C-alkylation could be accomplished in excellent yield (95%) at room temperature by using potassium *tert*-butoxide as base in tetrahydrofuran (**10**, mp 167.5–168.0 °C; *m/e* 281.0899). This experiment underscores the real virtue of **8**. *Its anion is, in fact, stable enough such that under the alkylation conditions no β-elimination of the bridging heteroatom occurs.*[10] Attempts to perform similar sorts of alkylation reactions with the ribofuranosylacetate derivative **9** are troublesome, for it has been well established that β-elimination does occur in this case with scrambling of stereochemistry at the "anomeric" center.[11]

The alkylated β-keto ester intermediate **10** dissolved in a 1:1 mixture of tetrahydrofuran and water was now fragmented by the action of a saturated aqueous sodium bicarbonate solution (30 min, room temperature). Acidic workup gave in quantitative yield the acid ester **11**[12] which was reduced in turn with borane–tetrahydrofuran to furnish the corresponding alcohol (72% yield). Protection of the hydroxyl group by silylation (*t*-$BuPh_2SiCl$, imidazole, 4-(dimethylamino)pyridine, DMF, 92% yield) to give **12** set the stage for construction of a succinimide. This ring forming reaction was accomplished in a single step by treatment of **12** at room temperature with a 1:1:10 mixture of 2 M Na_2CO_3, 30% H_2O_2, and acetone.[13] On reduction of the excess peroxide with sodium bisulfite the dihydro analogue of showdomycin **13** was obtained as a mixture of diastereomers in 73% yield [*m/e* 452.1529 ($M^+ - t$-Bu)]. The 300-MHz ^1H NMR of **13** compared favorably with the spectrum of an authentic sample of the protected form of dihydroshowdomycin synthesized from the natural product by hydrogenation over palladium.[14]

For completion of the scheme, a minor adjustment of the oxidation state of the nitrogen heterocycle and, lastly, deprotection of the hydroxyl groups were required. While a number of obvious and not so obvious reagents were considered which might effect the dehydrogenation reaction in a single step, such methods had either been examined by others before[15] or else failed when attempted in our hands. We thus resorted to a conventional selenenylation–selenoxide elimination sequence.[16] Treatment of **13** with 3 equiv of lithium isopropylcyclohexylamide at −78 °C for 20 min followed by the addition of 3.2 equiv of phenylselenenyl chloride at the same temperature with slow warming to −20 °C gave a crude mixture of selenenylated products. The mixture was oxidized directly with sodium periodate in methanol–water (5:2) and then refluxed in carbon tetrachloride in the presence of calcium carbonate to effect selenoxide elimination. The protected form of showdomycin was generated in 90% yield on the basis of consumed starting material [*m/e* 450.1373 ($M^+ - t$-Bu)]. Deprotection of the hydroxyl groups by treatment with a 4:1 trifluoroacetic acid–water solution at room temperature for 1.5 h completed the synthesis of **1**.[17]

Further work is now in progress to generate **1** in optically active form from an optically active allene and extend our scheme to the preparation of some new *C*-nucleoside isosteres.

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Supplementary Material Available: TLC, mp, IR, 300-MHz ^1H NMR, and MS data of all new compounds (5 pages). Ordering information is given on any current masthead page.

(9) An X-ray analysis of this material is now being carried out, and the results of this study will be reported in due course.
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(12) No attempt has presently been made to resolve this acid, although it should clearly be possible in light of Noyori's work.[4]
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(14) We thank Dr. Nakagawa of Shionogi Laboratories for an NMR spectrum of the acetonide of dihydroshowdomycin.
(15) Rosenthal, A.; Chow, J. *J. Carbohydr. Nucleosides, Nucleotides* **1980**, *7*, 77.
(16) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.
(17) The synthetic material was identical in all respects (^1H NMR, IR, MS, and TLC data) with a sample of the natural product obtained from Shionogi Laboratories.

Oxo–Peroxo Oxygen Exchange in Peroxovanadium(V) and Peroxomolybdenum(VI) Compounds

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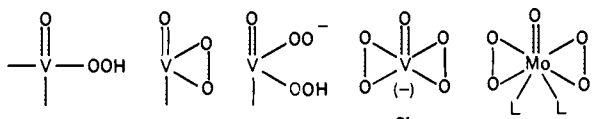
Recent studies on the vanadium(V)-catalyzed oxidation of sulfides by hydrogen peroxide in ethanol and dioxane–ethanol have shown that monoperoxo- (**1**) and diperoxovanadium(V) species (**2**), the latter as an anion, are formed under appropriate circumstances.[1-3] In particular, monoperoxo appears to be the only species present in dioxane–2.5% ethanol (v/v), even at high $[H_2O_2]/[V^V]$ ratio, whereas in ethanol solvent the monoperoxo is prevalent only at low hydrogen peroxide concentration.

The structure of peroxo species in solution is still uncertain:[4] they may have either the open structure **1a**, **2a** or the cyclic ones **1b**, **2b**; equilibrium interconversion between open and cyclic



1a **1b** **2a** **2b** **3**

structures may also occur. Thus, the identification of the real oxidizing species in these metal-catalyzed processes is of current interest.

We have found that, under conditions where **1** is the only peroxo species present[3] or at least the dominant one, ^{18}O labeled hydrogen peroxide undergoes a fairly fast oxygen exchange (~50% label loss in 10–20 h at 25 °C).

Molybdenum(VI) peroxo species exhibit similar reactivity in sulfide and olefin oxidation.[5] They are thought to have a similar structure, i.e., **3**. Thus, we tested their ability to catalyze the oxygen exchange reaction, and indeed, we observed with Mo(VI) catalyst, too, the same reaction, though it occurs at a quite slower rate (~50% label loss in 100 h at 40 °C). A selection of the results so far obtained is reported in Table I.

In the general procedure, 6×10^{-3} M solution of H_2O_2 of appropriate enrichment[6] (see Table I) in the indicated solvent containing the catalyst[7] (1×10^{-4} M) and variable amounts of water (either added or contained in the solvents and reagents used or both) were allowed to react in a thermostatic bath under

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(3) Bortolini, O.; Di Furia, F.; Modena, G.; Scrimin, P. *J. Mol. Catal.* **1980**, *9*, 323.
(4) Side-bonded peroxo compounds of vanadium(V) (Wieghardt, K. *Inorg. Chem.* **1978**, *17*, 57) have been reported, which have, however, ligand environment and formal charge different from **1b**.
(5) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1981**, *11*, 107.
(6) The ^{18}O-enriched hydrogen peroxide was prepared by direct conversion of $H_2{}^{18}O$ vapor in an electric discharge. For details, see: Ball, R. E.; Edwards, J. O.; Jones, P. *J. Inorg. Nucl. Chem.* **1966**, *28*, 2458.
(7) $VO(acac)_2$ and $MoO_2(acac)_2$ were used. Vanadyl acetylacetonate in ethanol undergoes fast and irreversible oxidation,[1] yielding triethyl vanadate, $VO(OEt)_3$. The displacement of one or both the acetylacetone ligands from $MoO_2(acac)_2$ in EtOH has been previously observed. See: Di Furia, F.; Modena, G.; Curci, R.; Edwards, J. O. *J. Chem. Soc.*, **1980**, *Trans. 2*, 457.

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Table I. Oxygen Exchange under V(V)[a] and Mo(VI)[b] Catalysis[c]

entry	solvent	catalyst	H_2O_2 enrich,[d] %	t,[e] h	(M + 2)/M,[f,g] %	^{18}O incorp,[g] %	label loss,[g] %
1	EtOH[h]	$HClO_4$	0	24	5.1 ± 0.4	0	0
2	EtOH[h]	$VO(acac)_2$	5.9	6	10	4.9 ± 0.7	17 ± 1.5
3	EtOH[h]	$VO(acac)_2$	12	18	8.1	3	75
4	dioxane–EtOH 97.5:2.5 v/v[i]	$VO(acac)_2$	12	0	17.1	12	0
5	dioxane–EtOH 97.5:2.5 v/v[i]	$VO(acac)_2$	12	25	11.1	6	50
6	EtOH[i]	$MoO_2(acac)_2$	18.2	0	23.3	18.2	0
7	EtOH[i]	$MoO_2(acac)_2$	18.2	17	21.9	16.8	8
8	EtOH[i]	$MoO_2(acac)_2$	18.2	24	18.9	13.8	24
9	EtOH[i]	$MoO_2(acac)_2$	18.2	120	12.6	7.5	59

[a] At 25.00 ± 0.01 °C. [b] At 40.00 ± 0.02 °C. [c] Reactions were run in a total volume of 50 mL, $[H_2O_2] = 5.7 \times 10^{-3}$ M, [cat] = 1×10^{-4} M, and quenched by addition of a twofold excess of *p*-tolyl methyl sulfide over H_2O_2. [d] Initial enrichment of H_2O_2 measured (see text) from the enrichment of the sulfoxide obtained under acid catalysis. [e] Time allowed for the exchange reaction before adding the sulfide. [f] Reference 9. [g] Uncertainties, shown only for the first entry of any row, indicate the probable error. [h] $[H_2O] = 0.15$ M. [i] $[H_2O] = 0.5$ M.

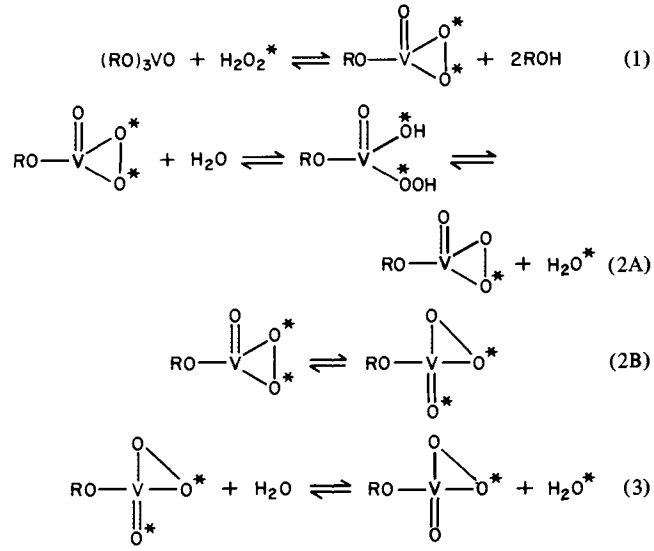
nitrogen atmosphere. At selected times the reaction was quenched by addition of an excess of *p*-tolyl methyl sulfide. The reaction was complete within a few minutes. The sulfoxide thus obtained was analyzed, either directly by GC–MS[8,9] or after isolation and purification (chromatography on silica gel) by MS,[9] and the (M + 2)/M ratio determined. The label loss was estimated with the aid of the (M + 2)/M values for (i) the sulfoxide of natural isotopic composition obtained by oxidation with "light" H_2O_2 (entry 1 in Table I) under the same experimental conditions and (ii) the sulfoxide obtained by $HClO_4$-catalyzed oxidation with the same ^{18}O enriched hydrogen peroxide used in the exchange experiments. This latter value provides the maximum enrichment attainable. Before quenching the active peroxide oxygen present was titrated, and virtually no decomposition of the oxidant was observed.[10] There is little doubt that the isotopic composition of the sulfoxide oxygen reflects that of hydrogen peroxide. Among other considerations this agrees with the accepted mechanism of sulfide oxidation under acid[11] or metal[12] catalysis. On the other hand, it is known that sulfoxides may exchange oxygen with water, but this requires rather drastic conditions. Furthermore we have checked by direct experiments that a labeled sulfoxide under the reaction and isolation conditions described above does not undergo any label loss.

The results reported in Table I show that ^{18}O labeled hydrogen peroxide undergoes an extended oxygen exchange, likely with water present in the system, under the catalytic action of V(V) and Mo(VI) species. It is well-known that such a reaction is very difficult,[11] and, in fact, the only reported[13] example refers to solutions of H_2O_2 in FSO_3H.

The exchange reaction may be thought to be due either to an "external" (path A) or to an "internal" (path B) process, as depicted for the cyclic species in Scheme I (similar reaction may be written for Mo(VI)-catalyzed reaction).

The very extensive oxygen exchange observed requires as prerequisite, in both pathways, that bulk hydrogen peroxide be in equilibrium with the coordinated H_2O_2 (eq 1). In path B, the oxometal group exchange with water is also required. Both processes have been well characterized in closely related systems.[1-3,5,14] Path A amounts to a nucleophilic attack of water

Scheme I



on a peroxidic oxygen activated by the metal and does not require that the peroxo compound be cyclic. However, ethanol should be as good a nucleophile as water for the peroxidic oxygen, and being in much higher concentration, large amounts of ethyl hydroperoxide would be formed. However, neither ethyl hydroperoxide nor its decomposition products were detected.[15] This evidence seems to militate against path A even though eq 2A would be appealing for its simplicity. Path B is based on an unprecedented oxo–peroxo exchange which would be difficult to formulate for an end-on peroxo compound. It requires extensive bonding reorganization which, at this stage, is difficult to describe in detail.[16] The primary role of the coordinating metal ion is shown, among other things, by the different rates with V(V) and Mo(VI) compounds. The slow rate of the Mo(VI)-catalyzed reaction also

(8) 1.5-m column packed with chromosorb WAW, DMCS coated with 10% ucv 982.

(9) Measured on a Hitachi Perkin Elmer RME-6D mass spectrometry, utilizing the 156/154 × 100 ratio. The natural abundance of ^{34}S in determining the height of the M + 2 peak, 5.1% of M for the sulfoxide of natural abundance (Table I), was taken into account.

(10) Dilute H_2O_2 solutions in the presence of V(V) and Mo(VI) derivatives are known to be stable, and this is consistent with their high selectivity observed in the oxidation of sulfides and alkenes.[1-3,5]

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(15) The GC analysis of the reaction mixture does not show the presence in sizeable amounts of unexpected compounds. The formation of EtOOH is also inconsistent with the following kinetic evidence: the rate of oxidation of the sulfide (see experiment 3 of Table I) has been measured and found to follow the pseudo-zero-order equation typical of oxidation by H_2O_2[1,2,5] with a value of the constant identical with that measured when the sulfide is added soon after the mixing of the reagents.

(16) The overall process is likely to be more complex than that shown in Scheme I. In fact the results of reactions carried out employing labeled water and unlabeled hydrogen peroxide do not quantitatively match those of the direct ones reported in Table I. Measurable, but always smaller than expected, enrichments of the sulfoxide were obtained as the label would be diluted into the bulk solvent (likely with ethanol present in the system). Accordingly, preliminary experiments indicate that under these conditions some enrichment of EtOH occurs, possibly via a V(V)- and Mo(VI)-catalyzed oxygen exchange between water and ethanol.

explains why this exchange was not observed earlier.[17,18] The possibility of an oxygen exchange was also investigated by other authors in the vanadium(V) hydroperoxide system,[19] but no evidence of it was found. However, in this case the peroxo species cannot have the cyclic side-bonded structure and hence the oxygen exchange would have to take place by a different route.

The understanding of the reaction implied by the findings reported herein will certainly require further experimental work; however, the unveiling of this fairly easy oxygen exchange of hydrogen peroxide calls for caution in interpreting studies both in chemistry and in biochemistry.

Acknowledgment. We thank R. Salmaso (this CNR center), G. F. Miozzo (this institute) for setting up the electric discharge apparatus and Dr. S. Da Olio (CNR, Padova) for measurements of ^{18}O abundances. We are indebted to Professor J. McIsaac (Western New England College, Springfield, MA) for helpful information on the discharge apparatus. Thanks are due to the referees for helpful comments and suggestions.

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(18) The aim of these investigations[17,19] was to study the possibility of incorporation of the oxygen of the oxometal group into the product of oxidation. However, the results are also pertinent under the point of view discussed in this paper.
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Farnesylpyrophosphate Synthetase. A Stepwise Mechanism for the 1'-4 Condensation Reaction[1,2]

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Farnesylpyrophosphate synthetase (EC 2.5.1.1) is a key enzyme in the biosynthetic pathways for several important classes of terpenes, including sterols, dolichols, and possibly ubiquinones.[3,4] It catalyzes the 1'-4 condensation[5] between isopentenyl-PP (**1**-PP) and dimethylallyl-PP (**2**-PP) or geranyl-PP (**3**-PP), reactions typical of the sequential five-carbon polymerizations that constitute the major building steps in terpene metabolism. While conducting experiments with farnesylpyrophosphate synthetase that established the electrophilic nature of the condensation reactions,[3,6,7] we became interested in the timing of the changes in covalent bonding that occur during the (a) ionization, (b) condensation, and (c) elimination phases of the reaction (Scheme I).

It is commonly assumed that the topology of the substrates in the E·S complex is optimal for coupling of **1**-PP with the hydrocarbon moieties of **2**-PP or **3**-PP.[3] In such an orientation, the π electrons of the C(3)-C(4) double bond in **1**-PP are, coincidentally, in a suitable position to assist with heterolysis of the carbon-oxygen bond during catalysis. Several studies have shown, however, that the extent to which π electrons participate during ionization depends on the demand for stabilization by the developing electron-deficient center[8] and the availability of the electrons in the neighboring group,[9-13] even when the two groups are properly positioned. In addition, two phenomena are associated with participation by π electrons. First, a threshold exists for participation by the neighboring group, and below this threshold, anchimeric assistance of the ionization step is not observed.[8] Second, above the threshold, the electron-deficient center is subtantially *less* sensitive to substituent effects than a corresponding system where participation cannot occur.[8] In this communication we report the results of a linear free energy study with farnesylpyrophosphate synthetase which indicates that cleavage of the carbon-oxygen bond in **3**-PP is a discrete step,

Scheme I. Reorganization of Covalent Bonds during 1'-4 Condensation

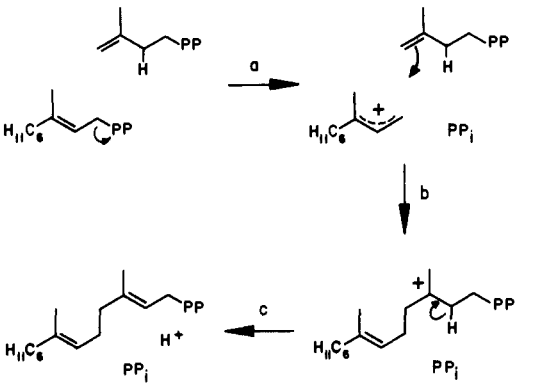

Table I. Kinetic Constants[a] for 1'-4 Condensation of 1·PP with **3**-PP, **5**-PP, **6**-PP, and **7**-PP

allylic substrate	$V/V^{3\text{-PP}}$	$k_s/k_s^{3\text{-PP}}$	$K_M^{1\text{-PP}}$, μM
3-PP	1	1	0.45 ± 0.05
5-PP	1.75×10^{-2}	3.72×10^{-4}	0.35 ± 0.1
6-PP	1.90×10^{-6}	4.03×10^{-8}	0.56 ± 0.3
7-PP	3.62×10^{-7}	7.70×10^{-9}	0.20 ± 0.1

[a] Measured at 37 °C in 10 mM Pipes, 1 mM $MgCl_2$, 10 mM β-mercaptoethanol, 0.1 μM NaN_3, 0.1% BSA, pH 7.0.

Table II. First-Order Rate Constants for Solvolysis of **3**-Ms, **5**·Ms, **6**-Ms, and **7**·Ms[a]

reactant	T, °C	acetone/H_2O (v/v), %	k, s^{-1}	$k/k^{3\text{·Ms}}$
3-Ms	0	90	$1.46 \pm 0.18 \times 10^{-3}$	
	25	90	$2.57 \pm 0.14 \times 10^{-2}$	
	60	90	0.74[b]	1
5-Ms	60	90	$5.68 \pm 0.29 \times 10^{-4}$	7.7×10^{-4}
6-Ms	60	40	$7.31 \pm 0.39 \times 10^{-4}$	
	60	50	$2.90 \pm 0.07 \times 10^{-4}$	
	60	90	1.60×10^{-6} [c]	2.2×10^{-6}
7·Ms	60	40	$1.19 \pm 0.32 \times 10^{-4}$	
	60	50	$4.78 \pm 0.45 \times 10^{-4}$	
	60	90	2.95×10^{-7} [d]	4.0×10^{-7}

[a] Measured by the conductance method and analyzed by curve fitting with the nonlinear least-squares procedure of Powell and MacDonald: Powell, D. R.; MacDonald, J. R. *Comput. J.* **1977**, *15*, 148-158. [b] Extrapolated from lower temperatures, $\Delta H^{\ddagger} = 18.6$ kcal/mol, $\Delta S^{\ddagger} = -3.5$ eu. [c] Extrapolated from 40% and 50% acetone/H_2O using the mY correlation of Winstein and Grunwald; $m = 0.69$: Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770-2777. [d] Extrapolated from 40% and 50% acetone/H_2O; $m = 0.68$.

[†] National Institutes of Health Research Career Development Awardee, 1975-1980 (HL-00084).
[‡] National Science Foundation undergraduate research participant.
(1) Support of this research by the National Institutes of Health, GM-21328 and RR-07092, is gratefully acknowledged.
(2) Abbreviations used in this communication are BSA, bovine serum albumin; farnesyl-PP, farnesyl pyrophosphate; geranyl-PP, geranyl pyrophosphate; isopentenyl-PP, isopentenyl pyrophosphate; Pipes, piperazine-*N*,*N*'-bis(2-ethanesulfonic acid); PP_i, inorganic pyrophosphate.
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