Substrate Specificity. When a solution containing 0.015 M CoSO₄ and 0.25 M PMIDA at pH 1.5 is allowed to react at 95 °C and under 450 psig of O₂ pressure, the PMIDA is completely converted in ~ 3 h. When the PMG product or other close

structural analogues such as NTA (nitrilotriacetic acid), *N*-Me(PMG), bis(phosphonomethyl)glycine (4), or *N*-(2-carboxyethyl)(PMG) (5), are reacted under the identical conditions, there is no oxidative conversion of the substrate.



Discussion

The cobalt-catalyzed O₂ oxidation of PMIDA has been studied in considerable detail with the aim of developing a kinetic and mechanistic understanding of this complicated system. In such a system, it is only through such mechanistic insight that our ultimate goal of developing a commercially viable process could be possible. To be commercially viable, this process must satisfy several criteria; the most important of these are high selectivity at high conversion in a batch reactor and with high payloads of substrate. We chose to investigate Co in detail because, unlike Mn, Co will catalyze the conversion at high PMIDA payloads. Unfortunately, the selectivity decreases as payload increases, producing phosphate. This, we found, could be to some extent solved by increasing the oxygen pressure, but the pressures required to keep the selectivity above 90% become very high and consequently are not viable process options. Another problem faced in this chemistry is the production of the [(*N*-methylamino)methyl]phosphonic acid, MAMPA. Its formation is diminished as O₂ pressure increases, but only very high O₂ pressures (>2000 psig) will suppress its complete formation. It became a major focus of our mechanistic studies to understand the source of these effects with the goal of eliminating these problems.

From the results of the kinetic and mechanistic studies, a consistent mechanism can be proposed. The key step in this sequence must be the nature of the oxygen activation (or reduction) step. At pressures up to 1000 psig, this catalytic chemistry is first-order in O₂ pressure as well as [Co] and [PMIDA]. This suggests that an unidentified Co^{II}(PMIDA) complex reacts with O₂ in a rate-determining step to yield an intermediate Co^{III}-(PMIDA)(superoxo) complex in analogy to many other known systems (see Scheme I).¹⁷ It is well established that a variety of Co^{II}(amine) complexes react with O₂ to generate μ -peroxo-dicobalt(III) dimers,¹⁸⁻²¹ which are hydrolyzed in acidic water to yield Co(III) complexes and hydrogen peroxide. Since hydrogen peroxide is detected in these reactions at very high levels and the levels reached are a function of the PMIDA substrate loading under any given set of reaction conditions, it is consistent that oxygen is reduced to hydrogen peroxide with Co(II). The formation of a Co^{II}(PMIDA) complex occurs as a preequilibrium, which in this system at pH 1-2 would be very unfavorable. An estimate of the value of K_1 can be calculated from the value of the protonation constants reported in Table IV. The value of K_{eff} at pH 1 and at 25 °C (where $K_{\text{eff}} = [\text{Co}(\text{PMIDA})]/\{[\text{Co}]_{\text{added}} + [\text{PMIDA}]_{\text{added}}\}$) was calculated by standard treatment and found to be 0.07.¹⁶ Thus, under the catalytic conditions, the actual value should be less at elevated temperatures such that only a very small amount of the Co(II) is complexed. This is consistent with our observation that the electronic spectra at room temperature and under catalytic conditions revealed only the presence of aquo-cobalt(II) ion. It is also consistent with the observation that the rate is inversely proportional to the [H⁺]. The oxygen activation portion of the mechanism is most consistent with equations 1-4.

At higher oxygen pressures, the rate-determining step no longer involves oxygen but remains first-order in [Co] and [PMIDA].

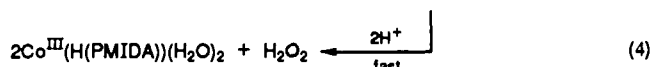
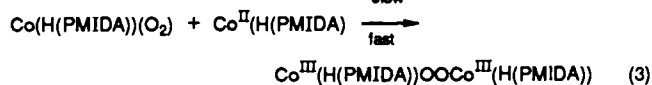
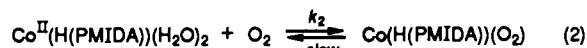
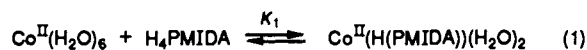
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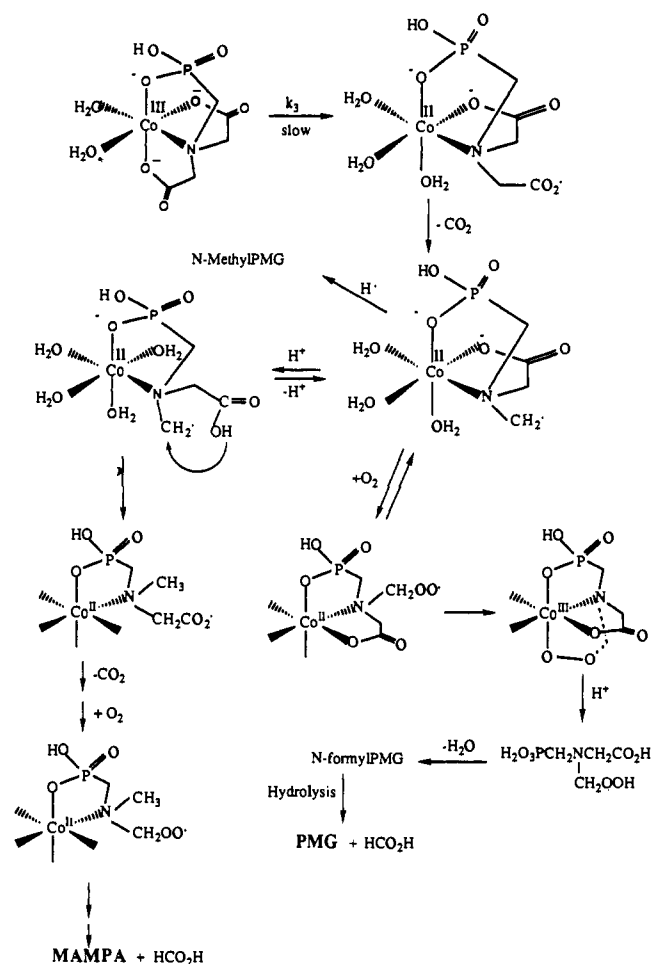
This is consistent with Co(III) as the actual oxidant of the PMIDA ligand. Since the binding constant of Co(III) for the PMIDA is over 10 orders of magnitude greater than for Co(II), it is most likely that it is the coordinated PMIDA that is oxidized. Support for the contention that prior ligand coordination is important is that poorer binding ligands do not get involved in this catalytic chemistry; i.e., the product PMG is not oxidized in this system. That other similar binding ligands such as 4 and 5 are not oxidized in this system is not understood, but clearly the catalysis is ligand specific.

The Co(III) oxidation of the PMIDA substrate could be seen to occur through three well-documented pathways: (1) outer-sphere oxidation of the tertiary amine to yield the amine radical cation whose subsequent deprotonation and oxidation would yield upon hydrolysis the PMG product and glyoxylic acid, (2) oxidative dehydrogenation to yield an iminium cation whose subsequent hydrolysis would yield PMG and glyoxylic acid,²² and (3) oxidation of the carboxyl that, followed by CO₂ loss, would yield an *N*-methylene carbon radical intermediate²³ (Scheme I) whose subsequent fate would determine the product mix. Since both pathway 1 and 2 predict that only glyoxylic acid (it is not observed experimentally) and PMG would be produced and the *N*-methyl or *N*-formyl derivatives are not, it appears that pathway 3 is the most consistent with experimental observations. This type of pathway is summarized in the scheme. The key feature of this oxidation is the formation of the *N*-methylene carbon radical. It is at this point in the reaction sequence that a potential branch in the reaction pathway can occur, leading to various side products such as MAMPA. Since Co(II) is labile, an equilibrium between a bidentate Co(II) species with a free pendant *N*-carboxymethyl side chain and the coordinated *N*-carboxymethyl species is proposed. Since O₂ is an excellent trapping agent of carbon centered radicals, one pathway would lead via an intermediate hydroperoxide to the *N*-formyl(PMG), which would hydrolyze to PMG under the reaction conditions. The dehydration of α -hydroperoxides of tertiary amines even in water is spontaneous.²⁴ This pathway is consistent with our observation that greater than equilibrium levels of *N*-formyl(PMG) are produced; thus, we believe that *N*-formyl(PMG) is an intermediate in the pathway to PMG in this catalytic system.

The homolytic abstraction of a H atom by the *N*-methylene radical from other H atom donors is an endothermic process in this system since the H atom sources are O-H bonds. As a consequence, very little *N*-methyl(PMG) is produced in this system. We propose that the origin of the MAMPA byproduct is in fact an intramolecular H atom transfer from the *N*-carboxyl group to the *N*-methylene radical via a cyclic six-membered-ring intermediate. The resultant species would be the *N*-methyl-*N*-methylene radical whose subsequent reaction with oxygen would lead to the *N*-formyl-*N*-methyl species, which would hydrolyze to MAMPA and formic acid (Scheme I).

The mechanism of this catalytic system as depicted in eqs 1-4 and the scheme is consistent with the kinetic studies. An integrated rate expression for the loss of PMIDA can be derived in terms of all the observable quantities, including [Co]_t, which is equal

Scheme I



to the sum of free Co(II) plus complexed Co(II) and complexed Co(III) (eq 5). The equilibrium formation of a bidentate,

$$[\text{Co}]_t = [\text{Co}(\text{II})]_{\text{free}} + [\text{Co}^{\text{II}}(\text{PMIDA})] + [\text{Co}^{\text{III}}(\text{PMIDA})] \quad (5)$$

phosphonate/amine chelated [Co^{II}(H₃PMIDA)]⁺ complex can be expressed as the equilibrium constant (K₁) (eq 6). Use of the

$$K_1 = \frac{[\text{Co}^{\text{II}}(\text{H}_3(\text{PMIDA}))][\text{H}^+]}{[\text{H}_4(\text{PMIDA})][\text{Co}^{\text{II}}]} \quad (6)$$

proper substitutions and mathematical manipulations gives the expression for the reaction velocity (eq 7). Thus, the scheme

$$V = \frac{2k_2k_3K_1[\text{O}_2][\text{Co}]_t[\text{H}_4(\text{PMIDA})]}{k_3K_1[\text{H}_4(\text{PMIDA})] + k_2K_1[\text{O}_2][\text{H}_4(\text{PMIDA})] + k_3[\text{H}^+]} \quad (7)$$

predicts that a first-order [PMIDA], [Co], and [O₂] dependence could be observed especially at low pH and that, at a sufficiently high O₂ pressure, a zero-order [O₂] dependence would occur, as observed. Thus, at high P_{O₂}, the second term of the denominator in eq 7 would predominate and eq 7 can be approximated by eq 8. Since [H₄(PMIDA)] can never exceed ~0.15 M due to a

$$V = 2k_3[\text{Co}]_t \quad (8)$$

solubility limit even at 100 °C, the k₃[H⁺] term could be expected to dominate the denominator under lower O₂ pressures ([O₂] at 200 psig and 90 °C will be <10⁻⁴ M) and under the acidic reaction conditions generally employed (pH < 1) so that eq 7 is approximated by eq 9. This expression is consistent with observed kinetics

$$V = 2k_2K_1[\text{O}_2][\text{Co}]_t[\text{H}_4(\text{PMIDA})]/[\text{H}^+] \quad (9)$$

and lends further support for the proposed mechanism depicted in the scheme.

Additional support for these mechanistic proposals comes from the results of the oxidations carried out in D₂O. First, the reaction exhibits an observed rate ratio k_{H₂O}/k_{D₂O} = 4.1. It is known that

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weaker acids generally are dissociated to a greater extent in light water than in D₂O, or simply $K_{HA} > K_{DA}$.²⁵ For example, the dissociation of acetic acid has been studied in detail²⁵ and reported to be $K_{HA} = 1.84 \times 10^{-5}$ and $K_{DA} = 0.555 \times 10^{-5}$; thus, $K_{HA}/K_{DA} \approx 3.3$. The observation of a slower rate in D₂O is consistent with such an equilibrium isotope effect for dissociation of H₄(PMIDA) to ionized forms, which complex to Co(II), yielding Co^{II}(PMIDA) complexes. This corresponds to the preequilibrium K_1 . Thus, in D₂O, H₄(PMIDA) is a weaker acid and the extent of ionization and consequently complex formation are diminished. The magnitude of k_{H_2O}/k_{D_2O} (4.1) is also close to the expected ratio of K_{HA}/K_{DA} for a weak acid such as PMIDA. A second important aspect to the results in D₂O is that the MAMPA byproduct in D₂O is quantitatively present as the mono[d]methyl species. If the equilibrium of the scheme is actually operative producing an intramolecular pathway for H atom transfer, there should exist a kinetic isotope effect on this process, resulting in less MAMPA as was observed and it would be expected to be the mono[d]methyl product as well.

The intermediacy of a discrete Co^{III}(PMIDA) complex as the actual intermediate, leading to oxidation of the PMIDA, was confirmed by the independent generation of a Co^{III}(PMIDA) complex. The spectrum of this key intermediate species could be conveniently monitored so that kinetic information regarding its decay to Co(II) and products could be obtained. The rate constants obtained for this process at various temperatures were used to calculate an activation energy, which is very similar to that found for the catalyzed chemistry at very high O₂ pressure. This indicates that the proposed oxidation of the coordinated PMIDA ligand by the Co(III) ion is at least a kinetically viable step for the second rate-determining step in the catalytic case. The products obtained from this oxidation also support our proposed mechanistic scheme; namely, in the presence of O₂, the decay yields formic acid and *N*-formyl(PMG) (16% yield). Also, in the presence of O₂, there is much less MAMPA. The pH dependence of the decay of the Co^{III}(PMIDA) was studied spectrophotometrically, and it was found that the rate slowed down as the pH decreased. This also suggests that it is the completely bound PMIDA ligand and the coordinated carboxylate that are oxidized

by the Co(III) ion in analogy to the oxidation of α -amino acids by Co(III).²³

Since hydrogen peroxide is produced in this system and the levels are dependent upon the amount of substrate, it seems reasonable that the yield loss observed as substrate loading increases could be due to undesired oxidations caused by H₂O₂. In fact, we observed in separate experiments that Co(II) will slowly react with H₂O₂ in hot water to generate Co(III) and presumably hydroxyl radicals. Such chemistry would not be desirable in this system since the generation of hydroxyl radicals would lead to the indiscriminate, unselective oxidations. Consequently, we believed that, to eliminate the overoxidation chemistry that produces phosphate in this system, the H₂O₂ must be scavenged. Since bromide is known to react with H₂O₂ producing bromine and hydroxide,²⁶ we attempted to eliminate peroxide with the addition of Br⁻. The result is that only a catalytic amount of Br⁻ is required to eliminate the buildup of hydrogen peroxide and to provide a large selectivity increase to the more concentrated or higher payload systems, with no effect observed in the dilute systems. As a consequence, we have been able to develop a very high payload homogeneous catalytic process, which enables us to achieve high selectivities at high PMIDA loadings and with high PMIDA conversions. A unique feature of this catalysis is that oxidation occurs on the bound substrate. The selectivity for substrate versus product oxidation is a consequence of the much higher binding constant of the Co(II) ion with the substrate PMIDA than with the product PMG.

Acknowledgment. We recognize the many useful suggestions provided by Dr. Raymond Grabiak, Dr. Peter Rogers, and Professor John Groves and thank John Long and Ron Beasley for their assistance in developing analytical methods and Dr. Fred Stover for his assistance in measuring binding constants.

Registry No. 3, 84767-96-4; 4, 2439-99-8; PMIDA, 5994-61-6; PMG, 1071-83-6; AMPA, 1066-51-9; MAMPA, 35404-71-8; *N*-MePMG, 24569-83-3; NTA, 139-13-9; CoSO₄, 10124-43-3; CoF₂, 10026-17-2; CoCl₂, 7646-79-9; CoBr₂, 7789-43-7; Co(ClO₄)₂, 13455-31-7; Co(SCN)₂, 3017-60-5; CoI₂, 15238-00-3; CO₂, 124-38-9; HCOOH, 64-18-6; HCHO, 50-00-0; H₂O₂, 7722-84-1; Co^{III}(PMIDA), 132344-99-1.

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