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Electrophilic Oxygen-Atom Transfer Chemistry of α-Azohydroperoxides

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The ionic oxidations of alkenes, sulfides, and amines by α-azohydroperoxides are discussed. The reactivity and selectivity of cyclic α-azohydroperoxide **1** are similar to those of flavin 4a-hydroperoxide model compounds in heteroatom-oxidation. The α-azohydroperoxides show similar selectivity in epoxidation to that of peracids. The lack of a general acid catalysis requirement in aprotic medium as well as Hammett-type studies suggests a mechanism of oxygen-atom transfer that involves nucleophilic attack of the substrate on the terminal oxygen with concomitant transfer (hydrogen-bonding) of the hydroperoxy proton to the azo function. ^{17}O NMR data on enriched samples of α-azohydroperoxides show a solvent dependence that appears to correlate with kinetic data. However, solvent effects and intermolecular acid catalysis of the oxidations are generally minor effects. The intramolecular acid catalytic effects are of greater magnitude. α-Azohydroperoxides that contain phenolic groups show approximately 100-fold increased reactivity over those of electronically similar analogs. For α-azohydroperoxide ionic oxidations, selectivity appears to be essentially invariant, at a maximum value, and independent of reactivity.

INTRODUCTION

A group of enzymes termed mixed function oxidases or monooxygenases catalyze the transfer of one oxygen atom (formally from molecular oxygen) to a substrate with the aid of a number of cofactors (Scheme I) (*1*):

$$\text{Substrate} + O_2 + RH_2 \xrightarrow{E} \text{Oxidized Substrate} + H_2O + R$$
$$(RH_2 = \text{reducing agent})$$

SCHEME I

In cases in which no metal ions are necessary, flavin-requiring monooxygenases have been shown to catalyze a large number of reactions (*1*), including hydroxylations (*2a, b*), S- and N-oxidations (*2c*), and Baeyer–Villiger "type" oxidations (bacterial bioluminescence (*2d*), cyclohexanone oxidation to a lactone (*2e*)).

Flavin 4a-hydroperoxides (Scheme II) have been shown to be important intermediates (*1, 2*) in flavoprotein monooxygenase mediated oxidations. Many mechanistic alternatives have been postulated (*3*) to account for monooxygenase activity. One important group of mechanisms invokes transient, highly reactive oxygen-atom transfer species (oxenoid reagents) (*4*) as the active oxygen-atom

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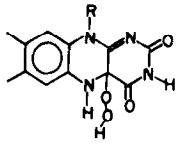


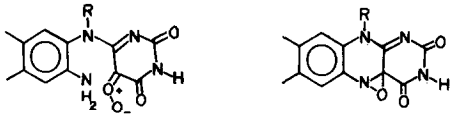
SCHEME II

transfer intermediate(s) based in part on the assumption that flavin 4a-hydroperoxides are not of sufficient reactivity. For example, carbonyl oxide (*4*) and oxaziridine (*5*) intermediates (Scheme III) have been proposed as the electrophilic species and have attracted considerable attention.

The synthesis of isolable model flavin 4a-hydroperoxide compounds by Bruice and co-workers (*6*) has provided strong mechanistic evidence that flavin 4a-hydroperoxides directly carry out certain of these oxidations. The synthesis of isolable oxaziridines by Davis (*7*) has shown these compounds to be good oxygen-atom transfer reagents (*7b*). Rastetter (*8*) has proposed, based on studies with aryloxaziridines, a mechanism for enzymatic oxidation of phenolates.

Due to the inherent complexity encountered, simple model compounds are often employed to provide a basis for an understanding of the biological systems. For example, peracid oxidation of alkylfurans has been studied as a model for the action of furanosequiterpenes which are hepatotoxins (*9*). Because of the close analogy of peracid chemistry to that observed in flavoprotein monooxygenase reactions, peracids have been suggested (*10*) as reasonable model compounds for these oxygen-atom transfer reactions. The availability of peracids provides for quick, convenient product studies for many of these reactions. Many electrophilic oxygen-atom transfer reagents seem to yield similar reaction products and/or distributions. Recent work on dioxiranes (*11*), three-membered cyclic peroxides, has resulted in the proposal (*11a*) of a dioxirane structure for the reactive intermediate in enzymatic oxidations. Criteria are beginning to be established to distinguish between dioxirane and carbonyl intermediates which will provide a better understanding of these possible reaction intermediates.

The intrinsic electrophilic reactivity of model flavin hydroperoxides seems to account very well for certain oxygen-atom transfer reactions such as heteroatom-oxidation. The limits of reactivity for direct reactions of flavin 4a-hydroperoxides have been established (*1–3, 12*) for several systems. The mechanistic alternatives available to biologically important hydroperoxides are not fully understood. Other intermediates or different pathways may be involved in the more difficult oxidations. The mechanistic relationships between the various electrophilic oxygen-



CARBONYL OXIDE OXAZIRIDINE

SCHEME III

atom transfer model compounds need to be explored. The chemical behavior of additional types of reactive hydroperoxides needs to be evaluated. Recently, we have shown (*13*) that a class of "alkyl" hydroperoxides, α-azohydroperoxides [R′R″C(OOH)—N=N—R] are of high reactivity in electrophilic oxygen-atom transfer to alkenes, sulfides, and amines. Two general types of α-azohydroperoxide are known: (1) acyclic and (2) cyclic. The reactivity of the only known cyclic α-azohydroperoxide, **1** (see below) approaches that of peracids and is essentially identical to that of "flavin hydroperoxides" in N- and S-oxidations. Acyclic α-azohydroperoxides, although of lower reactivity than the cyclic compound, are still many orders of magnitude more reactive than typical alkyl hydroperoxides. In addition, the mechanism of electrophilic oxygen-atom transfer reactions of α-azohydroperoxides is intriguing because these reactions, like those of flavin hydroperoxide model compounds and peracids, are of the first order in both hydroperoxide and substrate. Acid catalysis is not required. Thus there are good correlations of α-azohydroperoxide electrophilic oxygen-atom transfer chemistry with those of peracids and model flavin 4a-hydroperoxide compounds. Interestingly, reactivity and selectivity are not interdependent in these "reactive" hydroperoxide ionic oxidations. α-Azohydroperoxide chemistry may help determine the limits of "normal" electrophilic ionic reactions of hydroperoxides as well as open new areas of investigation.

RESULTS AND DISCUSSION

An important property of organic hydroperoxides [in addition to free-radical decomposition] (*14*) is their ability to transfer oxygen-atoms under mild conditions (Scheme IV) (*15–17*): Organic hydroperoxides are useful in the electrophilic oxidation of many classes of compounds: amines, sulfides, alkenes, etc. Characteristically, organic hydroperoxides (ROOH) transfer one oxygen-atom to a substrate (X) in a concerted or ionic manner to produce the alcohol (ROH) and the oxidized substrate (X=O). In general, the oxidizing power of an organic hydroperoxide (ROOH) in electrophilic oxygen-atom transfer reactions is directly related to the relative acidity of the corresponding alcohol (ROH). Thus, the relative reactivity series for oxygen-atom transfer reactions of hydroperoxides is: alkyl hydropheroxides $<$ H_2O_2 $\ll$ alkyl peracids $<$ aromatic peracids (*15*). In general the difference in reactivity of alkyl hydroperoxides and that of peracids is extremely large; such that, at times, the chemistry of the two types of compounds may appear unrelated.

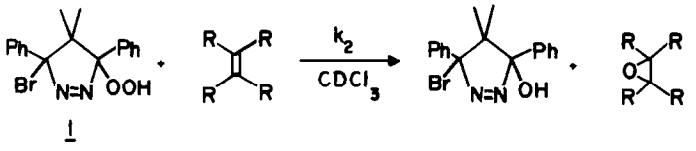
Alkene Oxidation

Hydroperoxides usually require (*15–17*) the presence of an added catalyst (*18*) to epoxidize isolated carbon–carbon double bonds. For example, alkenes are

$$R—OOH + :X \rightarrow R—OH + X=O$$

SCHEME IV

(essentially) "inert" to pure *t*-butyl hydroperoxide. Previously, direct epoxidation of alkenes had been noted for a number of unusual hydroperoxides (triphenylsilyl hydroperoxide (*19*), 2-hydroperoxyhexafluoro-2-propanol (*20*), α-hydroperoxy esters (*21*), and α-hydroperoxynitriles (*21*)). We have shown (*22*) that *cis*-3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole (**1**) will convert alkenes to epoxides in good yield under mild conditions (Reaction [1]) without added catalysts. The reaction was found to be of the first order with respect to each reactant (second order overall) in $CDCl_3$.



1 [1]

Compound **1** was found to be an extremely reactive hydroperoxide toward alkenes (Table 1). Qualitatively, the reactivity of **1** toward epoxidation appeared comparable to that of 2-hydroperoxyhexafluoro-3-propanol (*20*) and was at least an order of magnitude greater than that of α-peroxy-esters (*21*). The rate constant for the reaction of **1** with 2-methyl-2-butene was approximately two orders of magnitude slower than that of peracetic acid with 2-methyl-2-butene (*23*). The relative reactivity series of **1** with alkenes showed the selectivity of the epoxidation reaction to be surprisingly similar to those reported for peracetic acid epoxidations (*24*) and epoxidation by other reactive intermediates (*25*). This suggested that the mechanism for epoxidation of alkenes by **1** might be similar to that suggested for peroxy ketals (*21a*). Intramolecular proton-transfer (hydrogen-bonding) to the nitrogen of **1** could account for the increased reactivity compared to that of α-peroxy esters. The position of approach of the alkene shown in Scheme V is essentially identical with that suggested for peracid epoxidations (*26*).

The uncatalyzed reaction of 2,3-dimethyl-2-butene with a series of acyclic α-azohydroperoxides (substituted benzylazobenzene α-hydroperoxides), **2a–f**, was

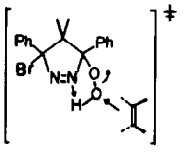
TABLE 1

OXIRANE YIELDS AND SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF ALKENES WITH **1**[a] IN $CDCl_3$ AT 34°C

Entry	Alkene	[conc.] (M)	% Yield epoxide[b]	k_2 ($M^{-1}s^{-1} \times 10^{+4}$)	Relative reactivity
1	2,3-Dimethyl-2-butene	0.33–0.75	94	31.3 ± 2.3	11.4
2	1,2-Dimethylcyclohexene	0.29–0.31	85	20.5 ± 1.5	7.45
3	2-Methyl-2-butene	0.64–1.12	79	2.75 ± 0.15	1.00
4	1-Methylcyclohexene	0.80–1.69	72	2.10 ± 0.27	0.764
5	Cyclopentene	2.23–3.64	41	0.32 ± 0.02	0.116

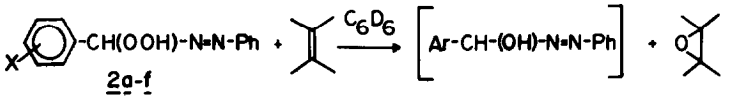
[a] $[1]_0 \sim 0.040$ to 0.10 M.

[b] Relative to internal standard (anisole).



SCHEME V

shown to produce (*27*) tetramethyloxirane and the unstable α-azohydroxides in high yields (Reaction [2]).



[2]

As for **1**, the epoxidation reaction was found to be of the first order with respect to both alkene and acyclic α-azohydroperoxide in the aprotic solvent. The presence of electron-withdrawing substituents on the hydroperoxide increased the rate of oxygen-atom transfer significantly while electron-donating substituents had the opposite effect. The rate data and final product yields for the reaction of **2a–f** with 2,3-dimethyl-2-butene are listed in Table 2.

The reactivity of the acyclic α-azohydroperoxides was similar to those (*21*) of α-hydroperoxy esters and hydroperoxy ketals. Acyclic α-azohydroperoxide, **2c**, was found to be approximately 10^{+2} times less reactive toward the oxidation of 2,3-dimethyl-2-butene in C_2D_6 than that (*22*) of cyclic α-azohydroperoxide, **1**, in $CDCl_3$. Unfortunately, the acyclic α-azohydroperoxides are not stable in $CDCl_3$ (*28*). Peracid epoxidations have been shown to be sensitive to solvent effects (*29*) (the epoxidation of cyclohexene by perbenzoic acid is three times faster in $CHCl_3$

TABLE 2

RATE DATA AND YIELDS OF TETRAMETHYLOXIRANE FOR THE REACTION OF 2,3-DIMETHYL-2-BUTENE (1.67 M) WITH X—Ar—CH(OOH)—N=N—Ph (**2a–f**) IN C_6D_6 AT 34°C

ROOH	X—	[ROOH] (M)	k_{obs} (s^{-1})	k_2 ($M^{-1}\ s^{-1}$)	% Yield of epoxide[a]
2a	*p*-MeO	0.18–0.35	2.5×10^{-5}	$1.5 \pm 0.1 \times 10^{-5}$	92
2b	*p*-Me	0.11–0.13	3.2×10^{-5}	$1.9 \pm 0.1 \times 10^{-5}$	94
2c	H	0.11–0.24	4.7×10^{-5}	$2.8 \pm 0.1 \times 10^{-5}$	87
2d	*p*-F	0.061–0.18	5.5×10^{-5}	$3.3 \pm 0.1 \times 10^{-5}$	90
2e	*p*-Br	0.085–0.11	7.5×10^{-5}	$4.5 \pm 0.2 \times 10^{-5}$	86
2f	*m*-NO_2	0.11	3.0×10^{-4}	$1.8 \pm 0.3 \times 10^{-4}$	96
		0.11[b]	1.7×10^{-4}	$2.0 \pm 0.3 \times 10^{-4}$	

[a] Average from two experiments; determined by ^1H NMR spectroscopy relative to internal standard.

[b] 0.85 M = [alkene].

than in benzene). It seems likely that solvent effects account for a portion of the large difference in reactivity between the acyclic and cyclic α-azohydroperoxides. In addition, the decreased reactivity of acyclic α-azohydroperoxides relative to that of **1** is likely to depend on a combination of the following factors. The basicity of the anti azo function of **2** is less than that of the syn azo group of **1**. The azo function in **2** is mobile while that of **1** is fixed. Intramolecular hydrogen bonding in **2** can occur with either nitrogen atom of the azo function while that in **1** can occur only with one of the nitrogen atoms.

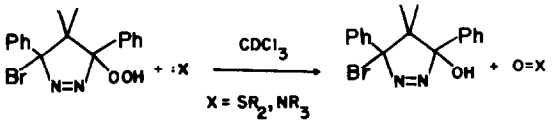
The Hammett-type plot of the second-order rate constants for the reaction of 2,3-dimethyl-2-butene with **2a–f** vs σ values showed a good LFER with a ρ value of $+1.11 \pm 0.12$ ($r = 0.996$). The rho value observed for epoxidation by **2a–f** is similar to those obtained (*29, 30*) for epoxidations with substituted perbenzoic acids in aprotic media. Epoxidations with **1** were found (*22*) to show similar selectivity to peracid epoxidations. These results clearly show that the mechanism for epoxidation by α-azohydroperoxides is similar to that of peracids (*26*) and to that of peroxy ketals (*21*). The transition state for the epoxidation reaction should involve partial intramolecular transfer (or hydrogen bonding) of the peroxy proton to a nitrogen atom during the nucleophilic attack of the alkene on the terminal oxygen atom similar to that shown in Scheme V.

Thus, there are numerous mechanistic similarities between epoxidation by peracids and those of other heteroatom-containing hydroperoxides especially α-azohydroperoxides. Interestingly, epoxidation of simple alkenes under electrophilic conditions by flavin hydroperoxide model compounds (*31*) has not been observed. Previously, Rebek (*21, 32*) has investigated the epoxidation of unactivated alkenes by many types of heteroatom-containing hydroperoxides. The structural similarities of flavin hydroperoxides of those of α-carbonyl-containing hydroperoxides resulted in Rebek's proposal that flavin 4a-hydroperoxides should epoxide alkenes due to the availability of the hydrogen bond of the hydroperoxy proton to the adjacent carbonyl group. Our studies (*22*) with α-azohydroperoxide also suggested that Rebek's proposal of epoxidation by flavin hydroperoxides should be feasible. However, a study (*32*) of the reactions of flavin hydroperoxide model compounds by Bruice and co-workers found no evidence for the electrophilic epoxidation of 2,3-dimethyl-2-butene in several solvent systems. Furthermore, it is pointed out that the "normal" relationships observed for heteroatom oxidation by model flavin hydroperoxides did not apply to the reaction with 2,3-diemthyl-2-butene. Thus it seems that flavin hydroperoxide model compounds behave in a manner different than expected by comparison with other reactive hydroperoxides. Apparently, "simple" electrophilic epoxidation is more complicated than it would appear. An understanding of the mechanistic considerations involved must await further experimentation.

N-Oxidation, S-Oxidation

In contrast to electrophilic epoxidation, "simple" alkyl hydroperoxides are known (*15–17*) to oxide heteroatoms (phosphines, amines, sulfides, etc.) at reasonable (measurable) rates. Thus, reactive hydroperoxides like α-azohydroperox-

ides would be expected to be able to carry out these ionic oxidations readily. For example, **1** has been shown (*33*) to undergo rapid oxygen-atom transfer reactions (uncatalyzed) with tertiary amines and sulfides to produce amine oxides and sulfoxides in high yield (Reaction [3]) in $CDCl_3$.



[3]

The N- and S-oxidations were found to be of the first order in both hydroperoxide and substrate in the "inert" solvent. No external proton source appeared to be required as noted for the epoxidation reaction. The more nucleophilic amines underwent oxidation faster than the less nucleophilic compounds. The reaction of **1** with benzyldimethyl amines was approximately 10^{+4}–10^{+5} times faster than the corresponding reactions using hydrogen peroxide or *t*-butyl hydroperoxide (*34*). The reactivity and selectivity of **1** toward tertiary amines in $CDCl_3$ were essentially identical to those of flavin 4a-hydroperoxides with amines in *t*-butanol (*35*). The greater reactivity of **1** with sulfides than with amines is in accord with the results of similar oxidations with 2-hydroperoxyhexafluoro-2-propanol (*20*). The reaction of **1** with diphenyl sulfide is approximately two orders of magnitude faster than that of diphenyl sulfide with hydrogen peroxide (*36*). Additionally, the reaction of sulfides with **1** is approximately five times more sensitive to substituent effects on the sulfide than observed in the hydrogen peroxide oxidation. The results are summarized in Table 3.

In general, the rate of oxidation of amines by hydroperoxides is known (*15*) to respond to the nucleophilicity of the amine and to the electrophilicity of the peroxide. Thus, the similarity of the selectivities for oxidation of a series of amines by various reactive hydroperoxides is as expected. N-Oxidation has been shown not to be catalyzed by acids (in contrast to observations for S-oxidation).

TABLE 3

SECOND-ORDER RATE CONSTANTS AND PRODUCT YIELDS FOR THE REACTION OF SULFIDES AND AMINES WITH **1**[a] IN $CDCl_3$ AT 34°C

Substrate[b]	k_2 (M^{-1} s^{-1})	Oxide	% Yield	Relative reactivity
BzSMe	Fast	BzS(0)Me	93	>90
PhSMe	0.95	PhS(0)Me	94	90
BzSPh	0.80	BzS(0)Ph	90	67
Ph_2S	0.012 ± 0.005	Ph_2SO	92	1
Et_3N	0.48	$Et_3N \rightarrow O$	100	436
$BzNMe_2$	0.15	$BzN(0)Me_2$	97	134
N-Methylmorpholine	0.10 ± 0.04	*N*-Methylmorpholine oxide	95	91
$PhNMe_2$	0.0011	$PhN(0)Me_2$	90	1

[a] $[1]_0 = 0.08$ M.

[b] $[\text{Substrate}]_0 = 0.08$ M.

No acid catalysis has been observed for N-oxidation with **1** or with FlEtOOH (*35*). The high reactivity of **1** for N-oxidation in the "inert" solvent ($CDCl_3$) as well as the observed reaction order has been rationalized, in part, by a mechanism in which an intramolecular hydrogen-bond is involved in the transition state (similar to that shown in Scheme V for epoxidation). N-oxidations by flavin hydroperoxide model compounds have been studied (*31, 35*) in both protic (*t*-butanol) and aprotic (*p*-dioxane) solvents. In the aprotic medium a small decrease in rate constant was noted but the reaction remained of the second order overall. No external proton source was needed. A mechanism was suggested (*35*) which involved nucleophilic attack of the amine on the hydroperoxide with back-donation of the hydroperoxy hydrogen to the internal peroxy oxygen. The lack of a requirement for general acid catalysis for this reaction of the flavin hydropheroxide model compounds was attributed to the greater oxygen transfer potential of these hydroperoxides as compared to simple alkyl hydroperoxides. Thus, N-oxidations by **1** and flavin hydroperoxide model compounds appear to be analogous.

The oxidation of sulfides with a series of substituted benzylazobenzene α-hydroperoxides (**2a–f**) (*37*) produced the corresponding sulfoxides in good yield (~90%) in C_6D_6 at 34°C (Reaction [4]). As noted for S-oxidation with **1**, the reactions were found

$$\underset{\textbf{2a–f}}{\text{X—Ar—CH(OOH)—N=N—Ph}} + \text{R—S—R}' \xrightarrow[k_2]{C_6D_6} [\text{X—Ar—CH(OH)—N=N—Ph}] + \text{R—S(O)—R}' \quad [4]$$
$$\text{(unstable)}$$

to be of the first order with respect to α-azohydroperoxides and to sulfides in the aprotic medium. The reaction of BzSPh with acyclic α-azohydroperoxide, **2a** [*p*-MeO—Ar—CH(OOH)—N=N—Ph], in C_6D_6 was found to be slower than the corresponding oxidation with 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole (**1**) in $CDCl_3$ (*22*). The relative reactivity series of sulfides with α-azohydroperoxide, **2a**, was found to be: $Me_2S(25)$ > BzSMe(14) > PhSMe(2.5) > BzSPh (1.0) [see Table 4]. This is similar to that observed for the reaction of the sulfides with hydrogen peroxide in protic solvent (*36b*) and reflects the relative nucleophilicities of the sulfides. The second-order rate constants for the reaction of a series of substituted benzylazobenzene α-hydroperoxides with PhSMe and BzSMe exhibited an excellent correlation with sigma values. Both LFERs had rho values of approximately 1.0 (for BzSMe oxidation $\rho = 1.08 \pm 0.12$; for PhSMe oxidation $\rho = 0.88 \pm 0.07$). The epoxidation of a series of substituted thioanisoles with acyclic α-azohydroperoxides (**2a**) was carried out in C_6D_6 at 34°C in high yield. The kinetic data are summarized in Table 5. An excellent correlation with sigma values was obtained with a ρ value of -1.24.

The ease of S-oxidation would be expected to correlate with the pK_a's of the alcohol products in the hydroperoxide reaction. The sign of the ρ values for the S-oxidation by α-azohydroperoxides is in agreement with this interpretation. The magnitude of the ρ values obtained for S-oxidation with α-azohydroperoxides in

TABLE 4

YIELDS OF SULFOXIDES AND SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF *p*—MeO—ArCH(OOH)—N=N—Ph WITH R—S—R′ IN C_6D_6 AT 34°C

Sulfide	[R—OOH] (M)	[Sulfide] (M)	% Sulfoxide	k_2 (M^{-1} s^{-1})	Relative reactivity
Me_2S	0.077	0.0774	100	1.3×10^{-2}	25
BzSMe	0.147	0.146	92	$7.3 \pm 0.3 \times 10^{-3}$	
	0.023	0.240	100	$7.0 \pm 0.2 \times 10^{-3}$	14
PhSMe	0.34	0.085	100	1.3×10^{-3}	
	0.17	0.17	91	$1.4 \pm 0.2 \times 10^{-3}$	
	0.085	0.34	—	1.3×10^{-3}	
	0.041	0.328	100	1.3×10^{-3}	2.5
BzSPH	0.10	0.10	80	$5.4 \pm 0.1 \times 10^{-4}$	
	0.066	0.667	91	4.7×10^{-4}	1.0
PhSPh	0.15	0.60	—[a]	Too slow[a]	—

[a] The rate of R—OOH decomposition was faster than the rate of S-oxidation.

C_6D_6 is in agreement with that ($\rho = 1.05$) reported (*38*) for the oxidation of a dibenzylsulfide with substituted perbenzoic acids in isopropanol. Since peracid S-oxidations have been shown not to require general-acid-catalysis and are actually slowed by protic solvents, the differences in the nature of the solvents for these two cases may be of lesser consequence. ρ values for the S-oxidation of substituted thioanisoles with hydrogen peroxide in aq. ethanol ($\rho = -1.17$) (*34b*) and that with FlOOH in *t*-butyl alcohol ($\rho = -1.67$) (*39*) are of similar magnitude to that for α-azohydroperoxides ($\rho = -1.2$) in C_6D_6 and are in agreement with nucleophilic attack on oxygen by sulfur. The ρ value of 1.1 for alkene epoxidation (*27*) by **2a–f** is in excellent agreement with the value of 1.1 found for S-oxidation by **2a–f**.

TABLE 5

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF *p*—MeO—ArCH(OOH)—N=N—Ph WITH X—Ar—S—Me IN C_6D_6 AT 34°C

p—X[a]	[Peroxide][a] (M)	k_2 (M^{-1} s^{-1})	k_{rel}
—NO_2	0.249	$1.9 \pm 0.3 \times 10^{-4}$	0.14
—CN	0.325	$2.4 \pm 0.4 \times 10^{-4}$	0.2
—Cl	0.147	$8.6 \pm 0.6 \times 10^{-4}$	0.6
—H	0.206	$1.4 \pm 0.3 \times 10^{-3}$	1.0
—CH_3	0.162	$2.6 \pm 0.3 \times 10^{-3}$	1.9
—OCH_3	0.146	$3.6 \pm 0.4 \times 10^{-3}$	2.5
—NH_2	0.115	$1.1 \pm 0.1 \times 10^{-2}$	6.9

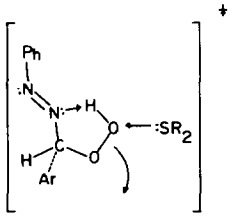
[a] $[Peroxide]_0 = [Sulfide]_0$; yield of sulfoxide >95% all cases.

The acyclic α-azohydroperoxides were found to be less reactive toward S-oxidation than flavin hydroperoxides. The reaction of PhSMe with **2a** in C_6D_6 was approximately one order of magnitude slower than the corresponding S-oxidation by an isoalloxazine hydroperoxide (FlOOH) (*39*) in *t*-butyl alcohol. The oxidation of thioxane in dry dioxane by another flavin peroxide, FlEtOOH, was found (*35*) to be ~3 times faster than the oxidation of dimethyl sulfide by **2a**. However, the oxidation of thioxane in dry methanol by FlEtOOH was found (*3, 35*) to be approximately 20 times faster than in dry dioxane. S-oxidation in aprotic solvent with hydroperoxides is subject, on the other hand, to acid catalysis (*15, 36*). The S-oxidation with **1** and with FlEtOOH (*31, 35*) did not require general-acid-catalysis. However, in contrast to the results for N-oxidation, α-azohydroperoxide S-oxidations do show (*37*) an increase in apparent k_2 values upon addition of small quantities of protic acids.

The lack of the requirement of general-acid-catalysis for S-oxidation has only been shown for flavin hydroperoxides, **1**, acyclic α-azohydroperoxides (**2a–f**), and peracids. The similar ρ values obtained for S-oxidation by peracids and α-azohydroperoxides suggest that both reactions have similar requirements. The mechanism of S-oxidation by peracids is well established and has been shown to involve intramolecular hydrogen bonding. Intramolecular hydrogen bonding would seem to be involved in the α-azohydroperoxide oxidations as well. By analogy with peracid and hydroperoxide S-oxidations, a mechanism involving nucleophilic attack of sulfur on the oxygen of the α-azohydroperoxide is consistent with the results. Concomitant transfer to the hydroperoxy proton to an azo-nitrogen would explain the lack of the requirement for general-acid-catalysis (Scheme VI, 5-center hydrogen bond in transition state assumed).

Bruice has shown (*31*) that the pK_a values of alcohol products (see Scheme IV) exhibit an excellent correlation with log k_2's for S-oxidation by a series of hydroperoxides including *m*-chloroperbenzoic acid in absolute *t*-butanol. It was noted that this relationship showed that intramolecular proton transfer did not provide a driving force for heteroatom oxidation. The mechanism for S-oxidation by flavin hydroperoxide model compounds was described as an S_N2 displacement by an unshared pair of electrons of the heteroatom upon the terminal oxygen of the hydroperoxide accompanied by proton transfer to the α-oxygen atom.

In conclusion, N- and S-oxidation by α-azohydroperoxides and by flavin hydroperoxide model compounds are closely related mechanistically. A fundamental point of contention involves the internal hydrogen bond as a driving force for these reactions.



SCHEME VI

^{17}O NMR Studies

To further focus on the mechanistic aspects of the uncatalyzed oxygen-atom transfer reactions of α-azohydroperoxides, we prepared ~10 atom% ^{17}O-enriched α-azohydroperoxides. The ^{17}O NMR data (*40*) for PhCH(O*O*H)—N=N—Ph (**2c**) were found to be solvent dependent (see Fig. 1). In C_6D_6, the ^{17}O NMR signals were poorly resolved, presumably due to internal hydrogen bonding. IR spectroscopy of **2a** in benzene showed the hydroperoxy proton to be hydrogen-bonded. Dilution experiments (IR) further showed that the observed hydrogen bonding was intramolecular and not intermolecular in nature (*40*). In CD_3CN and CH_3OH, two broad, well-resolved signals at ~250 and ~205 ppm were observed, consistent with the disruption of intramolecular hydrogen-bonding by CD_3CN or

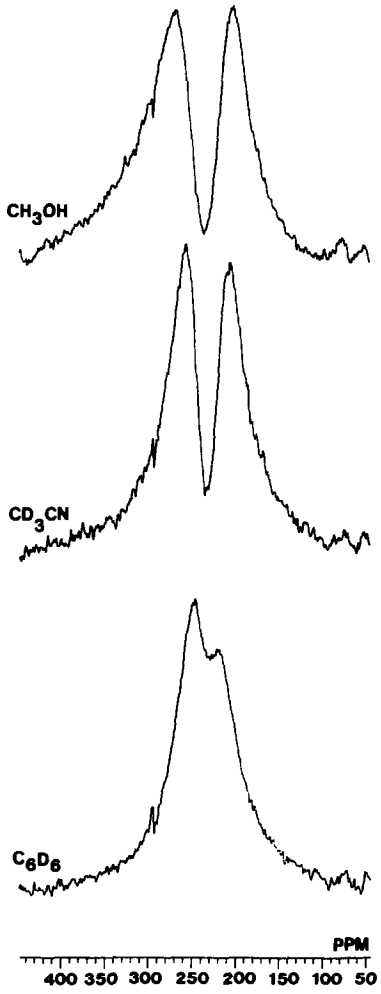


FIG. 1. Effect of solvents on the ^{17}O NMR data for PhCH(O*O*H)—N=N—Ph.

CH_3OH. In addition, in CH_3OH hydrogen-bonding effects to the "peroxy" oxygen of the α-azohydroperoxides were noted. These interpretations suggested that solvent effects on α-azohydroperoxide oxidations should be investigated.

A kinetic study of oxygen-atom transfer reactions was carried out in the three differing solvents. In general, relative to the data in C_6D_6, reactions carried out in CD_3CN were slower while those in CD_3OH were faster. The data are summarized in Table 6. Similar to observations with peracids (*41*), disruption of the intramolecular hydrogen-bond of the α-azohydroperoxides by CD_3CN as solvent would be expected to slow the oxidations. Analogous results would be expected in CD_3OH as solvent; however, the data for α-azohydroperoxides are in contrast to those for peracids (*41*). An interpretation of the solvent effects and the ^{17}O NMR spectroscopic data suggests that in C_6D_6, the reaction mechanism (*42*) is as previously shown in Scheme VI. In CD_3CN, disruption of the internal the internal hydrogen bonding slows the reaction with a possible change in mechanism. In CH_3OH as solvent, there appears to be a change in mechanism with the apparent "catalytic" effect being due to hydrogen-bonding of the solvent to the developing charge density on the "peroxy" oxygen (ses Scheme VI). ^{17}O NMR studies on hydroperoxides are limited (*40, 43*). A systematic investigation needs to be carried out on a series of reactive hydroperoxides to determine if ^{17}O NMR data (δ) can be correlated with relative reactivity in electrophilic oxygen-atom transfer chemistry. The present study (*40*) shows that ^{17}O NMR spectroscopy can be a valuable method for the determination of structure and a useful aid in mechanistic interpretations.

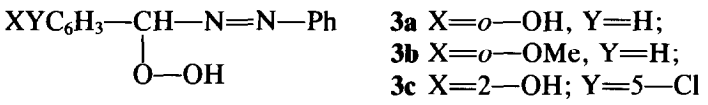
Intramolecular Acid Catalysis

Mechanistically, studies of α-azohydroperoxides have been intriguing. The ^{17}O NMR data (solvent dependence) seemed to correlate with the kinetics data for ionic oxidation in the varying solvents. Of particular interest were the results for methanol (*40*). In this protic medium, the ionic oxidations showed small, unexpected increases in k_2 values. The ^{17}O NMR data on the ^{17}O-enriched α-azohydroperoxides indicated intermolecular hydrogen-bonding between the solvent and the "peroxy" oxygen. This suggested that hydrogen-bonding with methanol was re-

TABLE 6

EFFECT OF SOLVENTS ON THE OXYGEN-ATOM TRANSFER REACTIONS OF *p*—$MeOC_6H_4$—CH(OOH)—N=N—Ph AT 32°C

Substrate	Product	Solvent	k_2 (M^{-1} s^{-1})	Relative reactivity
$Me_2C{=}CMe_2$	Epoxide	C_6D_6	1.5×10^{-5}	1.0
		CD_3CN	$2.4 \pm 0.1 \times 10^{-6}$	0.16
		CD_3OH	1.6×10^{-5}	1.1
BzSMe	Sulfoxide	C_6D_6	7.3×10^{-3}	1.0
		CD_3CN	$3.1 \pm 0.2 \times 10^{-3}$	0.4
		CD_3OH	$4.4 \pm 0.2 \times 10^{-2}$	6.0



SCHEME VII

sponsible for the small intermolecular catalytic effects noted on the oxidations. Our ^{17}O investigations as well as the preliminary solvent effect data have suggested (*40*) that intramolecular acid catalysis might be important in α-azohydroperoxide ionic oxidations. As a preliminary test of this hypothesis, we have synthesized (*44*) α-azohydroperoxides **3a–c** (Scheme VII). Contrary to expectations **3a** could be prepared either by autoxidation or by reaction with singlet oxygen in fair yield (~50%) despite the obvious antioxidant properties of phenols.

The epoxidation of 2,3-dimethyl-2-butene by α-azohydroperoxides **3a–c** was carried out in high yield in C_6D_6 at 32°C. The reactions were of the first order with respect to each reactant. The k_2 values for α-azohydroperoxides, **3a** and **3c**, were found to be 91- and 273-fold greater than that of electronically similar methoxy analog, **3b**. Data for *p*-methoxybenzylazobenzene α-hydroperoxide, **2a**, are included for comparison. Interestingly, **3b** was found to be roughly three-fold less reactive than its *p*-isomer, **2a**. The ionic oxidation of *p*-methoxythioanisole by α-azohydroperoxides, **3a–c**, was carried out in C_6D_6 as above. The yields of sulfoxide and the metastable α-azohydroperoxides were 85% or higher in all cases. As expected, the reactions were of the second order overall. S-Oxidation by the α-azohydroperoxides was found to be roughly 200-fold faster than epoxidation. The relative reactivity series for S-oxidation: **3c** (208) > **3a** (69) > **2a** (2.4) > **3b** (1) was similar to that obtained for epoxidation. The data are compiled in Tables 7 and 8.

The observed rate constants (k_2) for the α-azohydroperoxide oxidations did not depend on the initial concentrations of the compounds suggesting that the increased reactivities of **3a** and **3c** were due to intramolecular catalysis rather than to intermolecular effects. To determine the magnitude of possible intermolecular catalytic effects, oxidation experiments which included equivalent amounts of

TABLE 7

OXIDATION OF 2,3-DIMETHYL-2-BUTENE BY α-AZOHYDROPEROXIDES [$XYC_6H_3CH(OOH)—N=N—Ph$] **3a–c** IN C_6D_6 AT 32°C

	Peroxide[a]	[Alkene]$_0$	% Yield epoxide[b]	k_2 (M^{-1} s^{-1})	Relative reactivity
3b	X = *o*-OMe	1.24 *M*	89	$5.5 \pm 0.4 \times 10^{-6}$	1.0
2a	X = *p*-OMe	1.34 *M*	92	$1.5 \pm 0.2 \times 10^{-5}$	2.7
3a	X = *o*-OH	0.20 *M*	99	$5.0 \pm 0.3 \times 10^{-4}$	91
3c	X = 2-OH Y = 5-Cl	0.19 *M*	93	$1.5 \pm 0.2 \times 10^{-3}$	273

[a] [Peroxide]$_0$ = 0.1 M; Y = H if not designated.

[b] Determined by ^1H NMR integration relative to internal standard.

TABLE 8

OXIDATION OF *p*—MeO—C_6H_4—S—Me BY α-AZOHYDROPEROXIDES [XYC_6H_3—CH(OOH)—N=N—Ph] **3a–c** IN C_6D_6 AT 32°C

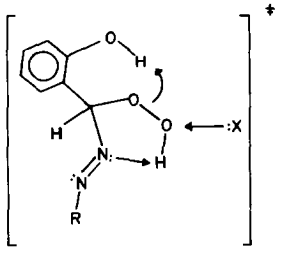
	Peroxide[a]	% Yield sulfoxide[b]	k_2 (M^{-1} s^{-1})	Relative reactivity
3b	X = *o*-OMe	85	$1.2 \pm 0.2 \times 10^{-3}$	1.0
2a	X = *p*-OMe	89	$2.9 \pm 0.3 \times 10^{-3}$	2.4
3a	X = *o*-OH	99	$8.3 \pm 0.2 \times 10^{-2}$	68
3c	X = 2-OH Y = 5-Cl	95	$2.5 \pm 0.3 \times 10^{-1}$	208

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

phenol and **3b** or **2a** were carried out. For both S-oxidation and epoxidation, the effect of intermolecular acid catalysis was a 3- to 4-fold increase (*44*) in the k_2 values, at least 30-fold smaller than those observed for **3a**. This clearly showed that the increased reactivity of **3a** and **3c** was due to intramolecular catalytic effects.

The effective molarities (*45*) (EM) for the oxidation of 2,3-dimethyl-2-butene and *p*-methoxythioanisole by **3a** were calculated to be 25 M and 33 M, respectively. The EM's are reasonable for general acid catalysis in this system. Molecular mechanics calculations (MM2) (*46*) showed that the *o*-hydroxyl group of **3a** is able to readily form a hydrogen-bond with the "peroxy" oxygen. This effect should stabilize the transition as shown in Scheme VIII. This interpretation is consistent with hydrogen-bonding effects observed in an ^{17}O NMR study on α-azohydroperoxides.

These results show that even acyclic α-azohydroperoxides can be designed that are very reactive. This suggests that the reactivity of a hydroperoxide in oxygen-atom transfer chemistry can be greatly increased by intramolecular acid catalysis. It is of interest to speculate that catalysis due to an acidic group in the active site of a monooxygenase might also increase the reactivity of flavin 4a-hydroperoxide intermediates in a similar manner. However, it is clear from these data that α-azohydroperoxides, in addition to being useful synthetic reagents, can be important probes into the mechanism(s) of ionic oxidations.



SCHEME VIII

Summary

In conclusion, heteroatom oxidations by α-azohydroperoxides, flavin hydroperoxide model compounds, and other reactive hydroperoxides are mechanistically similar. "Normal electrophilic behavior" dictates that these reactions depend on the nucleophilicity of the substrate and the stability of the resulting ROH (pK_a). A concern in aprotic and inert solvent deals with the concept of an internal hydrogen bond as an important driving force for electrophilic oxygen-atom transfer reactions of hydroperoxides. The results for flavin hydroperoxide model compounds have been interpreted to show that the internal hydrogen bond is not a necessary driving force for the oxidation. Results with heteroatom-containing hydroperoxides including α-azohydroperoxides have been interpreted to require the intramolecular hydrogen bond. Additional experimentation including deuterium isotope effect studies should be carried out to resolve these points.

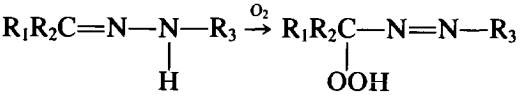
For "simple" epoxidation, the results for α-azohydroperoxides are similar to those for peracids and other reactive hydroperoxides. However, the results for flavin hydroperoxide model compounds are in marked contrast. Results with α-azohydroperoxides show that the reactivity in electrophilic oxygen atom transfer chemistry can be increased via intramolecular acid catalysis. This suggests that the reactivity of flavin hydropheroxides involved in enzymatic oxidations might be effected by the presence of acidic groups in the active site.

Another interesting mechanistic point is that the selectivities of reactive hydroperoxides toward a series of related substrates appear to be roughly constant and not related to the reactivity of the "hydroperoxide." For example, although peracids may be 10^{+3}- to 10^{+4}-fold more reactive than α-azohydroperoxides, the epoxidation selectivities for a series of alkenes and the electronic requirements of both peroxides are essentially indisguishable.

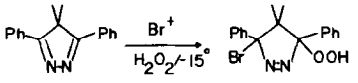
EXPERIMENT DETAILS

Synthesis

Many hydrazones readily undergo autoxidation (*14*, *47*), under mild conditions, to yield acyclic α-azohydroperoxides in good yield (Scheme IX). In fact, the α-azohydroperoxides of phenylhydrazones were synthesized (*47b*) by this method in 1914 (although the structures were assigned incorrectly as cyclic compounds). Much of the early work dealt with structure determination, mechanistic studies on the autoxidation, and (thermal) stability of the compounds. Recent studies have shown that acyclic α-azohydroperoxides may also be synthesized by



SCHEME IX



SCHEME X

use of singlet oxygen conditions (*14a, 48*) and/or autoxidation under pressure (*44*). This type of hydroperoxide is relatively unstable (to heat and/or light) and explosive. In many studies (*14*), the compounds are not removed from solution as many are extremely sensitive in pure form. Most α-azohydroperoxides can be safely stored in solution (<1 M) at low temperatures in the dark. Several of the more stable α-azohydroperoxides (for example, **2a**) can be safely isolated (1 or 2 g) and stored (dark) in crystalline form (wet with benzene) at −70°C for weeks with little detectable decomposition. In general, the preparation of α-azohydroperoxides should be carried out on as small a scale as possible with strict adherence to all safety procedures.

Landis reported (*49*) the synthesis of the only known example of the class of cyclic α-azohydroperoxides. *cis*-3-Bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole (**1**) was prepared (~75% yield) by the reaction of the cyclic azine with an electrophilic bromine source in the presence of H_2O_2 at low temperature (Scheme X) (*49*). While the preparation of **1** can be carried out in good yield if the published conditions are followed exactly, the method has not been extended to other examples. Compound **1** can be crystallized in pure form from petroleum ether/pentane mixtures containing a small amount of *trans*-3-hexane as stabilizer (*22*). Compound **1** can be stored in the dark at −35°C as the solid for months with little detectable decomposition.

ACKNOWLEDGMENTS

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