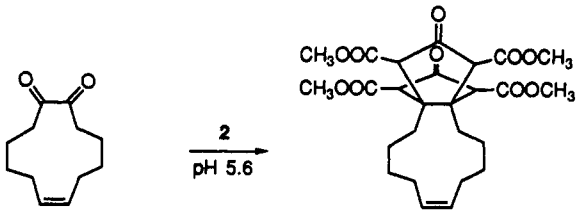
connection with 17,[19] the Cook-Weiss pathway was reestablished. This control experiment proceeded smoothly to deliver 18 in 70% yield.[20]



17 18

Other applications of medium-ring energetics to the control of chemical reactions can easily be envisioned. Recently, this principle was deployed so as to permit observation of the first reversible oxy-Cope rearrangement.[21]

Experimental Section

Tetramethyl (3*R*,3a*R*,12*S*)-2,3a,4,5,6,9,10,11-Octahydro-2-oxocyclodeca[*a*]pentalene-1,3,3a,12(3*H*)-tetracarboxylate (8). Dimethyl 1,3-acetonedicarboxylate (3.76 g, 21.2 mmol) was dissolved in aqueous $NaHCO_3$ solution (0.98 g, 11.7 mmol, 70 mL of water) and 6 (1.76 6, 10.6 mmol) was introduced followed by enough methanol to achieve dissolution (70 mL). After 3 days of stirring at rt, the homogeneous solution was cooled in ice and acidified to pH 1 with dilute HCl. The resultant precipitate was recrystallized from methanol to give large colorless prisms of 8 (2.07 g, 41%): mp 161-163 °C; IR ($CHCl_3$, cm^{-1}) 1755, 1680; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38-5.25 (m, 2 H), 4.58 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.642 (s, 3 H), 3.639 (s, 3 H), 3.46 (s, 1 H), 2.52-2.48 (br m, 3 H), 2.15-2.05 (br m, 1 H), 1.84 (m, 5 H), 1.53 (m, 2 H), 1.38 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 191.4, 181.8, 169.2, 167.4, 166.6, 161.4, 140.7, 138.2, 130.0, 129.5, 127.3, 67.4, 65.3, 52.8, 52.5, 52.4, 52.2, 24.7, 24.6, 24.3, 24.1, 24.0, 22.8; MS m/z (M^+) calcd 460.1733, obsd 460.1728.

Anal. Calcd for $C_{24}H_{28}O_9$: C, 62.59; H, 6.13. Found: C, 62.55; H, 6.11.

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Registry No. 2, 1830-54-2; 6, 99172-44-8; 8, 141119-96-2; 17, 141119-97-3; 18, 141119-98-4.

Supplementary Material Available: Crystallographic details, bond lengths, bond angles, torsion angles, positional parameters, anisotropic thermal parameters, and calculated positional parameters for the hydrogen atoms of 8 (12 pages). Ordering information is given on any current masthead page.

(19) Obtained by controlled catalytic hydrogenation (H_2, Pd-$BaSO_4$) of 7,8-diketocyclododecyne prepared according to ref 8.
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(21) Elmore, S. W.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 319.

Mechanism of Epoxidation of Vitamin K with Basic Hydrogen Peroxide

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Introduction

Vitamin K (1) has attracted attention because of its function as an obligatory cofactor in enzymic sequences central to blood clotting.[1,2] In a recent study of the mechanism of action of vitamin K, the role of molecular oxygen in the formation of vitamin K oxide (2) was explored.[2] A mechanism for this reaction has been suggested that is supported by the results of parallel ^{16}O-^{16}O and ^{18}O-^{18}O experiments in the oxygen-promoted oxidation of vitamin K hydroquinone and in the corresponding oxidation of the model systems, 2,4-dimethyl-1-naphthol and 2,3,4-trimethyl-1-naphthol.[2] Key features of this mechanism include (i) the formation of a dioxetane intermediate and (ii) the possibility that as many as two ^{18}O atoms are incorporated into vitamin K oxide (2) as a result of the molecular oxygen promoted oxidation process.[2]

Several years ago, Alder and co-workers[3a] reported that the enedione carbon-carbon double bond in *endo*-tricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,8-dione (3) can be selectively epoxidized using basic hydrogen peroxide to yield the corresponding *exo*-4,5-epoxide 4.[3b,c] One possible mechanism that would account for the formation of 4 is shown in Scheme I as a 1,2-addition/rearrangement mechanism. This mechanism postulates formation of a dioxetane intermediate 5 and is analogous to the mechanism suggested for the oxygen-promoted oxidation of vitamin K hydroquinone to vitamin K oxide.[2] An alternative, equally plausible, mechanism for the selective epoxidation of 3 to 4 can be envisioned is also outlined in Scheme I. Rather than proceeding through a dioxetane intermediate, the alternative 1,4-addition mechanism focuses upon initial Michael addition of HOO^- to the enedione carbon-carbon double bond, which is activated toward nucleophilic attack by conjugation with the adjacent carbonyl groups.[3b]

In the present study, we have investigated both the reaction of 3 and of vitamin K with basic H_2O_2, using $Na^{18}OH/H_2O_2$ and $NaOH/H^{18}O$-^{18}OH in separate labeling experiments. The results of these experiments unambiguously differentiate between the mechanisms shown in Scheme I.

Results and Discussion

Treatment of vitamin K with $H^{18}O$-^{18}OH and sodium carbonate in either aqueous or anhydrous ethanol results in exclusive formation of the ^{18}O-labeled epoxide (Scheme II). This is most readily demonstrated by analysis of the mass spectrum of vitamin K oxide-^{18}O. In the aqueous ethanol experiments, the molecular ion is observed at m/z 468 and the ratio of the m/z 468, 469, 470 peaks is 100:33.3:6.9. The calculated values are 100:34.4:6.3.[4] The same result was obtained under anhydrous conditions. Thus, the peak at 470 is completely normal in intensity indicating that only one atom of ^{18}O has been incorporated into vitamin K oxide. Analysis of the fragmentation pattern establishes unambiguously that the label is located at the epoxide oxygen.[2a] Treatment of the ^{18}O-labeled epoxide with aqueous base resulted in no change in the mass spectral pattern showing that all the ^{18}O was incor-

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(2) (a) Dowd, P.; Ham, S. W.; Geib, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 7734. (b) Ham, S. W.; Dowd, P. *J. Am. Chem. Soc.* **1990**, *112*, 1660. (c) Dowd, P.; Ham, S. W. *J. Am. Chem. Soc.* **1991**, *113*, 9403.
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(4) Beynon, J. H. *Mass Spectrometry and its Applications to Organic Chemistry*; Elsevier: Amsterdam, 1960; p 524.

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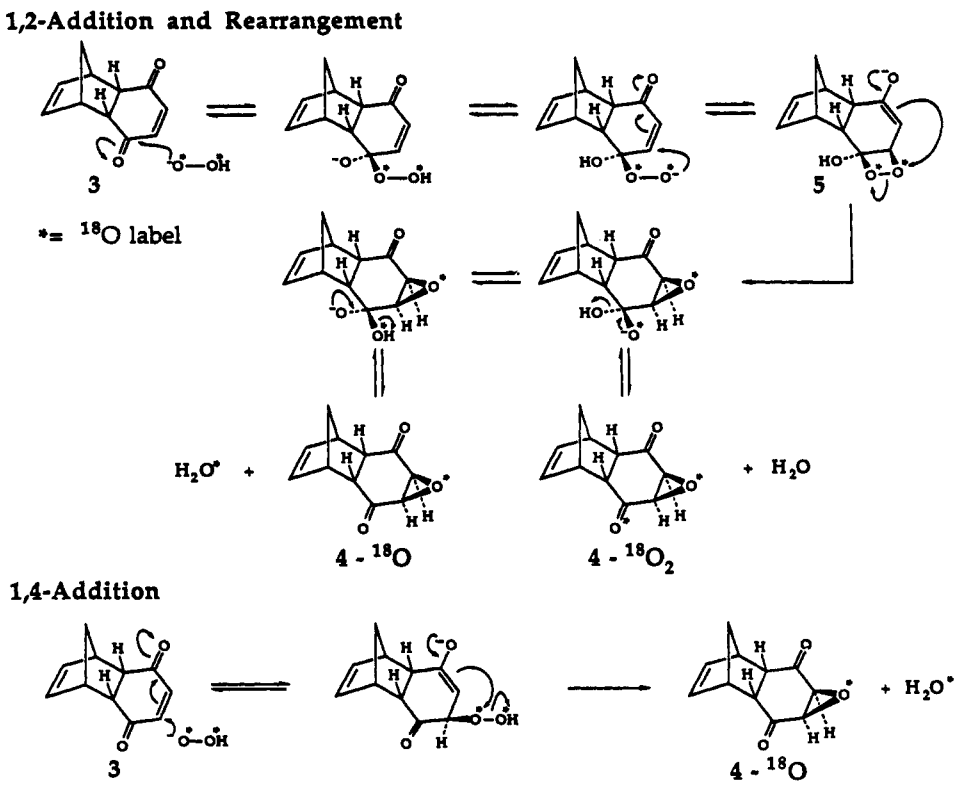
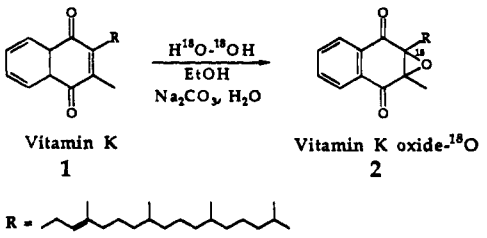
Scheme I



Scheme II



porated at the epoxide oxygen and none at the carbonyl groups. The carbonyl oxygens of vitamin K oxide readily undergo exchange under such conditions through a hydration–dehydration sequence.

In a parallel study, epoxidations of the dienedione 3 with $H^{18}O$–^{18}OH and with unlabeled H_2O_2 were performed in the presence of aqueous ethanolic Na_2CO_3. The mass spectrum of unlabeled 4[3] displays its molecular ion (M^+) at m/z 190; this peak is shifted to m/z 192 in the mass spectrum of the product formed upon oxidation of 3 with $H^{18}O$–^{18}OH. The mass spectra of both labeled and unlabeled 4 display $M^+ + 1$ peaks which possess the intensity expected for a C_{11} compound (calcd intensity 12.2% of M^+, found 11.4% in unlabeled 4, 11.6% in ^{18}O-labeled 4). No increase in the intensity of the $M^+ + 2$ peak was observed in ^{18}O-labeled 4 (calcd intensity 1.2%, found 1.1%) as compared with that of unlabeled 4 (found 1.6%).

The results of a control experiment established that oxidation of 3 with $H^{18}O$–^{18}OH in (unlabeled) aqueous ethanolic Na_2CO_3 affords 4 with exclusive incorporation of ^{18}O at the epoxide position and with no ^{18}O at the carbonyl positions. Thus, exposure of labeled 4 to aqueous ethanolic Na_2CO_3 at 50 °C for 3 h results in no detectable change in the appearance of the mass spectrum (i.e., the relative intensities of the peaks at m/z 190 and 192 remain unchanged).[5] Thus, no exchange of ^{16}O for ^{18}O has occurred under these conditions at the carbonyl position in 4, which is vulnerable to oxygen isotope exchange by base-promoted hydration–dehydration.[6] We conclude that no incorporation of ^{18}O into the carbonyl oxygens occurred during the epoxidation of 3.

A second control experiment established the tendency of the carbonyl groups to undergo ^{18}O exchange with the medium. Reaction of 3 with unlabeled H_2O_2 in labeled ($H_2{}^{18}O$) aqueous ethanolic Na_2CO_3 at 50 °C resulted in complete epoxidation of the starting material within 5 min. The product, 4, was mainly unlabeled epoxide (base peak m/z 190); however, a peak at m/z 192 (relative intensity 11.2%) was also observed. The additional ^{18}O label results from exchange of one of the carbonyl oxygens in 4 with the medium, since excess label was washed out by exchange with (unlabeled) aqueous ethanolic Na_2CO_3 at 50 °C. Thus, after 30-min reaction time, an aliquot was withdrawn and examined by GC/MS; the peak at m/z 192 had decreased in intensity to 5.5% of the parent ion (m/z 190). The remaining sample was then stirred at 50 °C for 3 h with fresh (unlabeled) aqueous ethanolic Na_2CO_3. At the conclusion of this experiment, mass spectral analysis of recovered 4 indicated the complete absence of ^{18}O label; the peak at m/z 192 was restored to its normal intensity (1.2%) appropriate for the intensity profile of the mass spectral region associated with the base peak at m/z 190.

Summary and Conclusions

A series of experiments with ^{18}O-labeled H_2O_2 and/or H_2O, with appropriate controls, indicates that epoxidation of 1 and 3 with basic $H^{18}O$–^{18}OH proceeds with incorporation of only one ^{18}O atom into the products 2 and 4. The results of mass spectral analysis attest to a direct Michael attack of HOO^- on the enedione carbon–carbon double bond in each substrate (1 or 3). We conclude that the mechanism of oxidation of vitamin K with basic H_2O_2

(5) Our determinations of mass spectral peak intensities are precise to ca. 1%.

(6) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 662–680.

follows a pathway fundamentally different from that suggested for oxidation of vitamin K hydroquinone with molecular oxygen.[2]

Experimental Section

Melting points are uncorrected. Compound 3 was synthesized by Diels-Alder reaction of cyclopentadiene with *p*-benzoquinone using a previously published procedure.[7] The material was recrystallized from hexane to afford bright yellow platelets: mp 78-79 °C (lit.[8] mp 77-78 °C). An authentic sample of 4 was prepared using the procedure described by Alder and co-workers.[3a] Pure 4 was obtained by recrystallization from EtOAc-hexane; this procedure afforded 4 as a colorless microcrystalline solid: mp 118-118.5 °C (lit.[3a] mp 118 °C). Hydrogen peroxide-$^{18}O_2$, purchased from Icon Services, Summitt, NJ, was found by mass spectroscopic analysis to contain 80% $^{18}O_2$ isotopic enrichment.

Gas Chromatography and Mass Spectroscopy. A Hewlett-Packard Model 5890, Series II, gas chromatograph (GC) connected directly to a Hewlett-Packard Model 5970 mass spectrometer (MS) was employed in this study. The GC column used was a 12-m × 0.2-mm i. d. fused silica capillary column which contained a film (0.33-μm thickness) of 100% dimethyl polysiloxane (Hewlett-Packard, HP-1). The sample was injected into the GC injection port, whose temperature was maintained at 250 °C, while the column temperature was maintained at 80 °C. Forty seconds after the sample had been injected into the GC, the column oven was heated rapidly to its final temperature of 300 °C (heating rate ca. 45 °C/min). The detector temperature was set at 280 °C. Oxygen-free helium was used as carrier gas (inlet pressure 7 psig; flow-rate 55 mL/min).

Reaction of 3 with Basic $H^{18}O$-^{18}OH. To a solution of 3 (17, mg, 0.10 mmol) in absolute EtOH (2 mL) was added with stirring $H^{18}O$-^{18}OH (75 mg, 2.0 mmol) and aqueous 3 M Na_2CO_3 solution (0.3 mL). The reaction mixture was stirred at 50 °C for 5 min, at which time an aliquot (0.2 mL) was withdrawn and quenched by the addition of water (1.0 mL). The resulting mixture was extracted with Et_2O (0.2 mL). To avoid possible oxygen exchange at the carbonyl groups, which might arise by contact with silica gel, the product was not purified by column chromatography. Instead, the ether layer was examined directly by GC/MS analysis. The GC/MS trace displayed a major peak with retention time 3.25 min, which corresponded to that of authentic 4 and which indicated that the reaction had proceeded to completion. The mass spectrum of the product (4) displayed the following peaks, m/z (relative intensity): 192 (M^+, 100), 193 (11.6) and 194 (1.1). Calcd natural abundance ratio for $C_{11}H_{10}O_3$: M^+:M^+ + 1:M^+ + 2 = 100:12.2:1.2.

The remainder of the sample was poured into water (10 mL) and extracted with Et_2O (3 × 5 mL). The combined ether extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo affording a brown solid (15 mg). The crude product was purified by chromatography on silica gel (10 g) by eluting with 1:4 EtOAc-hexane mixed solvent. Pure 4 (11.2 mg, 58%) was obtained as a colorless microcrystalline solid: mp 117-118 °C (lit.[3a] mp 118 °C). The ^1H NMR spectrum of this material was identical in all respects with that of authentic 4.

Vitamin K Oxide-$^{18}O_1$. Vitamin K (50 mg, 0.11 mmol) and $H^{18}O$-^{18}OH (75 mg, 2.10 mmol) in absolute EtOH (2.5 mL) were combined with 3 M aqueous Na_2CO_3 solution (0.3 mL). The resulting mixture was heated with stirring at 75 °C for 1 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined ether layers were examined by GC-MS. The GC-MS trace contained a peak with retention time 7.9 min whose mass spectrum displayed the following peaks, m/z (relative intensity): 468 (M^+, 100), 469 (33.3), and 470 (6.9). Calcd natural abundance ratio for $C_{31}H_{46}O_3$: M^+:M^+ + 1:M^+ + 2 = 100:34.4:6.3.

The combined ether extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo, affording a yellow oil (52.3 mg). The crude product was purified by column chromatography on silica gel (10 g), eluting with 1:19 EtOAc-hexane mixed solvent. Pure vitamin K oxide (45.4 mg, 88%) was obtained as a colorless oil with spectral properties identical to those of an authentic sample.[2]

Control Experiments. 1. Synthesis of 1-^{18}O under Anhydrous Conditions. To a mixture of 1 (10 mg) and 90% $H_2{}^{18}O_2$ (20 μL, Icon Services) in absolute EtOH (2.5 mL) was added Na_2CO_3 (20 mg), and the resulting mixture was heated at 60 °C. The progress of the reaction was followed by GC-MS, which indicated that the reaction had proceeded to 50% completion after 1 h. The mass spectrum of the reaction mixture confirmed the presence of vitamin K oxide-^{18}O with its molecular ion at m/z 468, M^+ + 1 peak at m/z 469 with relative intensity 34.3, and M^+ + 2 peak at m/z 470 with relative intensity 6.1. Calcd ratio of intensities M^+:M + 1:M^+ + 2 = 100:34.3:6.3).

2. Nonexchange of Vitamin K Oxide-^{18}O with H_2O. To a solution of vitamin K oxide-^{18}O (8.8 mg) in absolute EtOH (0.5 mL) was added to a solution of Na_2CO_3 (20 mg) in water (60 μL). The reaction mixture was stirred at 60 °C for 3 h, at which time the progress of the reaction was checked by GC-MS. The mass spectrum revealed no change in the relative intensities of the mass spectral peaks of the reaction product when compared with those of starting material. This result indicates that none of the ^{18}O label contained in the starting vitamin K oxide-^{18}O, prepared by oxidation of with $H^{18}O$-^{18}OH, resides in the carbonyl groups.

3. Nonexchange of 4-$^{18}O_1$ with H_2O. To a solution of 1.1 mg (0.0057 mmol) of 4-^{18}O (labeled at the epoxide oxygen by epoxidation of 3 with $H^{18}O$-^{18}OH) in absolute EtOH (0.1 mL) was added a solution of Na_2CO_3 (5 mg) in 20 μL of H_2O. The reaction mixture was stirred at 50 °C for 3 h and then checked by GC/MS. The mass spectrum of the product showed no change in the relative intensities of the peaks at m/z 190 and 192 as compared with the corresponding peaks in the mass spectrum of the starting material 4-$^{18}O_1$.

4. Epoxidation of 3 in $H_2{}^{18}O$. To a solution of 3 (4.0 mg, 0.023 mmol) in absolute EtOH (0.5 mL) was added unlabeled 90% H_2O_2 (15 μL, excess) and a solution of Na_2CO_3 (25 mg) in 0.1 mL of $H_2{}^{18}O$ [96% ^{18}O-enriched (Icon Services)]. The reaction mixture was stirred at 50 °C for 5 min and then checked by GC/MS. The mass spectrum of the product 4 displayed the following peaks, m/z (relative intensity): 190 (M^+, 100), 191 (13.3), and 192 (11.2). Calcd natural abundance ratio for $C_{11}H_{10}O_3$: M^+:M + 1:M^+ + 2 = 100:12.2:1.2.

5. Exchange of Carbonyl-Labeled 4-$^{18}O_1$ with H_2O. To a solution of 1.5 mg (0.0038 mmol) of 4 previously exchanged with $H_2{}^{18}O$ (vide supra) in 0.2 mL of absolute EtOH was added a solution of Na_2CO_3 (5 mg, excess) in 20 μL of H_2O. The reaction mixture was stirred at 50 °C for 30 min and then checked by GC/MS. The mass spectrum of the product indicated that the intensity of the peak at m/z 192 had become reduced to 5.5% of the parent ion at m/z 190. The sample was then stirred with the same concentration of fresh aqueous sodium carbonate solution (20 μL) at 50 °C for 3 h. The mass spectrum of the product displayed a peak at m/z 192 of normal intensity (1.2%).

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Tandem Pummerer-Type Rearrangement and Nickel-Catalyzed Alkylative Olefination of the Cyclic Dithioacetal *S*-Oxides of Aromatic Aldehydes with Grignard Reagents

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The nickel-catalyzed cross-coupling of various organosulfur compounds with Grignard reagents has been extensively studied.[1] However, to our surprise, we found

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