found here and none exhibits excursions whose direction depends upon the substrate isomer employed.[16]

Log (k_{CN}/k_W)[7] in aqueous KCN is 1.9 for 2-FA and 3.9 for 4-FA. The reported value for 4-FA is 3.8[9] and Ritchie[3] finds N^+ values near 3.9 for cyanation of a number of cations in water. Thus, it appears that 2-FA is the anomalous isomer. Hydrogen bonding by water to the methoxy group of 2-FA would place it very near the 2-carbon and allow photohydroxylation to occur preferentially. Similar complexation to 4-FA would leave a water molecule too distant and improperly oriented to displace a fluorine atom on the 4-carbon. The availability of cyanide as a charged nucleophilic may be compromised, as well, by varying solvent order.[17] Miscible water–alcohol mixtures are known to undergo intriguing changes in their thermodynamic and spectroscopic properties at $0.8 < \chi_{H_2O} < 1.0$.[18] Bulk solvent viscosity[13] and polarity (as exemplified by ϵ of aqueous *tert*-butyl alcohol solutions)[19] exhibit unexceptional changes. However, microscopic solvation (as measured by the partial molal heats of solution,[15b] transport numbers, and conductances of ions[20]) and microviscosity (as measured by internal pressure[13]) do exhibit extrema near $\chi_{H_2O} = 0.9$. *Therefore, any comprehensive explanation of our results must include the dynamic influence of solvent structure on both the substrates and the nucleophiles.*

Addition of small amounts of alcohol to water is known to increase total solvent order. Several qualitative and semiquantitative theories have been devised to express the microscopic alterations in intermolecular hydrogen bonding which must occur.[18,21,22] Application of these theories to our results will be discussed in a full report. Suffice it to say that alcohol molecules appear to induce formation of domains of highly structured water molecules which coexist with "free" (normal) water. When the total volume of the domains forces them to overlap (i.e., when $\chi_{t\text{-BuOH}} > 0.1$), solution order decreases.

Our results indicate that competitive aromatic nucleophilic photosubstitutions on 2-FA and 4-FA offer sensitive probes of both local solute–solvent interactions and the solvent structural changes which occur in the domain and free regions. Preliminary results with other water–alcohol mixtures demonstrate the generality of these phenomena. We intend to explore the extent of their importance upon other aromatic nucleophilic photosubstitutions.

Acknowledgment. Dr. Richard Boehm is thanked for his ideas concerning a possible microscopic model of aqueous *tert*-butyl alcohol solutions. The National Science Foundation is acknowledged for its support of this work (Grant No. CHE 83-01776).

Registry No. 1, 6609-56-9; 2, 90-05-1; 3, 874-90-8; 4, 150-76-5; 2-FA, 321-28-8; 4-FA, 459-60-9; KCN, 151-50-8.

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Intramolecular Catalysis of Oxygen Atom Transfer Reactions of α-Azo Hydroperoxides

Summary: α-Azo hydroperoxides containing phenolic groups were ~10^2 more reactive at epoxidations and S-oxidation than electronically similar analogues due to intramolecular acid catalysis of the ionic oxidations.

Sir: α-Azo hydroperoxides (α–hydroperoxy diazenes) have been shown to be important in free-radical chemistry.[2] Recently, we have shown[3] that α-azo hydroperoxides are of high reactivity in oxygen atom transfer reactions (reaction 1). Ionic oxidations by α-azo hydroperoxides occur

$$\underset{\alpha\text{-azo hydroperoxide}}{R_2C(OOH)N{=}NR} + :X \rightarrow \underset{\alpha\text{-azo hydroxide}}{R_2C(OH)N{=}NR} + X{=}O \quad (1)$$

under mild conditions and (in aprotic medium) do not require general acid catalysis.[3] The mechanism of these oxygen atom transfer reactions is similar to that of peracids[4] and those of other heteroatom-containing hydroperoxides.[5] Interestingly, the ionic oxidations by α-azo hydroperoxides exhibit high selectivities[3] that are independent of the relative reactivities. Intramolecular proton-transfer (hydrogen-bonding) of the "hydroperoxy" proton to the azo function in the transition state has been proposed[3] to account for the reactivity of this system. Development of more reactive reagents requires the use of functional groups that catalyze the ionic oxidations but do not disrupt the internal hydrogen bond. We report the synthesis and characterization of α-azo hydroperoxides designed to exploit intramolecular acid catalysis of oxygen atom transfer reactions.

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Scheme I

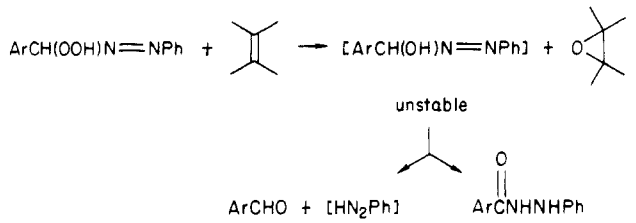


Table I. Oxidation of 2,3-Dimethyl-2-butene by α-Azo Hydroperoxides [XYC$_6$H$_3$CH(OOH)N=NPh] 1–4 in C$_6$D$_6$ at 32 °C

peroxide[a]	[alkene]$_0$, M	% yield epoxide[b]	k_2, M^{-1} s^{-1}	rel react.
2, X = *o*-OMe	1.24	89	$(5.5 \pm 0.4) \times 10^{-6}$	1.0
4, X = *p*-OMe	1.34	92	$(1.5 \pm 0.2) \times 10^{-5}$	2.7
1, X = *o*-OH	0.20	99	$(5.0 \pm 0.3) \times 10^{-4}$	91
3, X = 2-OH; Y = 5-Cl	0.19	93	$(1.5 \times 0.2) \times 10^{-3}$	273

[a] [Peroxide]$_0$ = 0.1 M; Y = H if not designated. [b] Determined by ^{1}H NMR integration relative to internal standard.

α-Azo hydroperoxides (ortho-substituted (benzylazo)-benzene α-hydroperoxides) **1–3** were synthesized by autoxidation of the corresponding hydrazones in benzene at ambient temperature (reaction 2). Under atmospheric

$$\text{XYC}_6\text{H}_3\text{CH=NNHPh} \xrightarrow{^3\text{O}_2/\text{pressure/dark}} \text{XYC}_6\text{H}_3\text{CH(OOH)N=NPh} \quad (2)$$

1, X = *o*-OH; Y = H
2, X = *o*-OMe; Y = H
3, X = 2-OH; Y = 5-Cl

conditions (with stirring), the autoxidation of *o*-MeOC$_6$H$_4$CH=NNHPh took place overnight with 90% isolated yields of **2**. The time could be reduced to several hours if the reaction mixture was subjected to a constant pressure of 100 psi of O$_2$ with no effect on the yield. Azo hydroperoxides **1** and **3**, despite the obvious antioxidant properties of phenols, were isolated in 50% yields when extended reaction times (O$_2$ pressure, 3 days) or if singlet oxygen conditions (O$_2$/dye/hν; 2 h) were employed. The compounds[6] (yellow solids, CAUTION!), recrystallized from benzene/petroleum ether, were of similar stability to that of para-substituted analogues.[3d] Compound **3** was found to be highly light sensitive and highly shock sensitive (when dry). The compounds can be stored safely (−70 °C, dark) in C$_6$D$_6$ solutions (or in crystalline form "wet" with C$_6$D$_6$) with no decomposition for several weeks.

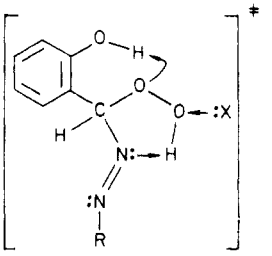
The epoxidation of 2,3-dimethyl-2-butene by α-azo hydroperoxides **1–3** was carried out in high yield in C$_6$D$_6$ at 32 °C. Tetramethyloxirane was stable under the reaction conditions, while the other products, α-azo hydroxides, underwent slow decomposition[3d] to the respective aldehydes and (presumably) PhN=NH plus the hydrazides (Scheme I). The reactions were of the first order with respect to each reactant. The k_2 values for α-azo hydroperoxides **1** and **3** were found to be 91- and 273-fold greater than that of electronically similar methoxy analogue **2**. The results are listed in Table I. Data for [(*p*-methoxybenzyl)azo]benzene α-hydroperoxide (**4**) are included for comparison.[3e] Interestingly, **2** was found to be roughly 3-fold less reactive than its para isomer (**4**).

Table II. Oxidation of *p*-MeOC$_6$H$_4$SMe by α-Azo Hydroperoxides [XYC$_6$H$_3$CH(OOH)N=NPh] 1–4 in C$_6$D$_6$ at 32 °C

peroxide[a]	% yield sulfoxide[b]	k_2, M^{-1} s^{-1}	rel react.
2, X = *o*-OMe	85	$(1.2 \pm 0.2) \times 10^{-3}$	1.0
4, X = *p*-OMe	89	$(2.9 \pm 0.3) \times 10^{-3}$	2.4
1, X = *o*-OH	99	$(8.3 \pm 0.2) \times 10^{-2}$	69
3, X = 2-OH; Y = 5-Cl	95	$(2.5 \pm 0.3) \times 10^{-1}$	208

[a] [Peroxide]$_0$ = [sulfide]$_0$ = 0.1 M all cases; Y = H if not designated. [b] Determined by ^{1}H NMR integration relative to internal standard.

Scheme II



The ionic oxidation of *p*-methoxythioanisole by α-azo hydroperoxides **1–4** was carried out in C$_6$D$_6$ as above. The yields of sulfoxide and the metastable α-azo hydroxides were 85% or higher in all cases. As expected, the reactions were of the second order overall. S-oxidation by the α-azo hydroperoxides was found to be roughly 200-fold faster than epoxidation. The relative reactivity series for S-oxidation **3** (208) > **1** (69) > **4** (2.4) > **2** (1) was similar to that obtained for epoxidation.[7] The data are compiled in Table II.

The k_2 values for the α-azo hydroperoxide oxidations did not depend on the initial concentrations of the compounds, suggesting that the increased reactivities of **1** and **3** were due to intramolecular catalysis rather than to intermolecular effects. To test the magnitude of possible intermolecular catalytic effects, oxidation experiments that included equivalent amounts of phenol and **2** or **4** were carried out. For both S-oxidations and epoxidation, intermolecular acid catalysis resulted in only a 3- to 4-fold increase, at least 30-fold slower than those observed for **1**. This clearly shows that the increased reactivity of **1** and **3** is due to intramolecular catalytic effects.

The effective molarities[8] (EM) for the oxidation of 2,3-dimethyl-2-butene and *p*-methoxythioanisole by **1** were found to be 25 and 33 M, respectively. The EM's are reasonable for general acid catalysis in this system. Molecular modeling calculations (MM2) suggest that the *o*-hydroxy group of **1** is able to readily form a hydrogen bond with the "peroxy" oxygen. This effect should stabilize the transition state as shown in Scheme II.

(6) The compounds [**1**, mp 90–91 °C; **2**, mp 56–57 °C; **3**, mp 78–80 °C] were too unstable (when dry) for combustion analysis. Instead the compounds were characterized by ^{1}H NMR spectroscopy and by determination of "active oxygen" content. In addition, the hydrazides, obtained by reduction of the compounds to the α-azo hydroxides and subsequent rearrangement, were isolated and the analyses for C, H, N were satisfactory. The aldehydes obtained from the α-azo hydroxides (Scheme I) as well as tetramethyloxirane and methyl *p*-anisyl sulfoxide were identified by comparison with authentic samples.

(7) The rate constants for S-oxidation and epoxidation by **3** in benzene are similar to those for these oxidations in chloroform by 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole.[3b,c] α-Azo hydroperoxides are much less reactive than *m*-chloroperoxybenzoic acid. Judging from the results of Schwartz and Blumbergs (Schwartz, N. N.; Blumbergs, J. N. *J. Org. Chem.* **1964**, *29*, 1976) for the reaction of *trans*-stilbene and *m*-chloroperoxybenzoic acid and correcting for the reactivity[4d] of tetrasubstituted alkenes, the rate constant for the epoxidation of 2,3-dimethyl-2-butene with *m*-chloroperoxybenzoic acid can be estimated to be roughly 10^3 greater than that for **1**. A similar difference in rate constant for S-oxidation can be estimated by extrapolation of the results of Overberger and Cummins (Overberger, C. G.; Cummins, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4250) for the oxidation of sulfides by peroxybenzoic acids in toluene at low temperature.

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The interpretation is consistent with hydrogen-bonding effects observed in an ^{17}O NMR and kinetic study[9] on α-azo hydroperoxides. The ^{17}O NMR data (solvent dependence) seemed to correlate with the kinetics data[9] for ionic oxidation in the varying solvents. Of particular interest were the results for methanol. In this protic medium, the ionic oxidations showed small increases in k_2 values. The ^{17}O NMR data on the ^{17}O-enriched α-azo hydroperoxides showed intermolecular hydrogen-bonding between the solvent and the peroxy oxygen. This suggested that hydrogen bonding with methanol was responsible for the small intermolecular catalytic effects noted on the oxidations.

Cyclic α-azo hydroperoxides were shown[3c] to be of similar reactivities and selectivities to those of flavin 4a-hydroperoxide model compounds[10] in N- and S-oxidations. The present results show that the reactivity of a hydroperoxide in oxygen atom transfer reactions can be greatly increased in intramolecular acid catalysis. Stable flavin 4a-hydroperoxides[10] and peracids are often taken[11] as chemical models for flavin monooxygenase activity. It is tempting to speculate that catalysis due to an acidic group in the active site of a flavin monooxygenase might also increase the reactivity of flavin 4a-hydroperoxides.

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Registry No. 1, 97783-03-4; 2, 97783-04-5; 3, 97783-05-6; 4, 2829-34-7; o-HOC_6H_4CH=NNHPh, 614-65-3; o-$MeOC_6H_4CH$=NNHPh, 21968-29-6; 2-HO-5-ClC_6H_3CH=NNHPh, 97783-06-7; 2,3-dimethyl-2-butene, 563-79-1; p-methoxythioanisole, 1879-16-9.

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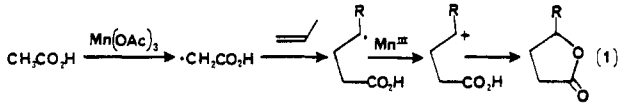
Manganese(III)-Based Oxidative Free-Radical Cyclization. Synthesis of (±)-Podocarpic Acid

Summary: The oxidative cyclization of unsaturated β-keto esters with $Mn(OAc)_3$ is described.

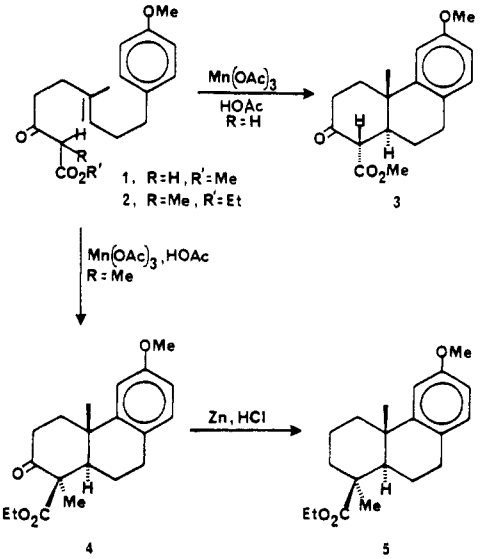
Sir: The use of free-radical carbon-carbon bond-forming reactions is undergoing a renaissance.[2] These reactions are being developed into powerful tools for the synthesis of complex targets. In particular, free-radical cyclizations of alkenes have become a valuable method for the synthesis of polycyclic compounds.[3] Unfortunately, these cyclizations are typically terminated by hydrogen atom transfer, which reduces the functionality in the product, usually rendering the initially unsaturated carbons inaccessible to further manipulation. Oxidative free-radical cyclization, in which the reaction is terminated by oxidation of the radical center to a carbocation that reacts with a nucleophile or loses a proton to give a new alkene, would therefore be a powerful addition to free-radical-based synthetic methods.[4]

The well-known, but underutilized, oxidative addition of acetic acid to alkenes with 2 equiv of manganese(III) acetate to give a γ-lactone (eq 1) provides the basis for a



solution to this problem.[5] Oxidative cyclization of unsaturated acids is not possible, since the solvent, acetic acid, is oxidized preferentially. Fortunately, unsaturated β-keto esters are suitable substrates, since they are oxidized much more rapidly than acetic acid.[5,6,7] While this work was in progress, Corey and Kang reported that unsaturated β-keto acids undergo oxidative free-radical cyclization on treatment with manganese(III) acetate to form both a cyclopentane ring and a γ-lactone.[8]

Treatment of β-keto ester 1[9] (0.1 M) in acetic acid with 2 equiv of $Mn(OAc)_3$ (15 min at 15-20 °C, 45 min at 20 °C) gives a 70% yield of the tricyclic adduct 3, mp 145-146



°C (lit.[11] mp 146-147 °C), which is a late intermediate in Welch's podocarpic acid synthesis.[11] $Mn(OAc)_3$ presum-

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(9) All starting materials were prepared by alkylation of the dianion of the corresponding acetoacetate ester in 60-90% yield.[10] The allylic bromide used for the preparation of 1 and 2 was prepared from 3-(4-methoxyphenyl)-1-propanol in four steps in 51% overall yield.

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