The optical purities[19] and theoretical yields of the residual (+)-(*S*,*S*) diester (**8**) were analyzed at the following time intervals: 90 min (68% ee; 95%); 150 min (95% ee; 64%); 210 min (>98% ee; 54%). Consequently, it is evident that to secure (+)-**8** of high optical purity, it is necessary to conduct the incubation for about 210 min to ensure the complete hydrolysis of (−)-**8**. The conversion of (+)-**8** into **3** may be achieved by selective chemical hydrolysis, because **8** possesses a C_2 axis of symmetry. However, in our experience, this transformation can be more advantageously effected in quantitative yields by exposure of (+)-**8** to PLE.

The esterase of *G. roseum* provides the synthetic organic chemist with a powerful chiral reagent for the preparation of the aforementioned valuable synthons in quantities sufficient for chiral syntheses. We are currently probing the enantiotopic specificity of this enzyme on structural units of the type $XCH(CH_3)$-$CHOHCH(CH_3)X$. The results of these investigations will be forthcoming.

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Cleavage of DNA by the 1,10-Phenanthroline–Copper Ion Complex. Superoxide Mediates the Reaction Dependent on NADH and Hydrogen Peroxide

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The 2:1 1,10-phenanthroline–cuprous complex [$(OP)_2Cu^+$] cleaves double-stranded DNA in a reaction that requires hydrogen peroxide.[1,2] One-electron reductants such as superoxide anion and thiol have previously been used to produce $(OP)_2Cu^+$ in situ from the 1,10-phenanthroline–cupric complex [$(OP)_2Cu^{2+}$].[2,3] The ability of NADH, an important intracellular two-electron reductant, to sustain the $(OP)_2Cu^+$-mediated cleavage has now been investigated, because we are interested in determining if this reaction shares the same useful cytotoxic properties as the DNA scission reaction of bleomycin and neocarzinostatin.[4-6] In this communication we wish to report that 0.1 mM NADH effectively facilitates the DNA cleavage reaction in the presence of 0.5 mM hydrogen peroxide. We further report that superoxide plays a central role in the chemistry by which the NADH maintains a kinetically significant concentration of $(OP)_2Cu^+$ for the DNA cleavage reaction.

$(OP)_2Cu^{2+}$ in the presence of NADH and hydrogen peroxide readily forms acid-soluble products from [^{3}H]poly[d(A-T)] (Figure 1). The cleavage reaction observed in the presence of NADH and hydrogen peroxide shares important properties with the reaction observed in the presence of thiol and hydrogen peroxide.[2] These include the production of inhibitors of *E. coli* DNA polymerase I and the inhibition of the cleavage reaction by intercalating agent(s) (e.g., ethidium bromide) and 2,9-dimethyl-1,10-phenanthroline, a cuprous ion chelating agent whose

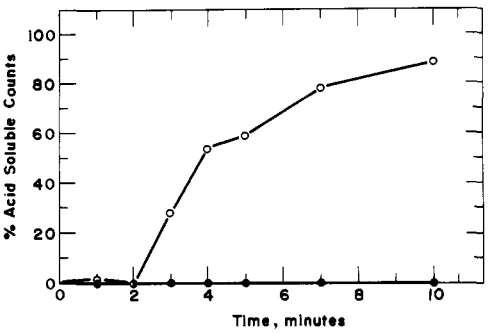

Figure 1. DNA cleavage by the 1,10-phenanthroline–copper complex facilitated by NADH and H_2O_2. [^{3}H]Poly[d(A-T)] (10 μg/mL) was incubated at 37 °C with 100 μM NADH, 20 μM OP, 2 μM cupric acetate, and 500 μM H_2O_2 in a Hepes buffer, pH 7.10. Acid-soluble counts were measured as previously described.[2] No other addition (○); 160 units/mL bovine erythrocyte superoxide dismutase (Worthington) (●).

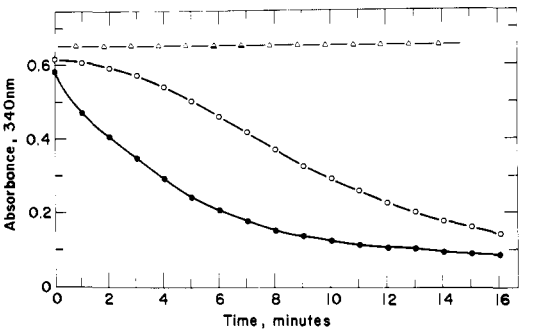

Figure 2. Oxidation of NADH by H_2O_2 catalyzed by $(OP)_2Cu^{2+}$. Hydrogen peroxide was added to a solution of NADH (100 μM), OP (20 μM), and cupric acetate (2 μM). Final concentration of H_2O_2, 500 μM. Total volume, 1 mL; pH 7.10 Hepes buffer; *T*, 21 °C. No other components (○); 140 μM 3-mercaptopropionic acid (●); 160 units bovine erythrocyte superoxide dismutase (△).

chelate does not degrade DNA. The important difference between them is that the reaction caused by NADH and hydrogen peroxide is inhibited by superoxide dismutase (Figure 1) whereas that observed with thiol and hydrogen peroxide is not.[2,3]

We and others have previously shown that diffusible superoxide anion produced by xanthine and xanthine oxidase does not cleave DNA on the time scale relevant here (Figure 1) in the absence of OP and cupric ion.[2,3,7,8] The sensitivity of the DNA cleavage reaction to superoxide dismutase therefore cannot be due to NADH, hydrogen peroxide, OP, and copper ion serving as a superoxide generator. It can, however, result if superoxide is important in mediating the formation of $(OP)_2Cu^+$, an essential coreactant in the cleavage reaction. Precedent for superoxide serving this function is the demonstration that the superoxide generating system, xanthine and xanthine oxidase, promotes an efficient catalase-sensitive DNA cleavage, because it increases the concentration of $(OP)_2Cu^+$ and hydrogen peroxide via the one-electron transfer reactions summarized in eq 1 and 2, respectively.[3] We propose that superoxide serves an analogous role

$$(OP)_2Cu^{2+} + O_2^{-}\cdot \rightarrow (OP)_2Cu^+ + O_2 \quad (1)$$

$$O_2^{-}\cdot + O_2^{-}\cdot + 2H^+ \rightarrow H_2O_2 + O_2 \quad (2)$$

in the NADH potentiated cleavage. This hypothesis is based on parallel kinetic studies of the DNA cleavage reaction and the oxidation of NADH by hydrogen peroxide catalyzed by $(OP)_2Cu^{2+}$.

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The oxidation of NADH by H_2O_2 catalyzed by $(OP)_2Cu^{2+}$ can be monitored by the decrease in the absorbance at 340 nm characteristic of the dihydronicotinamide moiety. The product of the reaction must be NAD^+, since NADH can be quantitatively regenerated at pH 9.0 with lactate and lactate dehydrogenase. Important features of both the NADH oxidation and the DNA cleavage include the (a) obligatory presence of OP, cupric ion, and hydrogen peroxide; (b) effective inhibition by superoxide dismutase; (c) inhibition by dimethyl sulfoxide (10 mM for 50% inhibition), an effective hydroxyl radical trap[9] but insensitivity to other hydroxyl radical traps such as mannitol, sodium formate, or sodium benzoate, all at 10 mM.

An induction phase is readily distinguishable in the kinetics of both processes. The lag in either reaction can be dramatically shortened by the addition of thiol (e.g., Figure 2). The kinetics of oxidation of NADH revealed other properties of the reaction mechanism leading to the formation of $(OP)_2Cu^+$ from $(OP)_2Cu^{2+}$ and NADH.[10] For example, the reaction proceeds more rapidly at pH 6.0 ($t_{1/2}$ = 6 min) than at pH 8.0 ($t_{1/2}$ = 12 min) under otherwise identical conditions (OP, 20 μM; Cu^{2+}, 2 μM; H_2O_2, 0.5 mM). In addition, the reaction rate does not exhibit a sharp dependence on molecular oxygen concentration despite the strong inhibition by superoxide dismutase. Solutions purged with nitrogen exhibited the same kinetics as reaction mixtures prepared under aerobic conditions; vigorously shaking previously anaerobic reaction mixtures with air did not lead to a change in the rate of absorbancy loss.

The observed lag in NADH oxidation is independent of the order of addition of reagents. Although the data reported in Figure 2 were obtained by adding hydrogen peroxide last, comparable kinetic profiles are evident if orders of addition are permuted in all possible ways. We propose the induction phase apparent in the DNA cleavage reaction, and the oxidation of NADH is the rate-limiting formation of the steady-state levels of $(OP)_2Cu^+$ essential for the DNA cleavage reaction and the net oxidation of the coenzyme. The abolition of the lag by 3-mercaptopropionic acid, an effective one-electron reductant of $(OP)_2Cu^{2+}$, supports this hypothesis. The inability of prior incubation of NADH to abolish the lag indicates that dihydronicotinamide cannot by itself accomplish the 1-electron reduction of the 1,10-phenanthroline–cupric complex. This observation is consistent with the stability of the NADH absorbance in the presence of 20 μM OP and 2 μM Cu^{2+} under aerobic conditions. Any $(OP)_2Cu^+$ formed by NADH reduction would be oxidized by molecular oxygen leading to the net oxidation of NADH.[11]

Hydrogen peroxide oxidizes NADH in a very slow but measurable reaction. It is possible that the 1-electron reductants generated in this reaction may be responsible for the initial formation of $(OP)_2Cu^+$. Although prior incubation of NADH and hydrogen peroxide did not relieve the lag noticeably, these unidentified species may be too reactive to accumulate and decrease the induction time. Evidence for the formation of the cuprous complex during the course of the reaction is the total blockage of the reaction by 2,9-dimethyl-1,10-phenanthroline and the relative rates of NADH oxidation and DNA cleavage observed with substituted phenanthrolines. For example, 5-nitro-1,10-phenanthroline which forms a stable cuprous complex because of the π acceptor ability of the nitro substitutent[12] is more effective in cleaving DNA and oxidizing NADH than OP under comparable conditions. 5-Methyl-1,10-phenanthroline is less effective than OP in both reactions since the methyl group increases the σ-donor strength of the ligand and preferentially stabilizes higher valent oxidation states.

Once formed the cuprous complex might lead to the series of reactions summarized in Scheme I. This scheme accounts for the net NADH oxidation and the coenzyme's ability to sustain a concentration of $(OP)_2Cu^+$ sufficient for DNA cleavage in the presence of H_2O_2. The first step in the scheme (eq 3), the oxidation of the cuprous complex by H_2O_2, has ample precedent in Fenton's reaction.[13] In solution the hydroxyl radical generated has two possible fates: (a) reaction with H_2O_2 with a second-order rate constant of 1.7×10^7 M^{-1} s^{-1} to produce hydroperoxyl radical (eq 4a)[14] or (b) oxidation of NADH (eq 4b). Since NADH and hydrogen peroxide are present at comparable concentrations, both reactions are possible. The hydroperoxyl radical, $HO_2\cdot$, can participate in several reactions in addition to its spontaneous dismutation. In an elegant kinetic study, Nadezhdin and Dunford have demonstrated that $HO_2\cdot$, but not its conjugate base superoxide anion, is an effective one-electron oxidant of NADH (eq 5).[15] This reaction is possibly responsible for the erroneous assignment of an acid pH optimum of the NADH oxidase essential in the respiratory burst of neutrophils.[16] It might also account for the acid pH optimum reported by Schellenberg and Hellerman for the oxidation of NADH by Fenton's reagent (i.e., ferrous ion and hydrogen peroxide)[17] and the accelerated rate of oxidation of the glyceraldehyde-3-phosphate dehydrogenase complex at pH 5.0 in the presence of superoxide generators.[18] An alternate fate for hydroperoxyl radical at pH 7.0 would be its ionization (eq 6) and subsequent reduction of $(OP)_2Cu^{2+}$ (eq 1).[19] The sensitivity of the net NADH oxidation to superoxide dismutase indicates that either step (eq 1 or 5) or both steps are quantitatively important in the reaction scheme.

Scheme I

$$(OP)_2Cu^+ + H_2O_2 \longrightarrow \cdot\ddot{O}H + (OP)_2Cu^{2+} + {}^-\ddot{O}H \quad (3)$$

$$\cdot\ddot{O}H \xrightarrow{H_2O_2} HO_2\cdot + H_2O \quad (4a)$$

$$\cdot\ddot{O}H \xrightarrow{NADH} NAD\cdot + H_2O \quad (4b)$$

$$HO_2\cdot + NADH \longrightarrow NAD\cdot + H_2O_2 \quad (5)$$

$$HO_2\cdot \rightleftharpoons H^+ + O_2^-\cdot \quad (6)$$

$$(OP)_2Cu^{2+} \xrightarrow{+O_2^-\cdot} (OP)_2Cu^+ + O_2 \quad (1)$$

$$(OP)_2Cu^{2+} \xrightarrow{+NAD\cdot} (OP)_2Cu^+ + NAD^+ \quad (7)$$

NAD· might be expected to undergo several transformations consistent with its redox potential of −1.00 V.[20] It could reduce $(OP)_2Cu^{2+}$ (eq 7) to complete a cycle, dimerize, or be oxidized by hydroxyl radical, superoxide, hydrogen peroxide (to regenerate hydroxyl radical), or molecular oxygen, if available.[21] The overall stoichiometry for the oxidation of NADH by hydrogen peroxide catalyzed by the 1,10-phenanthroline–cupric complex is 1.3 mol of H_2O_2 per mol of NADH.

Two distinct classes of intracellular reductants, dihydronicotinamides and thiols, can sustain the DNA cleavage reaction by 1,10-phenanthroline and copper ion in the presence of hydrogen peroxide. Thiol can sustain a steady-state level of $(OP)_2Cu^+$ sufficient for cleavage by reducing the cupric complex directly, because it is an one-electron reductant. In this communication we have also shown that NADH can be a source of reducing equivalents intracellularly but a multistep reaction scheme relying centrally on superoxide is involved. Although feasible, the occurrence of the DNA cleavage reaction intracellularly cannot be assumed in the absence of additional information on the transport of OP and copper into the cell and the prevailing levels of hydrogen peroxide.

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Two interesting perspectives of the biochemistry of superoxide are provided by the chemistry reported here. First, the facilitation of 1-electron reductions by NADH via hydroperoxyl radical may be one deleterious reaction of superoxide. Secondly, the inhibition of a reaction by catalase and superoxide dismutase does not necessarily imply the generation of hydroxyl radicals by the Haber–Weiss reaction. Both enzymes will also block reactions of hydroperoxyl radicals generated from hydroxyl radicals and hydrogen peroxide.[22]

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Ketene Dithioacetals as Synthetic Intermediates. Synthesis of Unsaturated 1,5-Diketones[1]

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Dithioacetals, in addition to their well established use as protecting groups[2] in organic synthesis, have found many applications as acyl anion equivalents,[3] most recently in the synthesis of ketones and α-phenylthio ketones.[3] They have also been utilized in the preparation of a variety of other organic functional groups including α,β-unsaturated ketones,[4] carboxylic acids,[5] α-chloro carboxylic acids,[6] *S*-methylthio carboxylates,[7] aldehydes,[8a] and β-keto esters.[8b] The corresponding monosulfoxide provides an attractive route to 1,4-dicarbonyl compounds with one carbonyl group being an aldehyde function.[9] Additional unsaturation as in vinyl ketene dithioacetals results in a dienic system that undergoes cycloaddition with reactive dienophiles.[10] A carbonyl-containing function or some other reactive, unsaturated group β to the dithioacetal carbon atom greatly extends the synthetic usefulness of these versatile intermediates,[11] especially in the synthesis of heterocycles.[12]

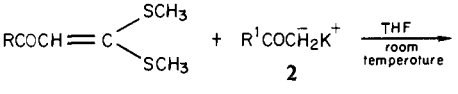
We now report a new and versatile synthesis of unsaturated 1,5-diketones from α-ketoketene dithioacetals. 1,5-Enediones are important intermediates in the synthesis of pyrylium and thiopyrylium salts[13] as well as pyridines[13,14] and have been prepared from β-chlorovinyl ketones and β-diketones or β-keto esters,[15] by HIO_4 oxidation of cyclopentane-1,2-diols,[16] or from pyridines and pyrylium salts.[17] None of these reaction sequences provides a general synthesis of this class of compound.

Table I. 1,5-Enediones[a] 3 Derived from α-Ketoketene Dithioacetals 1[21]

R	R^1	mp, °C	yield, %	M^+	ν_{CO} (KBr), cm^{-1}
C_6H_5	C_6H_5	106–108	76	267	1680, 1630
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	159–161	100	356	1655
C_6H_5	$2\text{-}C_4H_3S$	116–118	61	302	1700, 1680, 1645, 1625
C_6H_5	$2\text{-}C_5H_4N$	124–125	58	248	1680, 1640
$2\text{-}C_4H_3O$[b]	$2\text{-}C_4H_3S$	140–142	47	292	1690, 1670, 1640, 1620
$2\text{-}C_4H_3S$	$2\text{-}C_4H_3S$	161–162	74	308	1620
$2\text{-}C_4H_3S$	$5\text{-Cl-}2\text{-}C_4H_2S$	134–135	55	342	1623
$4\text{-}CH_3OC_6H_4$	CH_3	106–107	42	264	1710, 1640

[a] All colorless or cream needles. [b] Acetic acid workup.

Our new route involves the conjugate addition of a methyl ketone carbanion to the α-ketoketene dithioacetal, and as the latter are readily available from a wide variety of methyl ketones and alicyclic ketones, this procedure is characterized by the variety of substituents that may be introduced into the 1,5-positions. Addition of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one[18] (**1**; R = C_6H_5) (2.0 g, 8.9 mmol) to a solution of acetophenone (**2**; R^1 = C_6H_5) (1.07 g, 8.9 mmol) and potassium *tert*-butoxide (2.0 g, 17.8 mmol) in anhydrous THF, followed by stirring at room temperature for approximately 12 h, gave a red-brown precipitate of the potassium salt of **3** (R = R^1 = C_6H_5). This salt was



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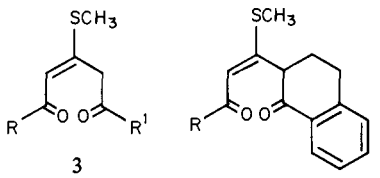

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collected and added to an ice-cold aqueous 4% HCl solution[19] and, on standing, the resultant oily material crystallized. 1,5-Diphenyl-3-(methylthio)-2-pentene-1,5-dione (**3**; R = R^1 = C_6H_5) crystallized from petroleum ether (bp 80–100 °C) as pale yellow prisms, mp 106–108 °C. Similarly **4** (R = $4\text{-}CH_3OC_6H_4$) obtained from **1** (R = $4\text{-}CH_3OC_6H_4$) and α-tetralone in 54% yield, separated from ethanol as colorless needles, mp 151–152 °C. The variety of substituents that can be incorporated into the 1,5-enediones by this reaction sequence is illustrated by the representative sample shown in Table I.

These reaction conditions yield[20] consistently the best results; e.g., sodium ethoxide in ethanol resulted in β-keto ester formation

† Corning Glass Works Foundation Fellow, 1978.

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(21) All products gave satisfactory analytical data (± 0.4%) for CHN where appropriate.

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