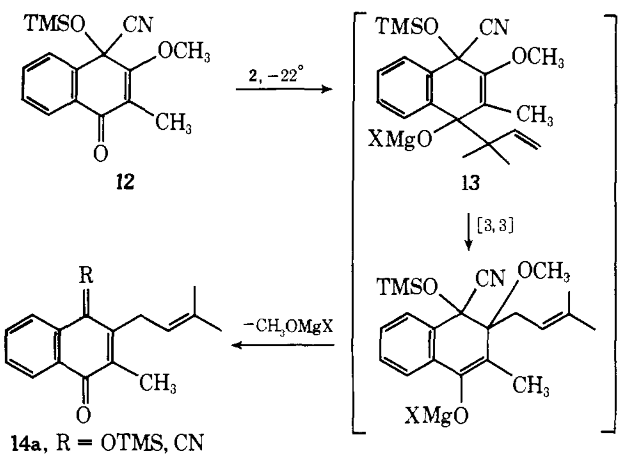
Scheme III



14a, R = OTMS, CN
b, R = O

pic process is no longer surprising in light of our recent studies on related rearrangements[17] and illustrates a potential bond reorganization which can occur if appropriate temperature control is not maintained during carbonyl addition. Deblocking **14a** with AgF under standard conditions afforded vitamin $K_{2(5)}$ (**14b**) in 71% overall yield after chromatography on silica gel (1:1 hexane–benzene).[18]

As a consequence of the excellent regioselectivity that has been observed in the addition of TMSCN to *p*-quinones,[5] a variety of *p*-allyl quinols are now accessible. Based upon the course of related Cope rearrangements[19] it is expected that unsymmetrically substituted *p*-allyl quinols will undergo allylic rearrangement in a predictable fashion leading to unsymmetrically prenylated benzoquinones. Aside from the synthetic consequences of this approach to quinone prenylation, the observation of exceptionally facile allyl-*p*-quinol Cope rearrangements should be viewed as good precedent for the possible reinterpretation of the mechanism of related allyl quinol rearrangements[20] and other reactions which may proceed through such intermediates.[4b,20b]

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Chemistry of Superoxide Ion. III. Quenching of Singlet Oxygen[1]

Sir:

Since McCord and Fridovich discovered that the enzymic function of erythrocuprein is the dismutation of superoxide radical to give hydrogen peroxide and oxygen,[2] numerous studies have appeared on the toxic effects of superoxide in biological systems.[3-7] Toxic effects have been attributed to hydroxyl radicals formed by reaction of superoxide with hydrogen peroxide, and it has also been reported that, although singlet oxygen does not appear to be a product of the enzyme-catalyzed dismutation of superoxide,[8,9] it may be produced in the uncatalyzed dismutation in aqueous solution.[8,10,11] Several authors have also reported that *no* singlet oxygen is produced in this process.[12,13]

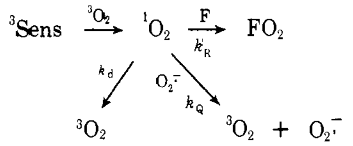
$$2O_2\cdot^- + 2H^+ \rightarrow H_2O_2 + O_2\ ({}^1\Delta_g \text{ or } {}^3\Sigma_g^-)$$

Krinsky found that human polymorphonuclear leukocytes kill a colorless mutant strain of *Sarcina lutea* more readily than a carotenoid-containing strain;[14] since carotenoids are powerful quenchers of singlet oxygen,[15] Krinsky postulates that singlet oxygen, perhaps produced by the dismutation of superoxide in leukocytes, may be an active bactericidal species.

Because of the interest in this topic, we undertook a quantitative study of the yield of singlet oxygen produced by the dismutation of tetramethylammonium superoxide[1] in organic solvents with added water, using various olefinic traps.[16,17] The results were erratic, depending on the acceptor and on the concentration of superoxide ion. It occurred to us that a possible explanation for the erratic results is that $O_2\cdot^-$ could quench singlet oxygen by electron transfer, according to the reaction shown below, and that this reaction might well be very rapid.

$${}^1O_2 + O_2\cdot^- \rightarrow O_2\cdot^- + {}^3O_2 + 22\text{ kcal}$$

In order to determine whether this reaction was occurring, we have studied the kinetics of photooxygenation of diphenylisobenzofuran (F) with added tetramethylammonium superoxide,[21,27] using the technique of Young[18] as used previously by our group.[19,20] The kinetic scheme for the reaction of the fluorescent F (rate constant k_R) with singlet oxygen, in competition with the quenching of singlet oxygen by $O_2\cdot^-$ (k_Q) and decay of ${}^1O_2$ (k_d) is as shown in eq 1.



$$\begin{tikzcd}[column sep=small] {}^3\mathrm{Sens} \arrow[r, "{}^3O_2"] & {}^1O_2 \arrow[r, "F", "k_R"'] \arrow[dl, "k_d"'] \arrow[dr, "O_2^{\cdot-}", "k_Q"'] & FO_2 \\ {}^3O_2 & & {}^3O_2 + O_2^{\cdot-} \end{tikzcd} \qquad (1)$$

Steady-state treatment[18] gives eq 2 (when [F] is very small)

$$\frac{-\mathrm{d}F}{\mathrm{d}t} = \phi_{^1O_2}\left(\frac{k_R[F]}{k_R[F] + k_Q[O_2\cdot^-] + k_d}\right) \simeq \frac{k_R[F]}{k_Q[O_2\cdot^-] + k_d} \tag{2}$$

and linear plots of log fluorescence of F vs. time are obtained, the ratio of the slopes of which (S_0/S_Q, in the absence and presence of $O_2\cdot^-$ respectively) plotted vs. $[O_2\cdot^-]$ gives a straight line of slope k_Q/k_d.

Concentrations of tetramethylammonium superoxide ranging from 3.5 to 18.4×10^{-5} M were used. The solutions were prepared by dissolution of a weighed amount of pure tetramethylammonium superoxide;[21] 1,3-diphenylisobenzofuran, purchased from Aldrich, was used (2.5×10^{-6} M); rose bengal was used as sensitizer (3.5×10^{-6} M); all solutions were prepared in a drybox; glassware was dried at 50 °C in a vacuum oven for ~24 h, then transferred via a desiccator into the drybox. Dimethyl sulfoxide was refluxed and purified by distillation over CaH_2 (83 °C, 17 mmHg; dry N_2); dry oxygen was bubbled (drybox) into the cells prior to the photolysis. Control experiments showed that no bleaching of rose bengal occurred, even at concentrations up to 3×10^{-3} M superoxide, and that diphenylisobenzofuran did not react with superoxide before the photolyzing light was turned on (no dark reaction), and that no fluorescence quenching by superoxide occurred. The photolyzing light, absorbed by rose bengal, was a Sylvania 500 Q/Cl tungsten-halogen lamp operated at 90–110 V with a Corning 3-68 filter (cutoff 540 nm) so that no light was absorbed by superoxide. The fluorescence was excited by a 1000-W Xe-Hg lamp (Hanovia, powered by an Oriel C-72-50 Power supply, operated at 790 W) (excitation λ 404 nm, slit 0.25 mm, emission λ 453 nm, slit 0.25 mm). A sample plot is shown in Figure 1. The value of k_Q/k_d obtained in this way is $3 \pm 0.4 \times 10^4$ M^{-1} ($P = 0.95$, $R = 0.995$). To find k_d in Me_2SO, k_R/k_d of 2-methyl-2-pentene in Me_2SO was determined by the same technique to be 18.2 ± 0.3 M^{-1}. Since k_R/k_d in methanol is 6.7 M^{-1} [18] and k_d in methanol is 1.4×10^5 s^{-1},[22] with the well-supported[23] assumption that k_R is insensitive to solvent, k_d in Me_2SO is calculated to be 5.2×10^4 s^{-1}. Thus the value of k_Q for superoxide calculated by this technique is 1.6×10^9 M^{-1} s^{-1}, only a factor of ten below the value for β-carotene.[15,24,25]

Similar studies were carried out in CH_3CN (dried by refluxing over P_2O_5 followed by distillation). However, superoxide ion at concentrations of 10^{-4} M and below is not stable in this solvent, and superoxide ion loss occurred during the runs, as shown by loss of inhibition; it was also shown that $O_2\cdot^-$ disappears rapidly in acetonitrile solution by following $O_2\cdot^-$ absorbance at 250 nm. Plots had to be extrapolated to zero time, with resulting loss of accuracy. The value of k_Q/k_d obtained in CH_3CN was $2 \pm 1.7 \times 10^5$; since k_d in CH_3CN is 3.3×10^4 s^{-1},[22] k_Q is $(7 \pm 6) \times 10^9$ M^{-1} s^{-1}.

Rosenthal found a much lower value for superoxide quenching of rubrene self-sensitized photooxidation, 3.6×10^7 M^{-1} s^{-1}.[26] We do not know how to account for the discrepancy. Possibly, loss of superoxide similar to our results in acetonitrile is occurring in his experiments.

It is clear that singlet oxygen, rather than the dye, is being quenched. The rate of quenching of triplet dye by oxygen is about 2×10^9 M^{-1} s^{-1}. Under pure oxygen, even if dye quenching by superoxide ion occurred at the same rate as oxygen quenching, 50% quenching of dye would occur at 10^{-2} M, rather than 3.3×10^{-5} M, as found. At 3.3×10^{-5} M superoxide, negligible dye quenching could occur.

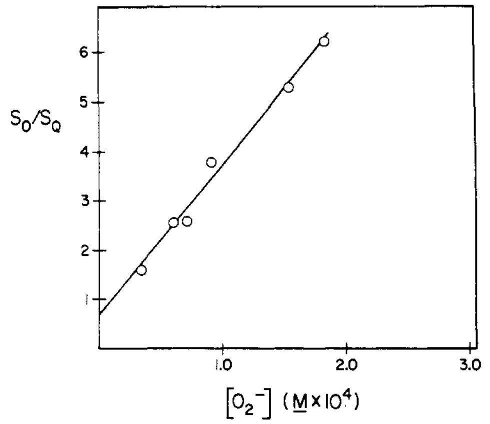


Figure 1. Quenching of diphenylisobenzofuran photooxygenation by tetramethylammonium superoxide in Me_2SO.

Using the value of the quenching rate of superoxide determined here, it is possible to back-calculate the amount of singlet oxygen formed in the dismutation reaction, which appears to be substantial. However, we are repeating these experiments at much lower superoxide concentrations in order to be more certain of the values, and will report these results in the future. It is also apparent that singlet oxygen quenching by superoxide ion would not be significant in aqueous systems of biological interest, where concentrations of superoxide can never be large.

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(27) Note Added in Proof. We have been informed by Professor L. Miller of a serious explosion which occurred during this preparation. We have had a small fire (which we attribute to the use of a paper Soxhlet thimble). Since using an all-glass extraction apparatus, no further incidents in some 20 preparations have been encountered. Caution is advisable.

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Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide under Alkaline Conditions

Sir:

A better means for direct cis dihydroxylation of olefins is needed. The existing methods[1,2] all have rather serious limitations, especially when large-scale reactions are considered. The reaction of an olefin with a stoichiometric quantity of osmium tetroxide in pyridine, followed by the appropriate reductive hydrolysis, is without doubt the most reliable procedure[2b,c] for effecting this transformation. However, the great expense[3] of osmium limits the use of this method and has been responsible for the development of alternative procedures wherein osmium is employed catalytically. The two popular catalytic systems rely on metal chlorates (Hofmann)[2a] or on hydrogen peroxide (Milas)[2d,e,f] as the stoichiometric oxidant. With certain types of olefins both the Hofmann and Milas reagents give rise to over-oxidation products (e.g., ketols and compounds resulting from cleavage of the carbon-carbon bond). We reasoned that such by-products might be suppressed under alkaline conditions[4] which would favor rapid hydrolytic removal of the diol from the coordination sphere of the osmium.

We found that whereas alkaline solutions of hydrogen peroxide decomposed violently[5] (oxygen evolution) in the presence of OsO_4, solutions of *tert*-butyl hydroperoxide[6] in the presence of base and OsO_4 were stable. These latter solutions were allowed to react with a variety of olefins to give good yields of vicinal diols (Table I).

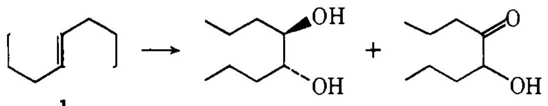
As shown in Table II for (*E*)-4-octene (**1**), this new reagent (case 1) gives more diol and less ketol than the Milas (case 3) or Hofmann (case 4) reagents. Case 2 reveals that the presence of base (Et_4NOH) is essential to the success of this new reagent.

Table I.[a] Diols from Olefins with *tert*-BuOOH, OsO_4, and Et_4NOH

Olefin	% yield[b] of diol	Olefin	% yield[b] of diol
1. 1-Decene	73	6. Cyclohexene	62
2. (*E*)-4-Octene	73	7. α-Methyl styrene	71
3. (*Z*)-4-Octene	61	8. 2-Methyl-2-butene[d]	63
4. Oleic acid[c]	70	9. 2-Methyl-2-hexene[d]	67
5. Oleyl alcohol	51	10. Tetramethyl ethylene	72
		11. 2,3-Dimethyl-2-octene[e]	69

[a] Except for oleic acid and oleyl alcohol, which were done on a 10 mmol scale, all reactions were carried out on a 100 mmol scale as described in the general procedure. [b] All yields were determined by isolation (distillation or recrystallization). [c] In this case 1 equiv of NaOH was added to titrate the acidic proton. [d] Several different modifications of the Hofmann and Milas procedures were also tried on these two trisubstituted olefins. The best yield of diol obtained with an H_2O_2 based reagent (Milas) was ~10%; ketol (~20%) was always the major product. (With these olefins our reagent gave a diol to ketol ratio of ~10:1). The ClO_3^- based methods (Hofmann) all gave principally recovered olefin and bad mixtures of oxidation products in trace amounts. [e] As in note *d* above, various modifications of the Hofmann and Milas procedures were also explored with this substrate. However, the tetrasubstituted olefin was completely inert to these reagents and was recovered unchanged.

Table II.



1 **2** **3**

Conditions[a]	Ratio[b] of diol 2 to ketol 3	% yield
1. *tert*-BuOOH, *tert*-BuOH, H_2O, Et_4NOH, 0°	10	73
2. *tert*-BuOOH, *tert*-BuOH, H_2O, 0°	0.5	<10[c]
3. H_2O_2, *tert*-BuOH, H_2O, 0° (Milas reagent)	0.6	<20[c]
4. $KClO_3$, dioxane, H_2O, 50° (Hofmann reagent)	?[d]	<5[c]

[a] A catalytic amount (0.2%) of OsO_4 was used in each case. [b] We have found that yields of vicinal diols such as 2 cannot be determined by GLC due to great (30%) fluctuation in response factors. Thus the GLC determined ratios of diol to ketol reported here are of only qualitative importance. [c] In these three cases yields were estimated by GLC; the large amount of ketol and other by-products made it impractical to isolate pure diol. [d] In this case the GLC trace was too complicated (four overlapping peaks) in the diol–ketol region to allow determination of the ratio.

General Procedure. A 500-ml one-necked, round-bottomed flask was charged with 200 ml of reagent grade *tert*-butyl alcohol, 15 ml of 10% aqueous Et_4NOH[7] (ca. 10 mmol), and 100 mmol of olefin. This solution was cooled[8] to ca. 0° by stirring in an ice-salt bath and 18 ml (ca. 160 mmol) of 90% *tert*-butyl hydroperoxide[9] was added, followed by 10 ml of 0.5% OsO_4 in *tert*-butyl alcohol[10] (ca. 0.2 mmol). The resulting brownish purple solution was stirred for 2 h at 0° then stored in a refrigerator (0–5°) overnight. At this point the solution was either pale yellow or colorless, and 100 ml of 5% aqueous $NaHSO_3$ was added and the mixture was allowed to warm to room temperature while stirring. This mixture was concentrated on a rotary evaporator to remove most of the *tert*-butyl alcohol and water, and the resulting residue was extracted with ether. The organic extract was washed with saturated brine, dried ($MgSO_4$), and concentrated to afford the crude diol product. Purification was effected either by distillation or recrystallization.

Except in those circumstances where the molecule is sensitive to base, this new procedure for cis dihydroxylation of olefins generally affords better yields than the existing methods[1,2] for this transformation. In the case of mono- and disubstituted olefins the advantage of this new reagent is most apparent when the olefin (e.g., 4-octene and α-methyl styrene) is sensitive to over-oxidation; with less sensitive olefins (e.g., cyclohexene and 1-decene) the yields are comparable to those reported using the Hofmann and Milas reagents. However, in the case of tri- and tetrasubstituted olefins this new reagent is clearly superior to the Hofmann and Milas methods. These latter reagents often fail completely (e.g., case 11, Table I) with these more substituted olefins or they give only poor yields (e.g., cases 8 and 9, Table I) of ketol and diol products. Since it has been shown that the rate of reaction of osmium tetroxide with olefins is enhanced by increased alkyl substitution,[11] the low reactivity