Tetrahedron Letters,Vol.26,No.17,pp 2051-2054,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

^{17}O-ENRICHED α-AZOHYDROPEROXIDES: ^{17}O NMR SPECTROSCOPY, ^{17}O-LABELING REAGENTS

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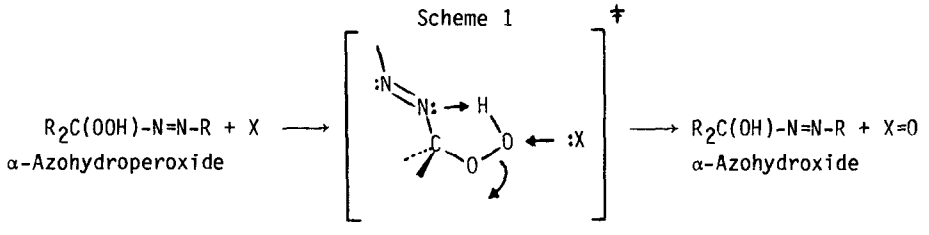
Summary: ^{17}O-enriched α-azohydroperoxides, prepared by autoxidation, are efficient ^{17}O-labeling reagents; ^{17}O NMR (CD_3CN) of **2** showed broad signals at δ 254 and 204 PPM; the solvent dependence of the ^{17}O chemical shifts and the kinetics of ionic oxidations are interrelated.

Despite the relative low receptivity of oxygen in NMR spectroscopy, the large chemical shift range makes it an important nucleus for the study of bonding in organic molecules.[1] Recently, a number of substituent chemical shift correlation studies on conjugated and non-conjugated oxygen systems have appeared.[2] However, ^{17}O NMR studies of peroxides and hydroperoxides have been limited to isolated reports.[3] Furthermore, the only reported ^{17}O NMR spectrum of an organic hydroperoxide, t-butyl hydroperoxide, was found[3b] to show one broad signal ($\nu_{1/2}$ ~1000 Hz) at 260 ppm. Natural abundance ^{17}O NMR data can not be obtained, at present, for most (unstable) organic peroxides. We report the first ^{17}O NMR data on ^{17}O-enriched α-azohydroperoxides. The chemical shift data for both oxygens of the hydroperoxides were found to show a unique solvent dependence. Since α-azohydroperoxides are of high reactivity in oxygen-atom transfer chemistry[4] (Scheme 1) [as well as in free-radical chemistry[5]], ^{17}O-enriched α-azohydroperoxides are important, new ^{17}O-labeling reagents.

Scheme 1



^{17}O-enriched α-azohydroperoxides, **1-3**, were prepared in 80% isolated yields by oxidation of the corresponding phenylhydrazones with one equivalent of 20 atom % ^{17}O-enriched molecular oxygen (Rxn 1). Enrichments of ~10 atom % ^{17}O were routinely achieved. The ^{17}O NMR spectra of the

$$XC_6H_4\text{-}CH{=}N\text{-}NHPh + {}^*O_2 \xrightarrow[\text{dark}]{C_6D_6} XC_6H_4\text{-}\underset{{}^*O\text{-}{}^*OH}{CH}\text{-}N{=}N\text{-}Ph \qquad \textbf{1}, X{=}p\text{-}MeO;\ \textbf{2}, X{=}H;\ \textbf{3}, X{=}p\text{-}Br \qquad (1)$$

^{17}O-enriched α-azohydroperoxides (**1-3**) were taken in C_6D_6, CD_3CN, and CH_3OH at 31 ±1°C. Figure 1 shows a composite of the ^{17}O NMR spectra for **2** that is representative. In C_6D_6, the ^{17}O NMR signals were poorly resolved for all three compounds. In CD_3CN and CH_3OH, two broad, well-resolved signals ($\nu_{1/2}$~1500-1800 Hz) were observed (all cases). The ^{17}O chemical shift data

seem to depend on the specific interactions of the solvents with the α-azohydroperoxides. In C_6D_6, the "hydroperoxy" protons are internally hydrogen-bonded to the azo function (determined by IR spectroscopy). However, in CD_3CN, hydrogen-bonding to the solvent becomes important. Addition of 5% CD_3CN to C_6D_6 solutions of the α-azohydroperoxides yielded ^{17}O-NMR spectra identical to those in CD_3CN as solvent.[6] In the case of CH_3OH as solvent, again the internal hydrogen-bond is disrupted plus hydrogen-bonding of the solvent to the "peroxy" oxygen is involved. The data are summarized in Table 1.

Table 1. ^{17}O Chemical Shift Data for XC_6H_4-CH(O_*O_*H)-N=N-Ph at 31°C.

No.	X	δ(PPM, C_6D_6)		δ(PPM, CD_3CN)		δ(PPM, CH_3OH)	
1	p-MeO	~245[a]	~215[a]	251	206	275	204
2	p-H	245	215	254	204	266	200
3	p-Br	245	213	249	196	254	195

a) $\nu_{1/2}$~3000 Hz, not resolved at 31°C.

Due to the large $\nu_{1/2}$'s for the ^{17}O signals for the α-azohydroperoxides and the resulting error in chemical shifts, the signals can not be correlated with the results obtained for benzyl alcohols.[2e] A tentative assignment,[7] based on the observation that the signal for α-azohydroxides is seen at ~27 PPM ($\nu_{1/2}$ ~450 Hz), would indicate that the "peroxy" oxygen chemical shift is downfield from that of the "hydroperoxy" oxygen. An interpretation of the observed solvent dependence of the chemical shifts, in accord with the above assignment, would require that hydrogen-bonding of the "hydroperoxy" proton with solvent results in shielding effects while hydrogen-bonding of the solvent to the "peroxy" oxygen produces deshielding.

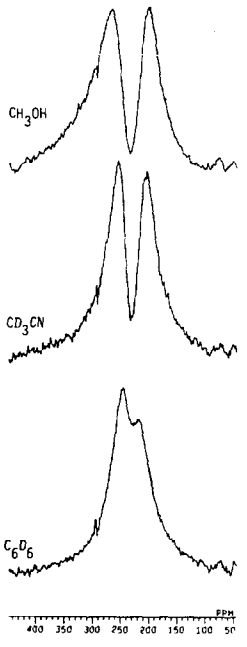


Figure 1. Effect of solvents on the ^{17}O NMR data for 2.

The observed solvent dependence of the ^{17}O chemical shifts is intriguing. ^{17}O NMR chemical shifts have been shown[1,2a,3a,8] to be sensitive to hydrogen-bonding effects. It seems clear that additional hydrogen-bonding results in deshielding[3a,8a] in saturated oxygen systems. Reuben suggested[8a] that hydrogen-bond donation also produced deshielding effects. However, in cases involving equilibria or hydrogen-bonding to various sites, the situation is unclear. For example, the ^{17}O chemical shift data [2e] for benzyl alcohols showed ~5 PPM shielding in changing solvent from toluene to acetone. Thus, disruption of the internal hydrogen-bond of the α-azohydroperoxides by solvent could result in shielding effects ("hydroperoxy" oxygen).

The oxygen-atom transfer reactions of the ^{17}O-enriched α-azohydroperoxides constitute a new, efficient, economical method for the incorporation of ^{17}O into organic substrates. Most enrichment procedures[1] involve the use of ^{17}O-enriched H_2O and are carried out under equilibrium conditions. Enrichment via ionic oxidation by α-azohydroperoxides generally requires only one equivalent and can be carried out in aprotic solvents. For example, the oxidation of alkenes, phosphines, and sulfides with the ^{17}O-enriched α-azohydroperoxides yielded the ^{17}O-labeled epoxides, phosphine oxides and sulfoxides in high yield (Scheme 1). Representative results are listed in Table 2.

Table 2. Isolated Product Yields and ^{17}O NMR Data for the Oxidation of Organic Compounds with ^{17}O-Enriched α-Azohydroperoxides in C_6D_6 at 32°C.

Substrate	Product	Yield (%)	^{17}O δ(PPM)[b]	$k_2M^{-1}sec^{-1}$
Ph_2PMe	$Ph_2P(*O)Me$	95	44(J_{P-O}=169 Hz)	fast
Me_2S	$Me_2S(*O)$	90	12	$1.3x10^{-2}$
PhSMe	PhS(*O)Me	81	0.6	$1.3x10^{-3}$
$Me_2C=CMe_2$	$Me_2C(-O*)CMe_2$	72	60	$1.5x10^{-5}$

a) 13±1 atom % ^{17}O. b) ±1 PPM.

The high reactivity of α-azohydroperoxides in ionic oxidations has been ascribed[4] to a mechanism in which intramolecular proton transfer (hydrogen-bonding) in the transition state (Scheme 1) can occur (similar to that of peracids[9]). Thus, the hydrogen-bonding differences observed by ^{17}O-NMR spectroscopy should affect oxygen-atom transfer chemistry. The kinetic data for the oxidation of BzSMe and 2,3-dimethyl-2-butene with α-azohydroperoxides were obtained in the three differing solvents (Table 3). The kinetic data clearly show that the oxidations are slowed in CD_3CN relative to those in C_6D_6. On the other hand, the results in the polar, protic

Table 3. Effect of Solvents on the Ionic Oxidations by α-Azohydroperoxide **1** at 32°.

Substrate	Product	Solvent	$k_2M^{-1}s^{-1}$	Rel. React.
$Me_2C=CMe_2$	epoxide	C_6D_6	$1.5\pm0.2x10^{-5}$	1.0
		CD_3CN	$2.4\pm0.1x10^{-6}$	0.16
		CD_3OH	$1.6\pm0.2x10^{-5}$	1.1
BzSMe	sulfoxide	C_6D_6	$7.3\pm0.2x10^{-3}$	1.0
		CD_3CN	$3.1\pm0.2x10^{-3}$	0.4
		CD_3OH	$4.4\pm0.2x10^{-2}$	6.0

solvent (CD_3OH) showed an increase. Similar to observations on peracids,[9] disruption of the intramolecular hydrogen-bond of the α-azohydroperoxides by CD_3CN (solvent) should slow the oxidations. While analogous results would be expected in CD_3OH as solvent, the data are in contrast to those of peracids.[9] An interpretation, consistent with the ^{17}O NMR data, suggests that the rate effects in CD_3OH may be due to the stabilization of the developing charge (in the transition state) on the "peroxy" oxygen (Scheme 1) by hydrogen-bonding of the solvent (a "catalytic" effect rather than a change in basic process).

In conclusion, ^{17}O-enriched α-azohydroperoxides can be readily prepared and used as ^{17}O-labeling reagents. This labeling method is highly efficient and economical for selected compounds. The ^{17}O NMR spectroscopy of the α-azohydroperoxides shows that the chemical shift data for the two oxygens are solvent dependent. There appears to be a correlation between the ^{17}O NMR solvent dependence and solvent effects on kinetic data for oxygen-atom transfer reactions.

The ^{17}O-enriched α-azohydroperoxides were prepared as follows: to 100 mg (0.51 mmol) benzal phenylhydrazone in 3 mL C_6D_6 in an evacuated, sealed 25 mL flask, 15 mL (~0.5 mmol) of 20 atom % ^{17}O-enriched molecular oxygen (MSD Isotopes) were added via a gas-tight syringe. N_2 gas was added via syringe to achieve a slight positive pressure. The reaction mixture was stirred in the dark overnight. Additional N_2 gas was added occasionally to keep a positive pressure to reduce leakage of unlabeled O_2 into the flask. Reaction progress was monitored by ^1H NMR

spectroscopy. After completion of the reaction, pentane was added to precipitate the α-azohydroperoxide. The yellow solid was collected (in the dark), washed with cold pentane, recrystallized from benzene/pentane, and stored (wet, CAUTION!)[4a] at -70°C [isolated yield 80%, 13 ± 1 atom % ^{17}O]. The spectral and physical data were in accord with literature values.[4]

The ^{17}O NMR spectra were recorded on a JEOL GX-270 Spectrometer equipped with a 10 mm broad band probe operated at 36.5 MHz. The samples of the~10 atom % ^{17}O-enriched α-azohydroperoxides were 0.2 M in C_6D_6, CD_3CN, and CH_3OH. The spectra were acquired at 31 ± 1°C and referenced to external deionized water. The instrument settings were: 30.12 KHz spectra width, 2 K data points, 90° pulse angle (28 μs pulse width), 200 μs acquisition delay, and 33 ms acquisition time. The spectra were recorded with sample spinning and were non-decoupled. The signal-to-noise ratio was improved by applying a 50 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.2 PPM by zero filling to 8 K data points. Under these conditions, S/N ratios of 20/1 were achieved after ~3 hrs. (~10^4 scans) for the α-azohydroperoxides despite typical half height band widths of ~1500 Hz. The estimated error in chemical shift is ±3 PPM. The ^{17}O-labeling reactions with ^{17}O-enriched α-azohydroperoxides were carried out according to published procedures.[4] Products were isolated by column chromatography and the atom % enrichments determined by MS analysis. ^{17}O spectra were taken on the isolated ^{17}O-enriched products as above except that 0.03 M solutions in C_6D_6 were used. After 10^3 scans (~10 min) S/N ratios of 20/1 were obtained.

Acknowledgement. ALB is a fellow of the Camille and Henry Dreyfus Foundation 1981-1986. Partial support for this work was provided by the GSU Research Fund. Mass spectral data were obtained at the Georgia Institute of Technology on an instrument supported in part by the NSF.

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6. Addition of CD_3CN was shown to produce better separation of the two signals and not "crossing" of the signals.
7. The ^{17}O NMR spectrum (CD_3CN) of the perbenzoate of **2**, prepared by reaction of **2** with benzoyl chloride, showed signals at δ 247 and 450 PPM. Since the effect of benzoylation on the chemical shift of the "peroxy" oxygen is unknown, there are two possible conditions: a) benzoylation of the hydroperoxide has essentially no effect on the chemical shift of the "peroxy" oxygen (~250 PPM deshielding effect on the adjacent oxygen) or b) benzoylation has an ~40 PPM deshielding effect on the "peroxy" oxygen (~200 PPM deshielding effect on the adjacent oxygen). If condition a) is true, then the assignment is correct.
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(Received in USA 23 October 1984)