sentially isoenthalpic; i.e., the bond dissociation energies of the Co–C bond in each pair of diastereomers are essentially identical. The argument against steric effects being the dominant factor assumes that the corrin is rigid and that, in all the alkylcobamides, the cobalt atom lies very nearly in the mean plane of the equatorial nitrogens. For such a situation, models clearly show that the α face is more sterically congested than the β face and, for bulky organic ligands, steric interactions do occur between the side chains and the axial organic group. Indeed, such interactions are believed to be the driving force behind the decomposition of thermally labile species such as β-benzyl-Cbl and β-neopentyl-Cbl.[50] However, the corrin is not rigid; it is quite flexible.[51] Flexing of the corrin with associated displacement of the metal atom from the mean equatorial nitrogen plane clearly relieves steric compression by the side chains on the face toward which the metal is displaced. Such flexing is thought to be responsible for the marked stabilization of the base-off species of β-benzyl- and β-neopentyl-Cbl relative to the base-on species (the so-called "base-on" effect).[50] Hence, the thermodynamics of the α/β diastereomerism might reflect a greater tendency for the corrin to flex "upward" with the cobalt displaced toward the α face in α-alkylcobamides than to flex "downward" with the cobalt displaced toward the β face in β-alkylcobamides. This possibility is currently under further study.

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Registry No. β-CF_3Cbl, 133318-72-6; α-CF_3Cbl, 133318-71-5; β-CF_3CH_2Cbl, 128050-97-5; α-CF_3CH_2Cbl, 128052-61-9; β-$NCCH_2$Cbl, 133318-69-1; α-$NCCH_2$Cbl, 133318-68-0; H_2OCbl, 20623-12-5; CF_3CH_2I, 353-83-3; $NCCH_2Br$, 590-17-0; CF_3I, 2314-97-8.

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(50) Brown, K. L.; Brooks, H. B. *Inorg. Chem.* **1991**, *30*, 3420–3430.
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Vanadium(IV,V) Salts as Homogeneous Catalysts for the Oxygen Oxidation of *N*-(Phosphonomethyl)iminodiacetic Acid to *N*-(Phosphonomethyl)glycine

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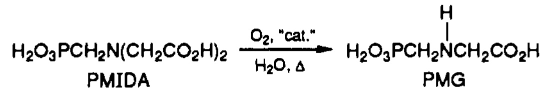
From screening studies we have found that several metal ions are capable of catalyzing the molecular oxygen oxidation of *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) to *N*-(phosphonomethyl)glycine (PMG), the active agent in the herbicide Roundup. Of these metal ions, vanadium, manganese, and cobalt salts were the most active, with the relative order of activity under a given set of conditions being V > Mn > Co. The vanadium-catalyzed PMIDA oxidations proceed at much faster rates and under milder conditions than with the other metals, but the chemistry suffers from lower selectivities. Kinetic and mechanstic studies reveal that the reactions are first-order in the [PMIDA], $[V]_{tot.}$, and $[H^+]$. In addition, the rate exhibits O_2 saturation kinetics, while increasing O_2 pressure increases the selectivity to PMG. From spectrophotometric, deuterium isotope, and other mechanistic studies, key mechanistic features have been elucidated: (1) An OV^{IV}(PMIDA(3−)) complex is first oxidized to V(V). (2) V(V) oxidation of a carboxyl moiety yields an intermediate carbon-centered *N*-methylenePMG radical. (3) The trapping of this radical with O_2 results in the formation of *N*-formylPMG, which hydrolyzes to PMG. (4) H atom abstraction by the *N*-methylenePMG radical leads to the undesired byproduct *N*-methylPMG.

Introduction

Molecular oxygen is an attractive oxidant for carrying out industrial processes, not only owing to its relatively low cost and abundance but also from an environmental standpoint, as its reduction does not yield salt products. Consequently, improved catalysis technology for performing O_2-driven oxidations is of considerable commercial significance. Monsanto currently converts *N*-(phosphonomethyl)iminodiacetic acid (PMIDA) to *N*-(phosphonomethyl)glycine (PMG) using a heterogeneously catalyzed oxygen-driven process:



$$\underset{\text{PMIDA}}{\mathrm{H_2O_3PCH_2N(CH_2CO_2H)_2}} \xrightarrow[\mathrm{H_2O},\ \Delta]{\mathrm{O_2},\ \text{"cat."}} \underset{\text{PMG}}{\mathrm{H_2O_3PCH_2\overset{H}{N}CH_2CO_2H}}$$

In the absence of added acid or base, PMIDA and PMG are only sparingly soluble in water (the ideal oxidation solvent). Consequently, the isolation of PMG product first requires the filtration of the heterogeneous catalyst from a highly dilute PMG solution, followed by an energy-intensive product concentration step. An effective homogeneous catalyst for the oxidation of PMIDA would eliminate the need for the filtration of the heterogeneous catalyst. In principle, high payloads could be achieved, thus avoiding the costs associated with a dilute reaction step.

For these reasons we began studies to determine if homogeneous catalysts could promote this oxygen-driven conversion of PMIDA to PMG. From our early screening studies we found that simple salts of Mn,[1] Co,[2,3] and V were very active homogeneous catalysts for the oxidation of PMIDA. Of these metals vanadium was the most active, although the observed selectivities with V were consistently less than observed with the other metals, producing as high as 50% *N*-methylPMG. With the goal of enhancing the selectivity of the vanadium-catalyzed PMIDA oxidation, we initiated a study of the mechanistic aspects of this novel vanadium chemistry. Prior to our studies of this problem, the catalytic oxidative dealkylation of a tertiary amine to a secondary amine with molecular oxygen had been demonstrated in only two cases,[4,5] and these were with unfunctionalized trialkylamines.

Experimental Section

Materials. All inorganic salts were purchased from Alfa Inorganics and used as received. The vanadium source used in the catalytic studies was vanadyl sulfate hydrate (22.15% V), and it was used as supplied by Alfa Inorganics. The PMIDA substrate was synthesized according to the procedure of Moedritzer et al.[6] Analytical standards for organic products such as PMG and AMPA ((aminomethyl)phosphonic acid) were obtained from Aldrich.

Procedure. For kinetic analysis of reaction rates at any given temperature, the reactions were run in triplicate. For the kinetic studies, 0.100 M aqueous PMIDA solutions were utilized for obtaining reaction profiles. All kinetic runs were performed in a Hastaloy C Autoclave Engineer's 300-mL autoclave stirred at 1500 rpm modified to bring oxygen into the reactor beneath the stirrer vanes. The reactor system

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(1) Riley, D. P.; Rivers, W. U.S. Patent 4965402, 1990.
(2) Riley, D. P.; Rivers, W. U.S. Patent 4898972, 1990.
(3) Riley, D. P.; Rivers, W.; Fields, D. *J. Am. Chem. Soc.*, in press.
(4) Riley, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1530.
(5) Correa, P. E.; Riley, D. P. U.S. Patent 4565891, 1983.
(6) Moedritzer, K.; Trani, R. R. *J. Org. Chem.* **1966**, *31*, 1603.
(7) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley & Sons: New York, 1988; p 788.

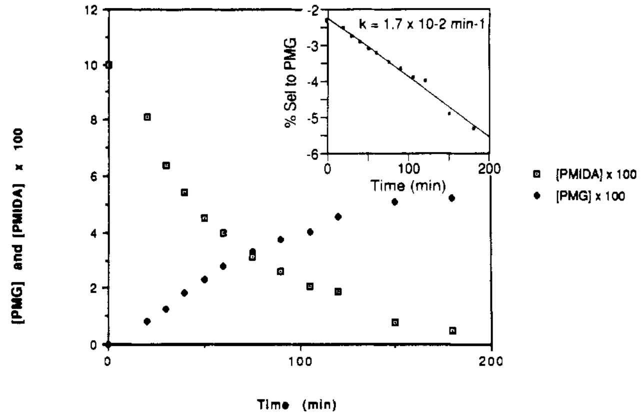

Figure 1. Vanadium sulfate catalyzed oxidation of PMIDA at 75 °C and 200 psig with [V] = 0.012 M and $[PMIDA]_i$ = 0.10 M. The inset shows ln [PMIDA] with time for this same reaction.

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 mL/min range on the inlet side. The flow rate utilized was 350 cm^3/min in the dilute systems studied for kinetic runs. On the outlet side of the reactor a Brooks Model No. 5850 flow indicator was employed. Tescom Model No. 26-1000 oxygen pressure regulators were used 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 O_2 reservoir and in the reactor were Validyne Model No. DP360-66 instruments. The heat control was provided by a standard Autoclave Engineer heater system employing a Love Model No. 1513-7188 proportional temperature controller with a solenoid for cooling water. An in-line Wilks Miran infrared CO_2 gas analyzer was employed on the exit side of the reactor to aid in monitoring the extent of reaction as % CO_2 evolved with the output going to a calibrated chart recorder. All gas lines and sample lines were constructed of Hastalloy C.

Analytical Studies. All reaction analyses were performed by using HPLC utilizing 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 by using an injection volume of 5 μL from a 10-μL Hamilton HPLC syringe. All phosphorus-containing materials were monitored by ligand-exchange HPLC using 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 V(IV or V) ion, H_2O_2, 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 $V^{IV,V}$(PMIDA) complexes in situ is described here. To generate the $O(H_2O)V^{IV}$(PMIDA-H) complex,[8] a 0.015 M aqueous solution of $VOSO_4$ was brought to the desired pH by the addition of H_2SO_4 or NaOH. The V(IV) complex has a "d–d" band maximum at 808 nm (ϵ = 18.0) in the pH range of interest (pH = 1–3). To generate the *cis*-$(O)_2V^V$(PMIDA-H) complex a solution that contains PMIDA at 0.015 M and V(V) ion (added as the $NaVO_3$ salt) at 0.15 M is brought to the desired pH by the addition of NaOH or H_2SO_4. The electronic spectrum of the resultant solution (devoid of any visible absorption bands) is then recorded on a Beckman Model DU-70 recording spectrophotometer.

Results

In Figure 1 is shown the reaction profile for a typical vanadium-catalyzed O_2 oxidation of PMIDA. Under these conditions the selectivity to PMIG is approximately 53% at high conversion (>95%). This magnitude selectivity is typical for the vanadium-catalyzed reactions under a wide variety of conditions. The other products (see Figure 2) produced in this reaction include 22% *N*-methylPMG, 6.6% AMPA, 2.1% *N*-MeAMPA, and 7.3% *N*,*N*-diMeAMPA—these materials also are representative of a wide range of reaction conditions. In addition, the PMG yield reported here reflects the total % PMG + % *N*-formylPMG, since the *N*-formylPMG hydrolyzes readily to PMG. At the 3-h point of the reaction shown in Figure 1 approximately 7% of the PMIDA converted to products is present as *N*-formylPMG. This level of *N*-formylPMG is much higher than equilibrium levels under these conditions (pH ~ 1, *T* = 75 °C).

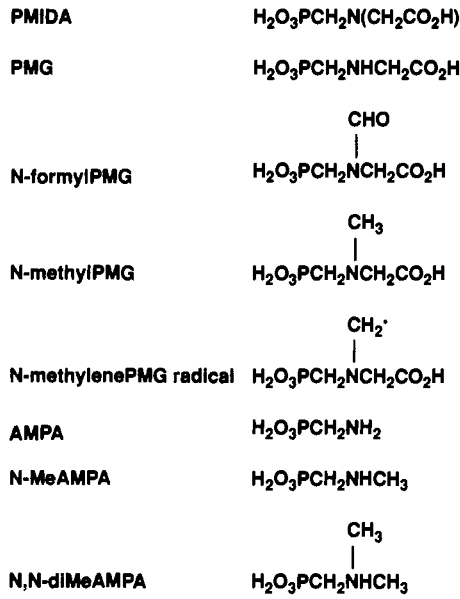

Figure 2. Structures for all abbreviated compounds cited in the text.

Unlike the cobalt chemistry described previously,[3] there is *no initiation period* observed in this chemistry with vanadium. Additionally, we have found that the chemistry proceeds at predictable rates with high PMIDA payloads (as high as 65% PMIDA by weight, 35% water), in contrast to catalysis with Mn, which suffers from catalyst precipitation. In all the experiments there was never any evidence of vanadium insolubility, even over wide pH range (0.5–7) or at high PMIDA loadings. We also observed that other sources of vanadium could be utilized with no effect on selectivity or rate as long as pH differences were considered; for example, $NaVO_3$ and V_2O_5 are suitable forms of vanadium.

Kinetic Studies. The effects of the different reactant variables on the reaction rate was studied in detail for the vanadium-catalyzed PMIDA oxidation. As noted in the Experimental Section, the source of vanadium was $VOSO_4$. Figure 1 illustrates an important feature of the vanadium chemistry, namely, that under these dilute conditions this reaction obeys first-order substrate kinetics. Thus, at 75 °C under 200 psig oxygen pressure the reaction has the pseudo-first-order rate constant equal to 0.0168 min^{-1} (slope of the ln [PMIDA] vs time plot of Figure 1) and a second-order rate constant equal to 1.4 M^{-1} min^{-1} (first-order rate constant/[catalyst]). The effect of vanadium concentration on the rate of PMIDA consumption was studied at 75 °C and under 200 psig oxygen pressure on a dilute PMIDA solution ($[PMIDA]_i$ = 0.10 M) and is depicted in Figure 3. The linear increase in rate as a function of [vanadium] indicates first-order behavior in [V]. Also the selectivity to PMG was consistently low ~ 58–62% in all of these runs with the byproduct profile identical with that discussed above for the reaction of Figure 1. This indicates that vanadium concentration is not by itself a significant variable for selectivity.

The role of oxygen pressure on the vanadium-catalyzed PMIDA oxidation was studied over an oxygen pressure range of 50–1200 psig at 75 °C and at a $[PMIDA]_i$ = 0.10 M and [V] = 0.007 14 M. The results depicted in Figure 4 show the first-order rate constant observed for PMIDA decay as a function of oxygen pressure. The reaction displays saturation kinetics in oxygen with

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[8] Wang, B.; Sasaki, Y.; Okazaki, K.; Kanesato, K.; Saito, K. *Inorg. Chem.* **1986**, *25*, 3745.

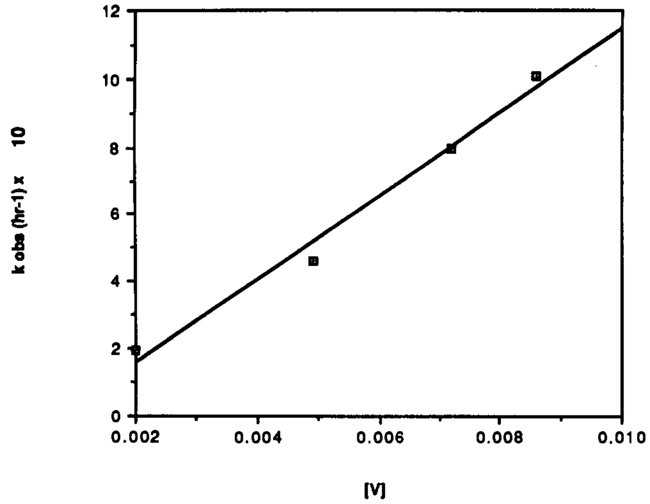

Figure 3. Observed first-order rate constant for PMIDA consumption as a function of the vanadium concentration at 75 °C and under 200 psig oxygen pressure.

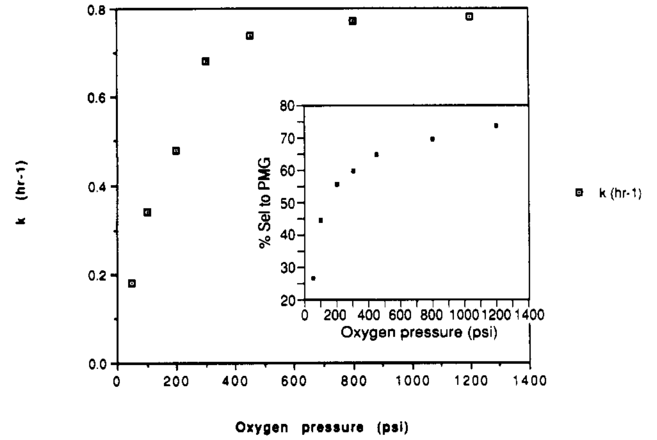

Figure 4. Oxygen pressure effect on the rate of PMIDA consumption for reactions at 75 °C with [V] = 0.007 14 M and $[\mathrm{PMIDA}]_i$ = 0.10 M. The inset shows the selectivity to PMG at each pressure.

the rate approaching first-order in oxygen at the lower pressures (<300 psig). An effect of oxygen pressure on the selectivity does occur with selectivity to PMG increasing with increasing oxygen pressure (see the inset of Figure 4 for the selectivity results for the reactions depicted in Figure 4) and with a corresponding decrease in the yield of methylated amine products. This type of pressure effect on the selectivity has been observed previously in the cobalt system.[3]

The temperature dependence of this vanadium-catalyzed reaction was studied at three temperatures (70, 75, and 80 °C) under two different oxygen pressures (350 and 1000 psig oxygen pressure) and $[\mathrm{PMIDA}]_i$ = 0.10 M and [V] = 0.010 M. Arrhenius plots for these two regimes were linear, and ln k values were obtained for the reactions by calculating k values from the slope of the linear ln [PMIDA] vs time plots. From the slope (E_a = slope × R) the activation energy is 26.1 kcal/mol at 250 psig and is 19.2 kcal/mol at 1000 psig. The magnitude of this activation energy at lower oxygen pressures indicates that the reaction rate is very sensitive to temperature—tripling every 10 °C! This value is nearly as high as that found in the Co system.[3] While temperature plays a major role in the rate of this reaction, the selectivity of the reaction to glyphosate was relatively insensitive to temperature changes under these dilute conditions. It should be noted again that the major impurity in these systems is *N*-methylglyphosate, and its production is most likely not by the well-known Eschenweiler–Clark reaction,[3,7] since the temperature is well below that where such chemistry occurs.

The effects of added acid (H_2SO_4) and added base (NaOH) on the rate and selectivity of the vanadium-catalyzed chemistry were studied at 80 °C and under 450 psig oxygen pressure on 0.10 M PMIDA solutions containing $[\mathrm{VOSO_4}]$ = 0.0072 M. In Table I the values for the second-order rate constants (first-order k values divided by [catalyst]) for the oxidation of PMIDA under these conditions are listed at various pH's. As can be seen, the pH has a profound effect on the rate and very little effect on the selectivity in this narrow pH range and under these conditions. These results are also depicted in Figure 5. The relationship between rate and $[\mathrm{H^+}]$ is linear over the narrow pH range that we studied.

Table I. Effect of pH on the Rate and Selectivity of a Series of PMIDA Oxidations under Conditions Described in the Text

pH	$[\mathrm{H^+}]$, M	rate, $\mathrm{min^{-1}\ M^{-1}}$	% selectivity
1.68	0.0209	7.55	64.0
1.79	0.0162	4.80	68.7
1.90[a]	0.0126	3.87	69.1
2.10	0.00794	2.92	63.6
2.24	0.00525	1.26	68.5

[a] Requires no added acid or base.

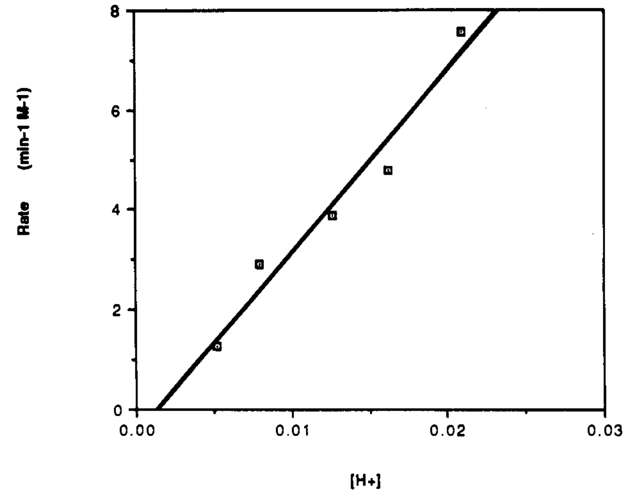

Figure 5. Plot of the second-order rate constant for PMIDA decay as a function of $[\mathrm{H^+}]$ under the conditions listed for Table I.

Spectrophotometric Studies. From our observations of the vanadium-catalyzed chemistry in glass Fischer–Porter bottles, we had noted that the reaction initially was a blue color due to the $\mathrm{V^{IV}(PMIDA(3-))}$ complex (a literature compound[8]). As the reaction was heated and subjected to an oxygen pressure of 50 psig, the color of the reaction turned to a deep red color indicative of vanadium(V). As these reactions near completion, the blue color indicative of vanadium(IV) reappears—at this point, essentially all of the $\mathrm{V^{V}(PMIDA(3-))}$ complex is consumed.

The $\mathrm{O(H_2O)V^{IV}(PMIDA(3-))}$ complex has a band maximum at 808 nm (ϵ = 18), identical with that reported in the literature,[8] whereas, the V(V) complex has no absorption maximum in the entire visible region. If the spectrum of the *cis*-$\mathrm{(O)_2V^{V}(PMIDA(3-))}$ complex is monitored with time, the V(V) complex decays to yield a V(IV) spectrum (the vanadyl sulfate spectrum is very similar to the $\mathrm{V^{IV}(PMIDA(3-))}$ spectrum). This decay process is shown for the *cis*-$\mathrm{(O)_2V^{V}(PMIDA(3-))}$ complex in Figure 6 at 44 °C. The spectrum was determined at various times, and the presence of a clean isosbestic point indicates that there are no stable intermediates or side reactions in the reduction of V(V) to V(IV) by PMIDA. The reduction of V(V) by PMIDA is a key step in the catalytic oxidation of PMIDA by vanadium. As a consequence, we studied this process in detail by the spectrophotometric method described above. We found that the simplest and most reproducible system was to start with sodium vanadate ($\mathrm{NaVO_3}$ as the source of V(V)) and PMIDA in water to which H_2SO_4 is added to obtain the desired pH. The growth of the 808-nm V(IV) band in the visible spectrum was followed as a function of time (decay of the $\mathrm{V^{V}(PMIDA(3-))}$ complex). This process was studied as a function of temperature and pH. The concentration of the $\mathrm{V^{V}(PMIDA(3-))}$ complex is directly

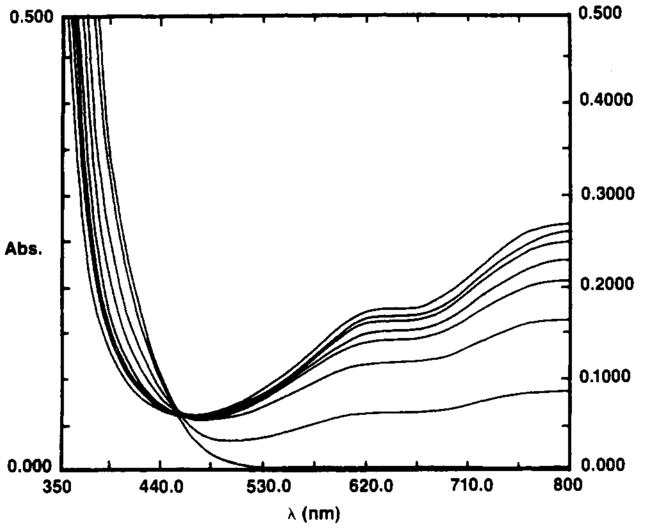

Figure 6. Visible spectra of the colorless *cis*-$(O)_2V^V(PMIDA(3-))$ complex at 44 °C as it changes with time, converting to the $(H_2O)V^{II}$ spectrum with band maximum at 808 nm (blue solution): $[V^V(PMIDA(3-))] = 0.015$ M; pH = 1.9. Spectra were recorded at the following times: t_0 = 5 s, 10 min, 25 min, 35 min, 45 min, 55 min, 65 min; $t_\infty = t_{75\,\text{min}}$.

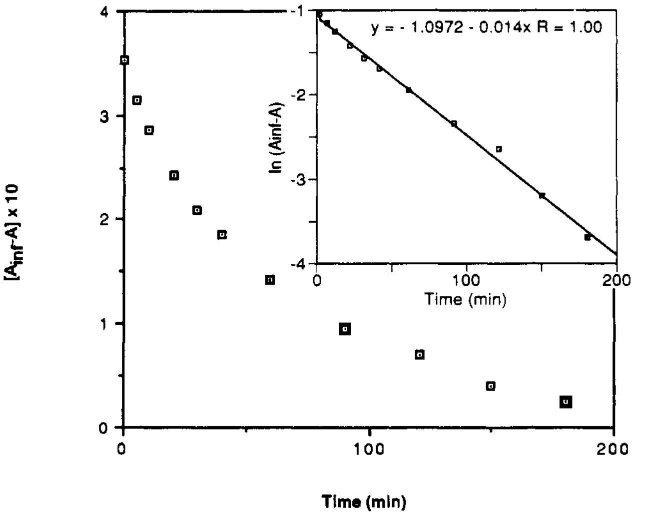

Figure 7. Plot of the $V^V(PMIDA(3-))$ decay monitored at 808 nm as a function of time at 35 °C and at pH = 1.7. In the inset is shown ln $[A_\infty - A_t]$ vs time (min) for this reaction.

Table II. Tabulated First-Order Rate Constants and Half-Lives for a Series of $V^V(PMIDA)$ Decays Studied by Spectrophotometric Techniques Described in the Text

trial no.	10^2k, min^{-1}	$t_{1/2}$, min	temp, °C	pH
1	1.35	51.4	35	1.7
2	2.103	33.0	40	1.7
3	3.20	21.6	45	1.7
4	1.83	37.9	35	1.5
5	0.083	834.3	35	2.5
6	4.94	14.0	35	1.0
7	0.2303	301.3	35	2.25
8	1.28[a]	54.1	35	1.7

[a] Run identical with first entry but under 50 psig oxygen.

proportional to the term (absorbance at infinite time)−(absorbance at time *t*).[9] In Figure 7 is shown a typical decay plot of this type, which was carried out at 35 °C with an initial [PMIDA] = 0.025 M = $[NaVO_3]$; H_2SO_4 was added to bring the pH to 1.70. In Figure 7 (inset) is the plot of ln $(A_{inf} - A_t)$ vs time for the decay depicted in Figure 7. As can be seen from the linear ln plot, this is a very well-behaved first-order process that proceeds in a linear decay over more than 4 half-lives. In Table II are listed the first-order rate constants and $t_{1/2}$ lives for a series of such studies when temperature and pH are varied.

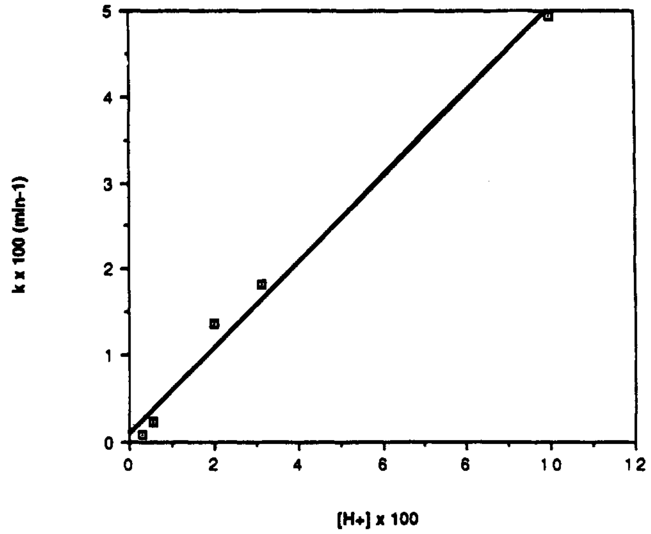

Figure 8. Plot of the first-order rate constant for the decay of *cis*-$(O)_2V^V(PMIDA(3-))$ vs $[H^+]$ at 35 °C and $[V]_i$ = 0.025 M.

Table III. Products from the $V^V(PMIDA)$ Decay at 35 °C under the Conditions Described in the Text, Where All V^V Disappeared as Monitored by the Spectrum of Each Run

	% yield[a]			% yield[a]	
product	a	b	product	a	b
PMIDA	47.6	57.11	*N,N*-diMeAMPA	11.3	8.16
PMG	10.9	15.05	phosphate	0.34	0.20
N-formylPMG	0	3.12	formaldehyde	25.3	27.3
N-methylPMG	5.9	3.02	formic acid	9.50	9.87
AMPA	10.0	9.35	glycolic acid	0	0
N-MeAMPA	3.6	3.18	glyoxylic acid	0	0

[a] pH = 1.7, [PMIDA] = 0.275 M, and [V] = 0.25 M; (a) anaerobic condition; (b) oxygen pressure = 50 psi.

Table IV. Effect of Solvent on the Rate and Selectivity of the Vanadium-Catalyzed PMIDA Oxidation at 200 psig Oxygen Pressure and at 75 °C, Where $[PMIDA]_i$ = 0.10 M and [V] = 0.005 M[a]

solvent	additive	rate const *k*, h^{-1}	% selectivity to PMG[b]	% selectivity to *N*-methylPMG
H_2O	none	1.01	53	23
D_2O	none	1.26	85	7.8

[a] All reactions run to >95% conversion. [b] Does not include *N*-formylglyphosate.

From the temperature-dependence data for the $V^V(PMIDA(3-))$ complex decay to V(IV) from Table II, an Arrhenius plot (linear ln *k* vs 1/*T* plot) was made and an activation energy was calculated to be 16.8 kcal/mol for the process. As can be seen in Figure 8, the first-order $V^V(PMIDA(3-))$ complex decay to V(IV) is directly proportional to the proton concentration—first order in $[H^+]$. The products of this decay process were monitored and are listed in Table III for two sets of conditions—both run at 35 °C and pH = 1.7 and with a 10% excess of PMIDA ([PMIDA] = 0.275 M): (a) anaerobically and (b) anerobically under 50 psig oxygen pressure.

Isotope Effects. The vanadium-catalyzed oxidation of PMIDA was studied in D_2O at 75 °C under 200 psig O_2 pressure by using [PMIDA] = 0.10 M and $[VOSO_4]$ = 0.0125 M. In Table IV are summarized some of the results of these studies. First, the reaction exhibits first-order PMIDA consumption kinetics in D_2O as in H_2O. Second, the reaction in D_2O is actually somewhat faster than in H_2O and the selectivity is markedly enhanced when the reaction solvent is D_2O. In order to isolate the various side

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[9] Wilkinson, F. *Chemical Kinetics and Reaction Mechanisms*; Van Nostrand Reinhold Co.: New York, 1980; pp 72–74.

Table V. Effect of Solvent on the Selectivity to Various Products of the V-Catalyzed PMIDA Oxidation[a]

product	% yield in H_2O	% yield in D_2O
PMIDA	4.76	4.26
PMG	27.44	48.36
N-formylPMG	1.66	4.95
N-methylPMG	22.96	12.16
AMPA	1.8	3.28
N-MeAMPA	3.72	3.39
N,N-diMeAMPA	33.21	13.89
formaldehyde	13.55	19.28
formic acid	27.03	37.08
phosphate	5.04	5.89

[a] See text for conditions.

Table VI. Formation Constants for Various Vanadium(IV,V) Complexes[a]

ligand	equilibrium	log *K*
IDA	$[VO^{2+}(L)]/[VO^{2+}][L]$	9.30[b]
	$[VO^{2+}(L)]/[VO^{2+}][L]$	11.7[b]
	$[VO_2^+(L)_2]/[ML][L]$	22.2[b]
N-MeIDA	$[VO^{2+}(L)]/[M][L]$	9.44,[b] 9.75[c]
	$[VO^{2+}(L)]/[M][L]$	10.2[b]
PMIDA	$[VO^{2+}(L)]/[M][L]$	≥14.5[c]
	$[VO^{2+}(HL)]/[H][ML]$	3.9[c]
PMG	$[VO^{2+}(L)]/[M][L]$	11.3[c]
	$[VO^{2+}(HL)]/[H][ML]$	3.7[c]

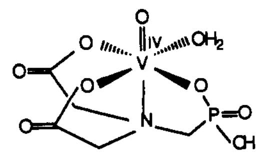
[a] All values determined at 25 °C under N_2. IDA = iminodiacetic acid. [b] From ref 11. [c] Measurements performed at 1–2 mM concentration in 0.1 N $NaClO_4$.

products of this reaction in sufficient quantity so that standard characterization techniques could be employed, the reaction in D_2O (and its control run) were run on a larger scale (32 g/125 mL of H_2O) by using 1.45 g of $VOSO_4$ catalyst under 45 psig oxygen pressure and at 68 °C. In Table V are the analytical results for these two experiments. This larger scale D_2O trial was subjected to low-pressure (50 psi) preparative-scale ion-exchange workup, and the AMPA, *N*-MeAMPA, *N*-diMeAMPA, PMG, and *N*-methylPMG fractions were isolated and characterized by FAB mass spectra and ^1H NMR spectroscopy. The ^1H NMR spectrum of the fraction containing a mixture of *N*-MeAMPA and AMPA showed the doublet (J_{PH} = 12.8 Hz) of the methylene of AMPA centered at 2.97 ppm, the broad methyl singlet of *N*-MeAMPA at 2.68 ppm, and the doublet (J_{PH} = 13 Hz) of the methylene of *N*-MeAMPA at 3.06 ppm with the integrated intensity ratios of methyl/methylene = 1.00 of *N*-MeAMPA—indicating completely selective mono-*d*-methylation of *N*-MeAMPA. The FAB mass spectrum of this mixture from water/glycerol indicated that no deuterium incorporation occurred in AMPA but that all of the *N*-MeAMPA contained one nonexchangeable deuterium (negative ion mass at *m/z* 125 corresponding to a mass of 126 (*N*-MeAMPA molecular weight = 125) incorporated into the molecule, and the FAB mass spectrum of diMeAMPA showed that two nonexchangeable deuterium atoms were incorporated into the molecule (negative ion mass 140 corresponding to a mass of 141 (*N,N*-diMeAMPA molecular weight = 139). Similarly, the FAB mass spectrum of *N*-methylPMG indicated that only *N*-methylPMG-d_1 was formed in the D_2O experiment.

Stability Constants. A key aspect in understanding the potential role of pH in this system and the source of the selectivity preference in this vanadium-catalyzed chemistry for the PMIDA substrate as opposed to the PMG product could reside in the magnitude of the binding constant of vanadium to the two potential ligands, PMG and PMIDA. In Table VI are listed some pertinent formation constants for vanadium complexes—including values for aqueous V^{IV} (as VO^{2+}) and aqueous V^V (as VO_2^+)—as measured by potentiometric methods.[10]

Discussion

The formation of V^{IV}(PMIDA) complexes has been studied by Wang and co-workers previously.[8] This work shows that at pH < 3 the major V^{IV} species is the protonated vanadyl complex **1**, $[VO(PMIDA(3-))(H_2O)]^-$, containing the *trans*-oxo-nitrogen geometry. The kinetics of ligand exchange were studied in this system, and pH was shown to play a prominent role in the rate of anation; i.e., rate is proportional to $[H^+]$. The kinetics of oxidation were also studied by using the outer-sphere oxidant $IrCl_6^{2-}$, although no mention was made of the stability of the resultant complex nor of its structure. In other systems it has been demonstrated that oxovanadium(IV) complexes of amino polycarboxylates are readily oxidized in acidic aqueous solutions by outer-sphere oxidants to form *cis*-dioxovanadium(V) species,[12-14] which we presume is the solution structure of the V^V(PMIDA(3−)) complex in this system.



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The oxidative decarboxylation reaction promoted by V^V in this system is not without precedent, since vanadium(V) is known to promote the oxidative decarboxylation of ethylenebis[(*o*-hydroxyphenyl)glycine], yielding CO_2 and the SALEN ligand.[15,16] It was proposed that the V(V) center is reduced to V(III) and air-oxidized to yield the observed V^{IV}(SALEN) product. Acidic aqueous solutions of V(V) are also known to oxidatively degrade amino alcohols via one-electron V(V,IV) redox chemistry.[17] Also V(V) has been shown to be an effective reagent for the oxidative decarboxylation of 3-hydroxy carboxylic acids yielding olefins and CO_2. The mechanism of this oxidation proceeds through a vanadium(IV) 1,4-metallacarba diradical.[18]

Since we had previously investigated the mechanism of the cobalt system, it is illustrative to compare these two catalyzed reactions. First, cobalt is much less active than vanadium; for example, V catalysis is as fast at 70 °C as Co catalysis at 90 °C. Co catalysis makes phosphate as a major byproduct, which we found was due to overoxidation produced from hydrogen peroxide derived hydroxyl radicals, and *N*-MeAMPA (MAMPA) in up to 8–10% yields as a byproducts as well. V catalysis on the other hand generates large amounts of *N,N*-diMeAMPA and *N*-methylPMG as the major byproducts. The two systems do also share some common features. For example, both systems increase their selectivity as the oxygen pressure increases, both systems produce larger than equilibrium amounts of *N*-formylPMG in the reaction, and both systems exhibit very similar reaction kinetics (first-order in [catalyst] and [PMIDA], oxygen saturation kinetics, high activation energy).

As previously reported,[3] Co chemistry in this system suffers from an unfavorable preequilibrium owing to the relatively small formation constant of cobalt(II) with PMIDA (log *K* = 11.2). This means that less than 1% of the cobalt(II) is complexed to

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PMIDA at pH < 2—the pH of these unbuffered solutions. Vanadium(IV) has a much higher binding constant (Table VI) at least 10^3 times higher; consequently, most or all of the vanadium is complexed to PMIDA under the reaction conditions. Since there is a higher effective concentration of catalytically significant metal species present with V than with Co, both the absence of an initiation period arising from an unfavorable preequilibrium and the higher catalytic activity of vanadium are easily rationalized.

The rate-determining step for cobalt at low oxygen pressure is the oxidation of Co^{II}(PMIDA(3−)) to Co^{III}. This is identical with that observed in the V system; namely, the reaction is rate-determining in the oxidation of V^{IV}(PMIDA(3−)) to V(V) at lower oxygen pressures. The activation energy measured for this process with V is about 26 kcal/mol and for Co it was found to be ~28 kcal/mol[14]—very similar values. This result means that the higher activity of vanadium does not solely lie in its ease of oxidation with oxygen to V(V) but that there is more V^{IV}(PMIDA(3−)) complex in solution. The rate differences for catalysis are also dependent upon subsequent rate-determining steps; i.e., if a subsequent reaction is slow enough, then when the rate of oxidation of the catalyst is sufficiently high (as with very high oxygen concentrations), we should see oxygen saturation kinetics and the subsequent rate-determining step dominate the catalysis rate. This is in fact what is observed with both metals. Co and V show oxygen saturation kinetics with rate saturation occurring over similar oxygen pressure ranges. In the case of V the second rate-limiting step (high O_2 pressure regime) possesses a smaller activation energy, ~19 kcal/mol, than with Co, which has an activation energy for the catalysis at high O_2 pressure of ~26 kcal/mol.

The V^V(PMIDA(3−)) decay process was measured independently by spectrophotometric means and found to have a lower activation energy (~16.8 kcal/mol) than the V(IV) to V(V) oxidation process. The same type of study was performed with the reduction of Co(III) with PMIDA, and the activation energy for the cobalt process at the same pH = 1.7 was 27 kcal/mol. This clearly demonstrates that vanadium is a better catalyst than cobalt: not only is there a higher effective catalyst concentration due to the higher binding constant of V(IV) to PMIDA but the oxidized V is also a better oxidant of the coordinated PMIDA at the natural pH of the PMIDA system.

This last point is a very crucial one because any comparison of the rates of these two catalysts must be done at the same pH. For example, Co catalysis increases in rate linearly as a function of $1/[H^+]$, whereas V catalysis shows a marked rate increase as the $[H^+]$ increases—completely opposite effect of pH on the two systems. This last point is crucial for vanadium catalysis, since the rate increases linearly with $[H^+]$ but selectivity is unaffected over the narrow pH range studied. With V there is no pH-sensitive preequilibrium, since all the V is completely complexed to PMIDA. As a consequence, another source of the pH effect must be at work. Previous workers[8] have shown that two protonation equilibrium exist and have measured their values as $pK_{a1} = 3.8$ and $pK_{a2} = 8.4$. The first deprotonation was assigned to the phosphonate group; also at the pH of the unbuffered reactions (pH < 2) most of the V^{IV}(PMIDA(3−)) complex will be in the fully protonated form, **1**. That the rate increases as pH lowers is consistent with catalysis occurring with this fully protonated complex. When the vanadium is oxidized, the resultant V(V) center will be destabilized more in the protonated form relative to the deprotonated complex (Coulombics); as a consequence, it is reasonable that the rate loss observed on increasing the pH is simply due to the stabilization of V(V) that results from the fully deprotonated PMIDA ligand. The effect of pH was studied for the V^V(PMIDA(3−)) decomposition process, and as noted above, is a first-order process in $[H^+]$, consistent with the mechanism outlined below. The same study performed with Co^{III}(PMIDA(3−)) showed that as the pH increased, the rate decreased—again behavior opposite to that of the vanadium system. The origin of the opposite effect of pH on these two catalyzed reactions lies in their binding constants; the rate increase in the cobalt system as pH increases is likely due to increasing efficiency of binding the substrate to the metal, whereas V(IV) under the reaction conditions is fully complexed at the low pH. The pH also affects selectivity, with decreasing pH having a modest selectivity boosting effect. This is the same trend as is observed with Co and is consistent with the fact that at higher pH the binding of the product PMG (see Table VI—PMG binding constant to V is about 3 orders of magnitude less than the PMIDA value) will begin to compete for the metal. As a consequence, at high pH the product PMG will be oxidized directly by the V^V.

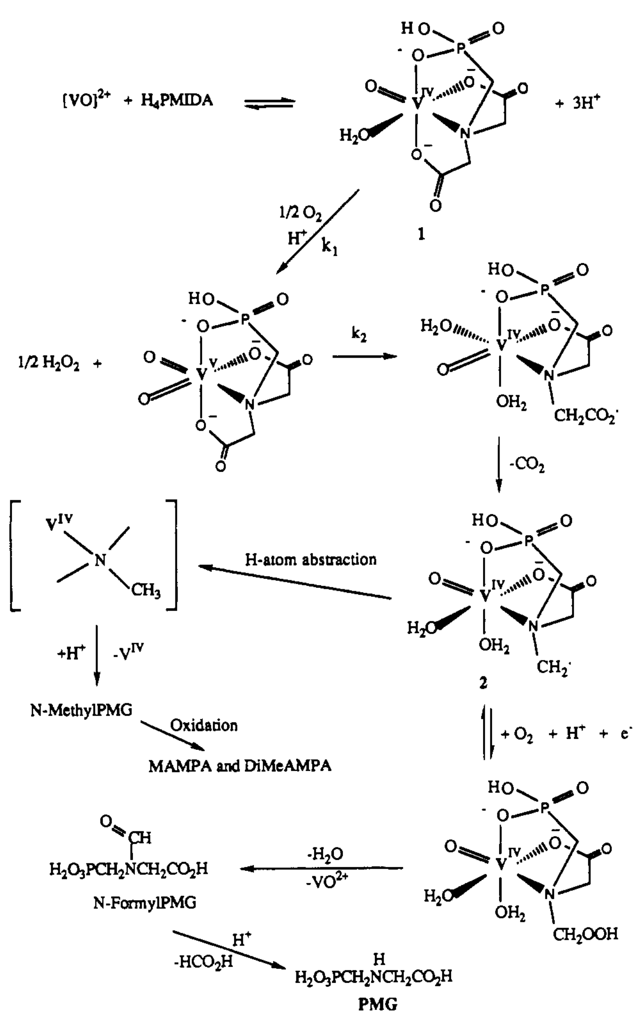
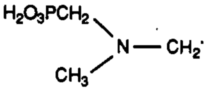


Figure 9. Mechanistic scheme for the vanadium-catalyzed oxygen oxidation of PMIDA to PMG and *N*-methylPMG.

The low O_2 pressure regime exhibits reaction kinetics which reveal that the rate-determining step involves the reaction of oxygen with V and PMIDA. This is best accommodated by the sequence in which a V^{IV}(PMIDA(3−)) complex is oxidized to V^V(PMIDA(3−)) by O_2. The actual details of the oxidation of the V(IV) are not known, but either a two-electron reduction of oxygen to hydrogen peroxide is operative or a one-electron reduction of O_2 to superoxide is likely operative. Since hydrogen peroxide is not detected in this system, we do not have evidence regarding the fate of oxygen as an oxidant in this system. The subsequent chemistry involves the reduction of V(V) by the coordinated ligand. All the evidence points to the mechanistic scheme shown in Figure 9. The fully protonated V^V(PMIDA(3−)) complex undergoes intramolecular electron transfer generating V(IV) and a proton plus the one-electron-oxidized carboxyl radical ligand in analogy to other known vanadium systems described above. This species would be expected to rapidly undergo irreversible decarboxylation to yield the PMG *N*-methylene radical species, structure **2**. Evidence for such a species comes from the studies of this reaction in D_2O and the types of products observed in this chemistry. As in the cobalt chemistry, it is the fate of this radical, **2** that governs the selectivity of this catalytic chemistry. Three major pathways all based on well-established precedent are believed to be operative. The first of these is the hydrogen atom abstraction reaction of the radical with a hydrogen atom source leading to selectivity losses, such as an NH, CH (of formic acid, for example), or OH (from solvent or intramolecular from a coordinated H_2O, free carboxyl, etc.). The net result is the production of *N*-methylPMG, which is the major byproduct of this chemistry. When the reaction is carried out in D_2O only monodeuterated methyl-substituted *N*-methylPMG is observed and the *N*-methylPMG is made in much lower yield. This is consistent with a deuterium isotope effect of the H atom abstraction, which lowers the yield, and is consistent with the intermediacy of radical **2**. *N*,*N*-DiMeAMPA is also a major byproduct in this V chemistry. The generation of this byproduct would most likely arise from a similar process to that generating *N*-methylPMG; namely, reoxidation of V^{IV}(*N*-methylPMG) to V(V) followed by oxidation of *N*-methylPMG to yield an intermediate methylene radical of structure **3**. The fact that in D_2O we observe much less *N*,*N*-diMeAMPA and that it contains only dideuterium-labeled product provides support for this mechanistic scheme.



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A second major pathway for the reactivity of the intermediate radical **2** is the reaction with O_2, an extremely efficient trapping agent for carbon-centered radicals.[19] The resultant (Figure 9) oxygenated radical could readily reoxidize the V(IV) center (the hydroperoxy radical would coordinate to V in a five-membered chelate ring) or accept a H atom from any of the potential donors H atom donors present. Such α-amino hydroperoxides are known to readily dehydrate in the presence (and absence) of metals to yield amides.[20] This generates *N*-formylPMG in this system, which would readily hydrolyze to PMG. This scenario is supported by the fact that we do observe much higher than equilibrium levels of *N*-formylPMG—especially in the higher payload reactions. As the reaction times increase, the levels of *N*-formylPMG decrease, supporting the intermediacy of *N*-formylPMG. The oxygen dependence on selectivity supports this mechanism also, since selectivity to PMG increases as oxygen pressure increases and this increase in selectivity is at the expense of *N*-methylPMG.

The V-catalyzed oxidation of PMIDA (Table IV) was found to exhibit a modest inverse isotope effect under conditions where the rate-determining step was O_2 oxidation of V^{IV}(PMIDA(3−)), $k_H/k_D = 1.25$. When the decay of the *cis*-*$(O)_2V^V$(PMIDA(3−)) intermediate complex was studied in D_2O, no isotope effect was observed. This modest isotope effect must be associated with the oxidation of the V^{IV}(PMIDA(3−)) complex by O_2. If inner-sphere electron transfer from V(IV) to oxygen is rate-limiting, it is possible that the rate of loss of bound water (breaking of the V–O(aqua) bond) could contribute to the facile binding of O_2 and hence contribute to the rate. This scenario would predict a faster rate in D_2O, since the V–O bond would be weaker with the less basic D_2O.[8]

Conclusions

The vanadium-catalyzed PMIDA autoxidation has been thoroughly studied, and the overall mechanistic sequence described here (Figure 9) is consistent with product studies, mechanistic studies, and kinetic studies. We have shown that an intermediate carbon-centered radical, **2**, is the intermediate whose subsequent reactivity governs the selectivity of the system. If this intermediate could be intercepted by another recyclable (or catalytic) cooxidant in this system and oxidized to the iminium cation, then hydrolysis of the iminium cation would yield PMG directly and formaldehyde. It is on this cooxidant approach that our current research efforts are focused, for such a scenario could offer high selectivity at very low O_2 pressures.

Acknowledgment. We recognize the many useful suggestions provides by Drs. Raymond Grabiak and Peter Rogers, and we want to thank John Long and Ronald Beasly with their assistance in developing analytical methods.

Registry No. PMIDA, 5994-61-6; PMG, 1071-83-6; *N*-formyl-PMG, 84767-96-4; *N*-methyl-PMG, 24569-83-3; AMPA, 1066-51-9; *N*-MeAMPA, 35404-71-8; *N*,*N*-diMeAMPA, 35869-68-2; vanadyl sulfate, 16229-43-9.

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