difference Fourier had a height of 0.38 e/A^3 with an estimated error based on ΔF[39] of 0.10. Plots of $\sum w(|F_o| - |F_c|)^2$ versus F_o, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. All calculations were performed on a Micro Vax II computer by using SDP/VAX.[40]

(39) Cruickshank, D. W. J. *Acta Crystallogr.* **1949**, *2*, 154-157.
(40) Frenz, B. A. The Enraf-Nonius CAD 4 SDP—A Real-Time System for Concurrent X-ray Data Collection and Crystal Structure Determination. In *Computing in Crystallography*; Schenk, H., OlthofHazelkamp, R., van Konigsveld, H., Bassi, G. C., Eds.; Delft University Press: Delft, Holland, 1978; pp 64-71.

Acknowledgment. Financial support from the National Institutes of Health AREA program (GM 38599) and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We also thank Robert Barmore, Robert Meadows, Margaret Mooney, Marie Alarid, and Professor Robert Doedens for their assistance.

Supplementary Material Available: Tables of atomic coordinates and anisotropic thermal parameters for **2b**, **6**, and **8d** (6 pages); a listing of observed and calculated structure factors for **2b**, **6**, and **8d** (39 pages). Ordering information is given on any current masthead page.

Oxidation of *N*-Alkylamides to Novel Hydroperoxides by Dioxygen

Russell S. Drago* and Richard Riley

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32611. *Received March 6, 1989*

Abstract: We report the facile, uncatalyzed, oxidation of 1-methyl-2-pyrrolidinone by O_2 at 75 °C and 3 atm pressure. Approximately 2 M concentrations of an oxidizing agent are formed in the neat solvent. DEPT and APT ^{13}C NMR as well as mass spectral analysis indicate that 5-hydroperoxo-1-methyl-2-pyrrolidinone is formed. The hydroperoxide is converted to 1-methylsuccinimide by peroxide decomposition catalysts.

In the course of studying solvent variation for metal-catalyzed oxidations of alkenes, we observed that the solvent 1-methyl-2-pyrrolidinone exhibited high selectivity for formation of epoxides. Cobalt(II)-catalyzed oxidation of 1-hexene with O_2 in this solvent produced 80 turnovers of 1,2-epoxyhexane in 24 h as the main product while a comparable reaction in acetonitrile produced 1-hexen-3-ol and 1-hexen-3-one almost exclusively. The selectivity to epoxide is expected for oxygen atom transfer reactions, and this suggested involvement of the solvent by chemical reaction. The mild conditions (75 °C and 50 psig of O_2) for a reaction involving this solvent prompted a study of the direct reaction of 1-methyl-2-pyrrolidinone with dioxygen.

It is well-known that the oxidation of *tert*-alkylamines to amine oxides occurs.[1-4] Metal-catalyzed oxygen atom transfer from *N*-oxides to alkenes leads to epoxides[5,6] and diols.[7,8] Amides have a very weakly basic nitrogen donor site, and conversion of this nitrogen to an *N*-oxide would be surprising. On the other hand, the stoichiometric oxidation of amides with ruthenium tetroxide[9] or persulfate[10] produces imides. Only low yields of imides are reported for the metal-catalyzed air oxidation of amides.[11,12] The metal-catalyzed (Co(II), Mn(II), Mn(III)) oxidation of amides with *tert*-butyl hydroperoxide or peracetic acid produces the corresponding imides in high yield.[13] The oxidation of straight-chain alkylamides is characterized by the autoxidation of the *N*-alkyl, CH, or CH_2 carbon. In 5- and 6-membered lactams, oxidation occurs at positions 5 and 6, respectively. *N*-Oxides are not obtained in these oxidations.

The selective epoxidation of alkenes by O_2 in this system parallels the activity of P-450. Furthermore, the amino acid proline or a proline segment in a polypeptide or protein chain has the same $(O)CNCH_2R$ functionality as 1-methyl-2-pyrrolidinone and could react in a similar fashion. These parallels to the P-450 system motivated us to try to understand the selectivity imparted to catalyzed oxidations by 1-methyl-2-pyrrolidinone. The findings may have relevance to the general understanding of the selectivity of monooxygenases and mixed-function oxidases.

Experimental Section

Materials. The 1-methyl-2-pyrrolidinone was HPLC grade from Aldrich and was used as received. The 1,5-dimethyl-2-pyrrolidinone, also from Aldrich, was vacuum distilled prior to use. The 2-pyrrolidinone and L-prolinamide were purchased from Aldrich and used as received. The $Co(octoate)_2$ (octoate = 2-ethylhexanoate) catalyst was an oil solution that was 12% cobalt(II) by weight. This catalyst was purchased from Mooney and used as received.

Methods. Proton and ^{13}C NMR spectra were run on a Varian XL-300 instrument in deuterated benzene or chloroform with TMS as an internal standard in all samples. ^{13}C NMR assignments were made using the attached proton test (APT)[14-16] and the distortionless enhancement by polarization transfer (DEPT)[17] programs available on the Varian XL-300.

GC–MS were performed on a Finnigan 700 ion trap detection system (ITDS) with a Varian 3400 GC containing a 15-m SPB-1 capillary column and by the University of Florida Microanalytical Laboratories on a Finnigan single quadrupole mass spectrometer connected to a Hewlett-Packard 5890A GC containing a direct on-column injector into a 30-m DB-1 column. Chemical ionization with methane was used to detect the parent ion of the peroxide because the molecular ion of the

(1) Pennsalt Chemicals Corp. U.S. Patent 3,274,252, 1966; *Chem. Abstr.* **1966**, *65*, 20005h.
(2) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588.
(3) Riley, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1530.
(4) Riley, D. P.; Correa, P. e. *J. Org. Chem.* **1985**, *50*, 1563.
(5) Bruice, T. C.; Nee, M. W. *J. Am. Chem. Soc.* **1982**, *104*, 6123, and references therein.
(6) Bruice, T. C.; Castellino, A. J. *J. Am. Chem. Soc.* **1988**, *110*, 158, and references therein.
(7) Matteson, D. S.; Ray, R. *Tetrahedron Lett.* **1980**, *21*, 449.
(8) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(9) Englehard Industries Inc. British Patent 900,107, 1962; *Chem. Abstr.* **1963**, *58*, 453e.
(10) Needles, H. L.; Whitfield, R. E. *J. Org. Chem.* **1966**, *31*, 341.
(11) (a) Lock, M. V.; Sagar, B. F. *J. Chem. Soc. B* **1966**, 690. (b) Sagar, B. F. *J. Chem. Soc. B* **1967**, 428. (c) Sagar, B. F. *J. Chem. Soc. B* **1967**, 1047.
(12) Riecke, A.; Schow, W. *Chem. Ber.* **1960**, *99*, 3238.
(13) Doumaux, A. R.; McKeon, J. E.; Trecker, D. J. *J. Am. Chem. Soc.* **1969**, 91, 3992.
(14) Rabenstein, D. L.; Nakashima, T. T. *Anal. Chem.* **1979**, *51*, 1465a.
(15) Lecocq, C.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 150.
(16) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.
(17) Dodderel, D. M.; Pegg, D. T.; Bendal, M. R. *J. Magn. Reson.* **1982**, *48*, 323.

0002-7863/90/1512-215$02.50/0

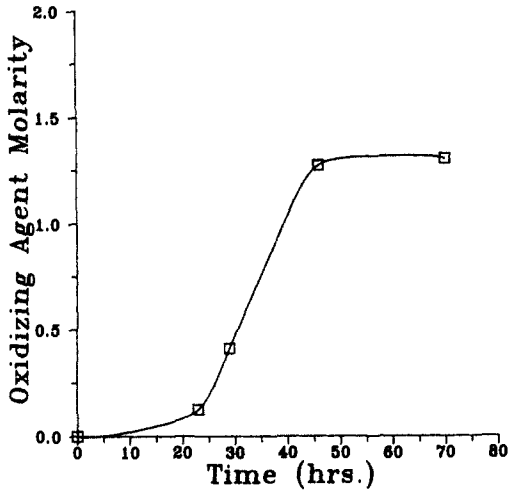


Figure 1. Oxidation of 1-methyl-2-pyrrolidinone at 75 °C under 50 psig of oxygen without a catalyst.

peroxide was not formed during normal ionization.

Oxidations were performed as described previously[18] with 1-methyl-2-pyrrolidinone and 1,5-dimethyl-2-pyrrolidinone serving as both substrate and solvent. For the oxidation of L-prolinamide and the acrylated L-prolinamide, acetonitrile was used as the solvent. Vacuum distillation of the 1-methyl-2-pyrrolidinone from the peroxide was performed at 1×10^{-4} mbar at 30–40 °C.

Peroxide concentrations were measured by taking 0.5–2-mL samples from the pressure bottles with a 12-in. stainless steel needle and immediately iodometrically titrating.[19] The 0.1 N $Na_2S_2O_3$ solution was made with standard solutions purchased from Aculute. The *N*-methylsuccinimide and 1-methyl-2-pyrrolidinone were separated on a Varian 3700 GC with a 6-ft stainless steel 15% FFAP (Chrom W, A/W 80/100-mesh support) column and integrated on a Hewlett-Packard 3390A integrator.

The acylation of L-prolinamide was performed by an adapted literature method.[20] L-Prolinamide (1.5 g), propionyl chloride (1.31 g), triethylamine (1.55 g), and 100 mL of methylene chloride were stirred overnight at room temperature in a 250-mL round bottom flask. Prior to the addition of propionyl chloride, the solution was briefly purged with nitrogen to remove moisture and then tightly sealed for the duration of the reaction. The next morning the solution was rotovapped at room temperature and filtered to remove triethylamine hydrochloride. The oxidation of these substrates was carried out with 0.5 g of L-prolinamide and approximately 1 g of the acylated prolinamide dissolved in 25 mL of acetonitrile in a Parr pressure bottle under 50 psig of oxygen.

The $Co(BPI)_2$ [BPI = 1,3-bis(2-pyridylimino)isoindoline][21a,b] and the (TPP)MnCl [TPP = tetraphenylporphyrin][22a-c] were synthesized by literature methods. The CoNa-Y zeolite catalyst was synthesized by aqueous cobalt(II) exchange with sodium Y-52 zeolite from Union Carbide (Lot No. 9680-84-1002) followed by 24 h in vacuo to remove water.

Results and Discussion

Uncatalyzed Reaction of O_2 with 1-Methyl-2-pyrrolidinone. The reaction of O_2 with neat 1-methyl-2-pyrrolidinone at 75 °C under 50 psig of molecular oxygen was shown by titration with thiosulfate to produce a large quantity of an oxidizing species whose formation as a function of time is shown in Figure 1. An induction period is observed, suggesting an autoxidation mechanism. By contrast, under the same conditions, 2-pyrrolidinone did not generate an oxidizing species, and furthermore the catalyzed reaction of alkenes with O_2 in this solvent did not occur under these conditions. The reaction of *N*-methylmorpholine with O_2 under these conditions does not form an oxidizing species, and we note that reaction to form the *N*-oxide is reported at higher temperatures and pressures.[4] At 75 °C, *N*-methylmorpholine decomposed to a brown solid.

Experiments were designed to determine the yield of product based on oxygen as the limiting reactant. The reaction of neat 1-methyl-2-pyrrolidinone at 75 °C under 50 psig of oxygen is carried out until all of the oxygen is consumed. The quantity of oxidant produced is determined by titration. The number of moles of oxygen is determined from the pressure, temperature, and volume of the gas. (1-Methyl-2-pyrrolidinone is not volatile at 75 °C.) A ratio of 1.5 mol of dioxygen is consumed to form 1 mol of the oxidizing species, representing a 67% yield based on O_2. The rest of the oxygen is either dissolved or used to form the other observed product, *N*-methylsuccinimide.

When a solution of this oxidizing species is deoxygenated with argon and placed in an oil bath at 75 °C with triphenylphosphine, triphenylphosphine oxide is formed in approximately 40% yield based on oxidant. The amount of triphenylphosphine oxide produced is estimated from the area of the P=O stretching frequency at 722 cm^{-1}. The oxidizing species produced by oxidation of 1-methyl-2-pyrrolidinone with molecular oxygen is capable of oxidizing triphenylphosphine to triphenylphosphine oxide without a catalyst.

To further investigate the nature and reactivity of the oxidizing species, the oxidation of 1-methyl-2-pyrrolidinone with O_2 was carried out in the presence of $Co(BPI)_2$, a known[23] peroxide decomposition catalyst. In the first 24 h of reaction, little oxidant is detected by iodine titration of the solution, but gas chromatography of the solution indicated that a large amount of *N*-methylsuccinimide is formed. The solution decolorizes, after 24 h, indicating that $Co(BPI)_2$ has decomposed, and from that time on a regular increase in the amount of oxidizing species is detected by iodine titrations. Since CoBPI is a peroxide decomposition catalyst, this experiment suggests that the oxidant formed in the reaction is 5-hydroperoxo-1-methyl-2-pyrrolidinone and that $Co(BPI)_2$ catalyzes the decomposition of this material to *N*-methylsuccinimide.

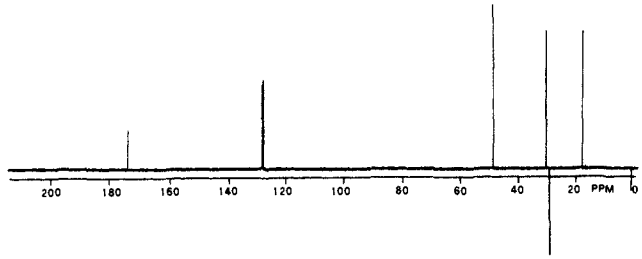
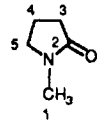
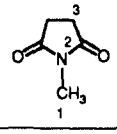
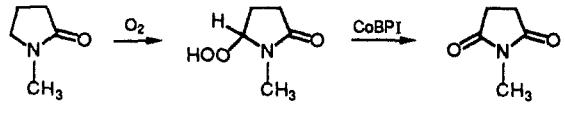


Figure 2. APT ^{13}C NMR of 1-methyl-2-pyrrolidinone (in C_6D_6, TMS).

Table I. DEPT and APT Assignment of ^{13}C NMR for 1-Methyl-2-pyrrolidinone and *N*-Methylsuccinimide

	carbon	^{13}C (ppm)	^1H (ppm)
	1	29.3	2.61 s
	2	174.3	
	3	30.8	2.06 t
	4	18.2	1.61 quint
	5	49.4	2.96 t
	1	24.1	2.64 s
	2	176.2	
	3	27.8	1.84 s



(18) Zombeck, A.; Hamilton, D. E.; Drago, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 6782.

(19) Sharpless, K. B.; Gao, Y.; Hanson, R. M.; Klunder, J. M.; Soo, Y. K.; Masamune, H. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(20) Suda, H.; Hosono, Y.; Hosokawa, Y.; Seto, T. *Kogyo Kagaku Zasshi* **1970**, *73*, 1250; *Chem. Abstr.* **1970**, *73*, 77571.

(21) (a) Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872. (b) Siegl, W. O.; Gagne, R. R.; Marrit, W. A.; Marks, D. N. *Inorg. Chem.* **1981**, *20*, 3260.

(22) (a) Barnett, G. H.; Hudson, M. F.; Smith, K. M. *Tetrahedron Lett.* **1973**, *30*, 2887. (b) Basolo, F. *J. Am. Chem. Soc.* **1978**, *100*, 4416. (c) Bouscher, L. L. *J. Am. Chem. Soc.* **1970**, *92*, 2725. (d) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayakashi, T.; Kodakek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000.

(23) Mimoun, H.; Brazi, E.; Saussine, L.; Robine, A.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1985**, *107*, 3534, and references therein.

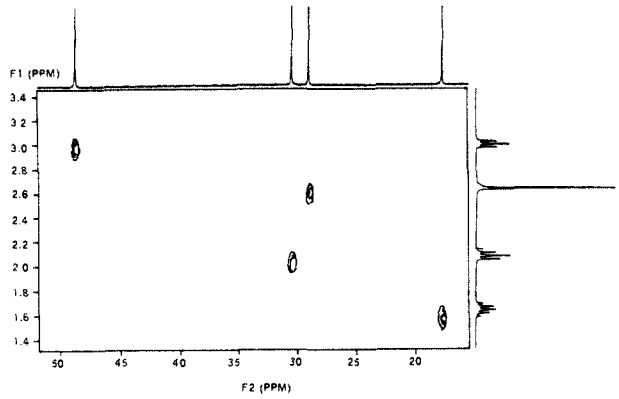
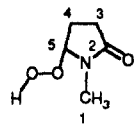


Figure 3. Proton/carbon 2-D correlation NMR of 1-methyl-2-pyrrolidinone (in C_6D_6).

Table II. DEPT ^{13}C Assignments for 5-Hydroperoxo-1-methyl-2-pyrrolidinone

	carbon	^{13}C (ppm)
	1	27.3
	2	175.1
	3	29.8
	4	23.7
	5	94.7

Spectroscopic Characterization of the Oxidant. Identification of the oxidizing species present in 1-methyl-2-pyrrolidinone after oxidation at 75 °C under 50 psig of oxygen was attempted with ^{13}C and proton NMR. The resonances for the carbon and proton spectrum of 1-methyl-2-pyrrolidinone are listed in Table I. The ^{13}C NMR spectrum is assigned with distortionless enhancement by polarization transfer and attached proton test (Figure 2) programs on the Varian XL-300 NMR spectrometer. The ^{13}C assignments that result are shown in Table I along with the proton assignments from 2-D NMR. The carbon–hydrogen correlation is made with the use of 2-D NMR (Figure 3) with the HETCOR program available on the Varian XL-300. The ^{13}C and proton NMR peaks for *N*-methylsuccinimide in Table I are also assigned with 2-dimensional NMR and APT. These assignments enable us to use NMR to follow the oxidation of the neat substrate.

By monitoring the oxidation of neat 1-methyl-2-pyrrolidinone at 75 °C, under 50 psig of oxygen over a period of 48 h, the formation of a new species is observed that is confirmed to be the 5-hydroperoxo-1-methyl-2-pyrrolidinone by NMR. The ^{13}C NMR spectrum of a sample that had been oxidized for 13.5 h (at 75 °C under 50 psig of oxygen) contains five new peaks. The DEPT analysis shows that the peaks at 23.7 and 29.8 ppm are CH_2 carbons, the peak at 27.3 ppm is a CH_3 carbon, the peak at 175.1 ppm is a carbon with no attached protons, and the peak at 94.7 ppm is a carbon with a single proton attached. Peak assignments in Table II result for the proposed product, 5-hydroperoxo-1-methyl-2-pyrrolidinone. This hydroperoxide is an appropriate undetected intermediate for the reported oxidations of 1-methyl-2-pyrrolidinone to *N*-methylsuccinimide. The 45.3 ppm downfield shift in the ^{13}C resonance of the 5-carbon of 1-methyl-2-pyrrolidinone upon formation of the hydroperoxide is comparable with the shift of 57.4 ppm observed in carbon of the ^{13}C downfield shift of the hydroperoxo carbon of cumene hydroperoxide compared to cumene. This provides further support for the assignments in Table II.

The products of the oxidation of 1-methyl-2-pyrrolidinone were also characterized by GC–MS. ITDS GC–MS was used to detect the formation of *N*-methylsuccinimide resulting in parent ions for *N*-methylsuccinimide and 1-methyl-2-pyrrolidinone at 114 and 100 amu, respectively (one greater than their molecular weights from the addition of a proton). The Finnigan single quadrupole mass spectrometer, equipped with a gas chromatograph containing an on-column injector, was used to observe the peroxide products. Chemical ionization with methane (CH_5^+) was used in response to problems with the stability of the peroxide during ion bombardment. Interpretation of the peroxide's GC–MS is complicated by the use of chemical ionization. In Table III an interpretation of the GC–MS data is given.

Table III. Interpretation of GC–MS Data for 5-Hydroperoxo-1-methyl-2-pyrrolidinone[a]

species	parent ion
1-methyl-5-peroxy-2-pyrrolidinone	132[b]
131 + $C_3H_5^+$ (41)	172
172 − H_2O (18)	154
131 + $C_2H_5^+$ (29)	160
160 − H_2O (18)	142
132 − H_2O (18)	114
131 − OOH (33)	98

[a] Formula weight 131. [b] Addition of a proton.

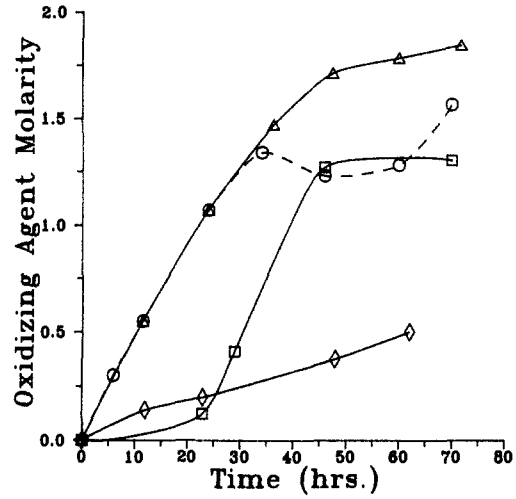


Figure 4. Catalytic oxidation of 1-methyl-2-pyrrolidinone by the Co-Na-Y zeolite at 75 °C and 50 psig of oxygen: △, CoNa-Y zeolite dried at 150 °C in vacuo; ○, CoNa-Y zeolite dried at room temperature in vacuo; □, Na-Y zeolite blank; ◇, uncatalyzed reaction.

The presence of a strong parent ion at 132 amu and the peak at 114 amu corresponding to the loss of water from the parent ion indicates that the oxidized product is the peroxide with formula weight 131. The loss of water by the ions of 172, 160, and 132 amu to form products at 154, 142, and 114 amu is persuasive evidence that a peroxide is present. The mass of the parent ion at 132 amu rules out the possibility of the oxidant being an *N*-oxide or a polymeric material.

Oxidation of 1-Methyl-2-pyrrolidinone at Other Conditions and with a Catalyst. When 1-methyl-2-pyrrolidinone is oxidized at 105 °c under 50 psig of oxygen, it rapidly decomposes to *N*-methylsuccinimide. The maximum concentration of peroxide (≈0.7 M) is attained within 6 h. At 105 °C the peroxide rapidly decomposes to *N*-methylsuccinimide as verified by ^{13}C and proton NMR. NMR indicates that the main oxidation product formed at 75 °C is the 1-methyl-5-hydroperoxo-2-pyrrolidinone, while virtually all of the oxidation product at 105 °C after 36 h is *N*-methylsuccinimide.

Our next studies involve an investigation of metal complex catalysis of this reaction. $Co(octoate)_2$, CoBPI, and (TPP)MnCl all rapidly decompose the peroxide to *N*-methylsuccinimide. At 75 °C under 50 psig of oxygen with the CoBPI and (TPP)MnCl catalysts, one observes small amounts of peroxide (≈0.1 M) in 5 h. This decreases to a trace amount after 24 h of reaction.

The ^{13}C NMR of the cobalt(II) octoate catalyzed reaction shows the presence of only *N*-methylsuccinimide. Thus, CoBPI, (TPP)MnCl and $Co(octoate)_2$ greatly increase the rate of decomposition of this new hydroperoxide. A CoNa-Y zeolite catalyst containing 4Co(II)/fwu (fwu = formula weight unit) oxidizes 1-methyl-2-pyrrolidinone at a faster rate and to a greater extent than the uncatalyzed reaction. The 24-h induction period that is present in the uncatalyzed oxidation of 1-methyl-2-pyrrolidinone is eliminated. A comparison of the two reactions is made in Figure 4. Also shown in Figure 4 is a comparison of two identical samples

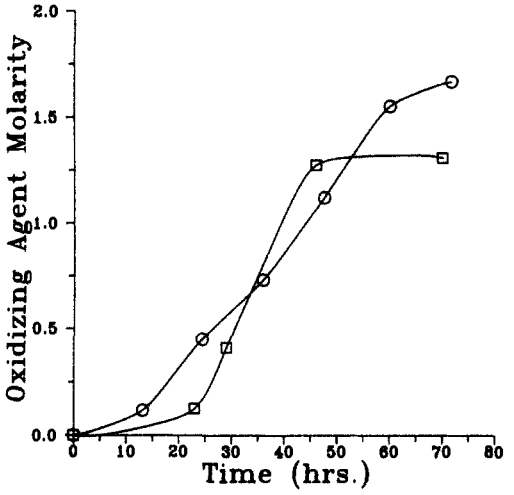
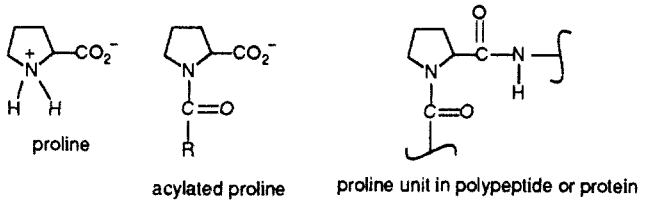


Figure 5. Oxidation of 1,5-dimethyl-2-pyrrolidinone and 1-methyl-2-pyrrolidinone without catalyst at 75 °C with 50 psig of oxygen: O, 1,5-dimethyl-2-pyrrolidinone; □, 1-methyl-2-pyrrolidinone.

of Co(II) in a Y zeolite dried under different conditions. The initial rates for the catalyst, dried at room temperature and 150 °C, are the same for the first 48 h, but after 48 h there was a drop in the product yield for the catalyst dried at room temperature. The CoNa-Y zeolite (pretreated at 150 °C) started to gradually level off at the same point in time but did not drop. The catalyst dried at room temperature is apparently the better peroxide decomposition catalyst. Either the dehydration of the free Co(II) in the Y zeolite or the movement of cobalt(II) from the large supercages to the smaller, less accessible sodalite cages causes the difference in behavior. Metal complex catalysis of the reaction to form hydroperoxide is shown to occur.

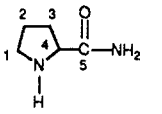
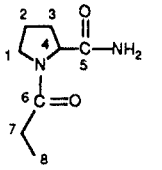
Extension to Other Substrates Containing the *N*-Alkylamide Functionality. The uncatalyzed reaction of O_2 with 1-methyl-2-pyrrolidinone was extended to 1,5-dimethyl-2-pyrrolidinone. As shown in Figure 5, an oxidant formed at even higher concentrations than with 1-methyl-2-pyrrolidinone. A change in the ^{13}C NMR of neat 1,5-dimethyl-2-pyrrolidinone was observed after 24 h of oxidation at 75 °C. The ^{13}C NMR of the reaction mixture showed that the product formed has peaks at 97.4 and 175.0 ppm. These two peaks parallel those for carbon 5 and carbon 2 of the 1-methyl-5-hydroperoxo-2-pyrrolidinone (Table II) and indicate that a stable hydroperoxide is being formed during the reaction.

The next substrate was selected to model functionality resembling that of 1-methyl-2-pyrrolidinone in a polypeptide. The involvement of peroxides in the P-450 shunt[24] prompted an investigation of this system. When the amino acid proline reacts to form a polypeptide or protein, the $OCN(CH_3)R$ functionality is introduced into the polymer. This is modeled by the acetylation of proline as shown below:



(24) Dawson, J. H. *Science* **1988**, *240*, 433. Ortiz de Montellano, P. R., Ed. *Cytochrome P-450*; Plenum: New York, 1985.

Table IV. ^{13}C NMR Peak Assignments for L-Prolinamide and Its Acylated Derivative

	carbon	^{13}C (ppm)
	1	47
	2	26
	3	31
	4	61
	5	179
	1	48.6
	2	24.9
	3	29.0
	4	59.9
	5	175.1
	6	171
	7	32
	8	22.4

L-Prolinamide was acylated by an adapted literature method.[25] The final product is separated from triethylammonium hydrochloride by filtration, and the ^{13}C NMR is reported in Table IV along with that of the starting material: L-prolinamide. The peak assignments for the ^{13}C NMR of L-prolinamide are based on the analogous assignments for 1-methyl-2-pyrrolidinone.

Acetonitrile solutions (25 mL) containing 0.5 g of L-prolinamide and another containing 1 g of acetylated prolinamide were subjected to oxidation by O_2. After 18 h of oxidation at room temperature under 50 psig of oxygen, titration shows that a small amount of peroxide forms in the acylated L-prolinamide and none forms in the L-prolinamide. The samples are then placed in oil baths at 50 °C under 50 psig of oxygen for 27 h. After 27 h, 1-mL samples of the two prolinamides are titrated and again only the acylated prolinamide contains peroxide. The acylated L-prolinamide is 0.082 M in peroxide, indicating that one-third of the acylated prolinamide is converted to the peroxide.

Other spot tests for peroxide gave positive results for peroxide only in the oxidized solution of the acylated prolinamide and none for the attempted L-prolinamide reaction. This result is consistent with only the CH_2 or CH of the alkylamide of the pyrrolidinone ring being readily oxidized by O_2 to the peroxide at low temperatures.

The oxidation of proline-type residues in proteins and polypeptides as well as catalyzed reactions of O_2 with other biological reducing substrates[26] to form hydroperoxides must be considered as candidate reactions for oxidation processes in its body. Hydroperoxides are present in vivo and are invoked in flavin-requiring monooxygenase reactions.[27] Flavin 4a-hydroperoxides are proposed as important intermediates in flavoprotein monooxygenase activity.[28] The reactions reported here may also play a role in the catabolism of proline.

Acknowledgment. We acknowledge and thank the support of this research by the U.S. Army CRDEC and by the National Science Foundation (Grant No.86 18766).

(25) Suda, H.; Hosons, Y.; Hosokawa, Y.; Seto, T. *Kogyo Kayaku, Zasshi* **1970**, *73*, 1250; *Chem. Abstr.* **1970**, *73*, 77571.
(26) Baumstark, A. L. *Bioorg. Chem.* **1986**, *14*, 326.
(27) Setner, K.; Mossey, V.; Ballou, D. P.; Neujahr, H. Y. In *Flavins and Flavoproteins*; Massey, V., Williams, C. H., Jr., Eds.; Elsevier: New York, 1982; p 335.
(28) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4017, and references therein.