ELECTRONIC NATURE OF α-METHOXY, AMINO, CYANO, AND MERCAPTO NITRONES

David E. GALLIS, James A. WARSHAW, Bruce J. ACKEN and DeLanson R. CRIST*

Department of Chemistry,
Georgetown University, Washington, DC 20057, U.S.A.

Received March 27, 1992
Accepted April 18, 1992

Dedicated with highest regards to Professor Václav Horák on the occasion of his 70th birthday.

The electronic nature of various C-substituted nitrones was investigated by IR spectroscopy and ^{13}C NMR as well as MNDO calculations. These include α-methoxy nitrones (imidate N-oxides) RC(OMe)=N(O)t-Bu with R = *p*-$MeOC_6H_4$ (*Ia*), C_6H_5 (*Ib*), *p*-$NO_2C_6H_4$ (*Ic*), and H (*Id*) and nitrones YCH=N(O)t-Bu with Y = CN (*IIIa*), n-BuS (*IIIb*), and $C_6H_5CH_2NH$ (*IIIc*). Upfield ^{13}C shifts of C(α), the iminyl (C=N) carbon, of imidate N-oxides *I* versus the corresponding imidates are less than the usual upfield shifts of imine N-oxides versus imines, suggesting less buildup of electron density on C(α) in the case of alkoxy nitrones. Charge density and π bond order values from MNDO calculations for C-methoxy-C-phenyl nitrones versus model systems confirm this result and indicate a more localized C=N π bond in nitrones bearing an α-methoxy group. For N-tert-butyl nitrones with an α heteroatom (nitrogen or sulfur), phenyl, or cyano group, C(α) shifts move downfield for π-donating groups and upfield for π-accepting groups. This "reverse substituent effect" as well as C=N stretching frequencies can also be readily explained by C=N π bond containment by lone pair groups. The reported enhanced cycloaddition reactivity of α-alkoxy nitrones and their electrochemical behavior are discussed in terms of HOMO energy levels.

The literature of aldo and keto nitrones has grown rapidly recently due to their importance in synthesis and as spin-trapping agents. This versatility derives in part from the rich assortment of reactions at C(α), the iminyl (C=N) carbon[1]. In some cases this carbon behaves as a cationic site (e.g., reactions with organometallic reagents and other nucleophiles[2]) and in others as having increased electron density from the N-oxide oxygen (e.g., upfield NMR chemical shifts[3] and from dipole moment calculations by Exner[4]).

In contrast, the synthesis, structural aspects and reactivity of acyclic α-alkoxy nitrones have only been investigated in the last few years. Ashburn and Coates[5] prepared

* The author to whom correspondence should be addressed.

C-ethoxy-C-phenyl-N-methyl nitrone by an amide acetal condensation and studied its cycloaddition reactions. In our laboratory, various C-methoxy nitrones were made from hydroxamic acids and found[6,7] to undergo redox reactions, electrophilic substitution and radical additions. One derivative, C-methoxy-N-tert-butyl nitrone, reacted with nucleophiles with displacement of methoxide in the manner of nucleophilic substitutions on esters. The C-methoxy-C-aryl-N-tert-butyl nitrones showed a striking solvent effect on *E/Z* configuration preference[8].

We now report results of a structural study to further our understanding of the electronic nature of nitrones YCR=N(O)t-Bu with Y = RO, RS, R_2N, or CN. Taking the nitronyl C=N(O)R group as analogous to C=O, one sees that these correspond to esters, thio esters, amides, and keto nitriles and thus can be regarded as in a higher oxidation state from the usual aldo and keto nitrones. Of particular interest are the α-alkoxy nitrones, since cyclic examples, oxazoline N-oxides, were reported to have enhanced reactivity in cycloadditions compared to the corresponding pyrroline N-oxides[5,9] and tended to exhibit a "reversed" regioselectivity[9,10]. Three approaches were used: *1*) comparison with more "well-known" model systems having different functional groups, *2*) MO calculations of charge density and bond order, and *3*) interpreting changes of chemical shifts or IR bands for structural changes within a C-aryl or C-heteroatom nitrone series.

EXPERIMENTAL

NMR data were taken on a Bruker AM 300WB spectrometer with an Aspect 3000 data system. Chemical shifts are given in ppm (δ) from internal TMS. ^1H data were acquired at 300.12 MHz with a dual $^1H/^{13}C$ 5 mm probe and signals were assigned on the basis of chemical shift and NOE. ^{13}C data were generally acquired at reduced temperature (ca −25 °C) at 75.47 MHz in $CDCl_3$ in a dual $^1H/^{13}C$ 5 mm probe by one of three methods: ^1H broad band decoupled ^{13}C (referred to below as BB) with a 5 – 6 s relaxation delay, ^1H decoupled with composite pulse decoupling (CPD), the equivalent of WALTZ-16 decoupling[11], with 1 – 5 s relaxation delay, and ^1H decoupled with CPD but no relaxation delay. The latter was used for *IIIa* and *IIIb* to insure adequate relaxation of C(α). Carbon signals were assigned on the basis of $^{13}C-\{^1H\}$ NOE, chemical shift, and in the case of isomer mixtures, relative intensity correspondence with signal intensities in ^1H spectra. IR data ($\tilde{\nu}$, cm^{-1}) were obtained on a Nicolet 7199 FT spectrometer in a 12 mm liquid cell with KCl windows.

Materials

Nitrone salts *II* were made by alkylation of the hydroxamic acids, and deprotonation on 0.5 mm silica gel plates with CH_2Cl_2–MeOH 9 : 1 afforded nitrones *I* as previously described[6]. Nitrones *III* were made by reacting *Id* with the appropriate nucleophiles[6]. Imidate *Vb* was made from N-tert-butylbenzimidate as described before[12] and further purified by the preparative TLC method above. All of these materials showed the same chromatographic properties and ^1H NMR as previously reported[6]. NOE data consistent with assigned structures were reported previously[8] for the following: *Ia*, *Ib*, *Ic*, *Id*, *IIa*, and *IId*.

Methyl N-tert-butylbenzimidate triflate *Vb* . HOTf was prepared by adding 8 g of methyl triflate to 5 g of N-tert-butylbenzamide in 15 ml of CH_2Cl_2. After 18 h under stirring at room temperature, the solvent was removed in vacuo. The crude product was washed with isooctane, dried at reduced pressure, and

dissolved in CH_2Cl_2. Partial evaporation of solvent at 0 °C gave white crystals. ^1H NMR spectrum: 1.58 s (9 H, t-Bu); 4.15 s (3 H, OCH_3); 7.61 – 7.58 m (5 H, ArH).

Spectral Data

All spectra were taken in $CDCl_3$ at 25 °C unless otherwise stated and on dilute solutions (ca 0.025 mol l^{-1}) to avoid dimerization of nitrones[13,14]. For ^{13}C data the chemical shift is followed by relative peak height and assignment in parenthesis.

Ia-E. $^{13}C-\{^1H\}$ NMR spectrum (CPD, –15 °C): 27.7 (9, $C(CH_3)_3$); 55.3 (3, *p*-OCH_3); 59.6 (3, OCH_3); 69.7 (1, $(CH_3)_3$); 113.3 (4, Ar); 119.9 (1, Ar); 131.1 (4, Ar); 52.7 (1, C=N); 160.4 (1, Ar). IR spectrum: 3 014 (m), 2 971 (m), 2 943 (m), 2 844 (w), 1 606 (m), 1 509 (s), 1 442 (w), 1 341 (m), 1 304 (w), 1 254 (vs), 1 197 (m), 1 177 (m), 1 029 (m).

Ib-E. $^{13}C-\{^1H\}$ NMR spectrum (BB, –15 °C): 27.6 (9, $C(CH_3)_3$); 59.4 (3, OCH_3); 70.35 (1, $C(CH_3)_3$), 127.7 (1, Ar), 128.0 (4, Ar); 129.2 (4, Ar); 129.9 (2, Ar); 152.0 (1, C=N). IR spectrum: 3 061 (w), 3 012 (m), 2 976 (m), 2 856 (w), 1 600 (vw), 1 494 (w), 1 445 (m), 1 367 (m), 1 339 (s), 1 223 (m), 1 200 (m), 1 183 (m), 1 971 (m), 1 028 (m).

Ic-E. $^{13}C-\{^1H\}$ NMR spectrum (CPD, 2 °C): 27.8 (9, $C(CH_3)_3$); 59.9 (3, OCH_3); 72.2 (1, $C(CH_3)_3$); 123.3 (4, Ar); 130.1 (4, Ar); 134.5 (1, Ar); 153.25 (1, Ar); 151.9 (1, C=N). IR spectrum: 3 021 (w), 2 978 (m), 2 922 (m), 2 839 (m), 1 728 (m), 1 603 (w), 1 528 (vs), 1 508 (s), 1 341 (vs), 1 287 (m), 1 201 (m), 1 182 (m), 1 117 (w).

IIa-E. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 27.1 (9, $C(CH_3)_3$); 55.7 (3, *p*-OCH_3); 62.5 (3, OCH_3); 70.55 (1, $C(CH_3)_3$); 114.85 (4, Ar); 115.1 (1, Ar); 131.3 (1, Ar); 163.9 (1, Ar); 174.2 (1, C=N).

IIa-Z. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 28.8 (9, $C(CH_3)_3$); 55.7 (3, *p*-OCH_3); 60.7 (3, OCH_3); 70.89 (1, $C(CH_3)_3$); 114.8 (4, Ar); 115.4 (1, Ar); 130.3 (1, Ar); 163.4 (1, Ar); 170.4 (1, C=N). IR spectrum: 3 521 – 2 600 (br), 1 610 (vs), 1 508 (w), 1 465 (m), 1 363 (m), 1 300 (s), 1 159 (m), 1 023 (m).

IIb-E. $^{13}C-\{^1H\}$ NMR spectrum (BB): 26.7 (9, $C(CH_3)_3$); 62.7 (3, OCH_3); 70.6 (1, $C(CH_3)_3$); 123.5 (1, Ar); 127.7 (4, Ar); 129.15 (4, Ar); 133.1 (2, Ar); 174.1 (1, C=N).

IIb-Z. $^{13}C-\{^1H\}$ NMR spectrum (BB): 28.45 (9, $C(CH_3)_3$); 60.7 (3, OCH_3); 70.8 (1, $C(CH_3)_3$); 123.7 (1, Ar); 128.1 (4, Ar); 129.5 (4, Ar); 133.3 (2, Ar); 169.8 (1, C=N). IR spectrum: 3 500 – 2 500 (br), 1 619 (vs), 1 365 (s), 1 302 (s), 1 153 (m).

IIc-E. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 26.85 (9, $C(CH_3)_3$); 63.3 (3, OCH_3); 72.0 (1, $C(CH_3)_3$); 123.5 (5, Ar); 130.6 (4, Ar); 135.4 (1, Ar); 150.3 (1, Ar); 172.4 (1, C=N).

IIc-Z. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 26.4 (9, $C(CH_3)_3$); 63.8 (3, OCH_3); 71.8 (1, $C(CH_3)_3$); 124.5 (4, Ar); 129.65 (4, Ar); 135.4 (1, Ar); 150.0 (1, Ar); 172.7 (1, C=N).

IId-Z. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 26.35 (9, $C(CH_3)_3$); 64.9 (3, OCH_3); 66.7 (1, $C(CH_3)_3$); 159.4 (1, C=N).

IIIa. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 27.95 (9, $C(CH_3)_3$); 74.5 (1, $C(CH_3)_3$); 112.7 (1, C=N); 128.1 (2, C=N). IR spectrum: 3 257 (w), 2 980 (s), 2 936 (m), 1 659 (m), 1 527 (vs), 1 369 (s), 1 263 (vs), 1 193 (m), 1 122 (m), 1 078 (m).

IIIb. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 13.5 (3, $(CH_2)_3CH_3$); 21.6 (2, $S(CH_2)_2CH_2CH_3$); 27.9 (9, $C(CH_3)_3$); 30.97 (2, $SCH_2(CH_2)_2CH_3$); 32.7 (2, $SCH_2CH_2CH_2CH_3$); 68.6 (1, $C(CH_3)_3$); 133.7 (2, C=N).

IIId. $^{13}C-\{^1H\}$ NMR spectrum (CPD): 13.53 (3, $N(CH_2)_3CH_3$); 19.6 (2, $N(CH_2)_2CH_2CH_3$); 27.2 (9, $C(CH_3)_3$); 33.0 (2, $CH_2CH_2CH_2CH_3$); 44.9 (2, $NCH_2(CH_2)_2CH_3$); 62.5 (1, $C(CH_3)_3$); 137.0 (2, C=N).

Vb-E. $^{13}C-\{^1H\}$ NMR spectrum (BB, CD_2Cl_2, –51.0 °C): 31.8 (9, $C(CH_3)_3$); 52.5 (3, OCH_3); 57.35 (1, $C(CH_3)_3$); 127.6 (4, Ar); 128.0 (4, Ar); 129.45 (1, Ar); 136.8 (2, Ar); 157.1 (1, C=N).

Vb-Z. $^{13}C-\{^1H\}$ NMR spectrum (BB, CD_2Cl_2, –51.0 °C): 29.9 (9, $C(CH_3)_3$); 52.6 (3, OCH_3); 57.35 (1, $C(CH_3)_3$); 128.3 (4, Ar); 128.45 (4, Ar); 129.9 (1, Ar); 134.2 (2, Ar); 157.5 (1, C=N).

VIa-Z. $^{13}C-\{^1H\}$ NMR spectrum (BB): 28.3 (9, $C(CH_3)_3$); 70.7 (1, $C(CH_3)_3$); 128.3 (4, Ar), 128.7 (4, Ar); 129.5 (2, C=N); 129.9 (2, Ar); 131.1 (1, Ar).

MO Calculations

A MOPAC program was used for MNDO calculations on a Digital VAX 11/750. Structures were geometry-optimized to minimize heats of formation. The starting geometry for calculations of *VIIa* was taken by combining data from *IX-Z* (ref.[14]), acetaldehyde[15], and benzene[15]. After energy minimization, the optimized values of *VIIa-Z* were used as the basis for initial dimensions of all other structures. In order to reduce computer time, the following were optimized in structures *VIIa-Z*, *VIIb-E*, and *Ib-E* and carried over to other structures containing those functional groups: H–C bond lengths and H–C–H bond angles in methyl groups; C–C bond lengths and N–C–C bond angles in tert-butyl groups; and C–C–C bond angles in phenyl rings. All other parameters were optimized. For C-methoxy-C-phenyl systems, the phenyl and OCH_3 twist angle was initially set to 0° ($H_3C-O-C(\alpha)-C(\text{phenyl})$*syn*-periplanar).

As an indication of the accuracy of calculation the value for C–C π bond orders in phenyl carbons of *Ib* range from 0.442 to 0.460, close to the expected 0.5. Also, one would expect the charges on all methyl carbons of tert-butyl of *Ib* to be the same, while calculated values vary by 0.005. The C–N π bond order for *IVa*, with a severely twisted phenyl, is 0.967, close to the expected 1.0. Selected HOMO and LUMO energy values, in eV, are as follows: *Ib*: –8.38, 0.09; *IVb*: –9.40, 0.16; *Vb*: –9.64, –0.07; *VIa*: –8.76, 0.22. HOMOs are essentially π in character and localized on the nitrone function. Values of Σc_i^2 are 0.95 and 0.87 for PBN and *Ib*, respectively, where c_i are p_z coefficients for C(α), N, and N-oxide oxygen. The coefficients cited in text are p_z (out of plane) atomic orbital coefficients.

RESULTS

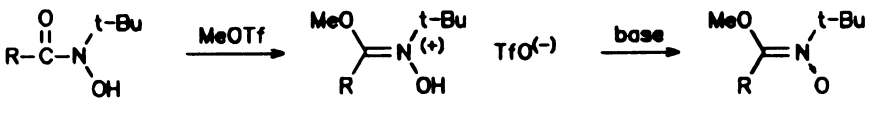
C-Alkoxy nitrones *I* were prepared as previously described[6] by alkylation of the hydroxamic acid with methyl trifluoromethanesulfonate (methyl triflate). As indicated in Scheme 1 the resulting triflate salts *II* were deprotonated on silica gel to give the desired nitrones *I*. Treatment of *Id* with various nucleophiles gave a series of aldo nitrones *III* with C-heteroatom bonds[6].

Spectroscopic Behavior

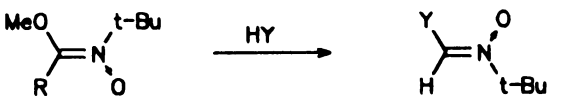
^{13}C NMR spectra of *I* and *II* were taken in $CDCl_3$ where *Ia – Id* exist exclusively as the *E* isomers, and *II* as a mixture of configuration isomers[6]. Selected chemical shifts and IR stretching frequencies of *I* and *II* are shown in Table I along with related compounds. The C(α) shifts of *I* exhibit the so-called "reverse polar effect" (ref.[16]) with the more electron-withdrawing nitro derivative somewhat more upfield. The tert-butyl carbon bonded to nitrogen, however, behaves in the normal fashion with electron-withdrawing groups producing downfield shifts. Comparison of data for *II* with *I* shows that protonation causes a downfield shift in C(α) and somewhat higher values of $\tilde{\nu}$(C=N).

Chemical shifts and IR data for *III* in chloroform are given in Table II. The same chemical shift trends found for *I* also occur with *III*, with the π electron-accepting CN derivative *IIIa* having the most upfield C(α) shift and most downfield quaternary tert-

butyl shift. The C=N stretching frequency is the highest for a π electron-donating group (n-BuNH) and lowest for the π electron-accepting CN group. Values of δ plotted vs σ_R^+ and of $\tilde{\nu}$(C=N) plotted vs σ give reasonable trends, as shown in Figs 1 and 2, respectively.



I, II	R
a	*p*-MeOC$_6$H$_4$
b	C$_6$H$_5$
c	*p*-NO$_2$C$_6$H$_4$
d	H



III	Y
a	CN
b	n-BuS
c	C$_6$H$_5$CH$_2$NH
d	n-BuNH
e	C$_6$H$_5$NH

SCHEME 1

MO Calculations

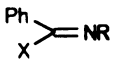
The semi-empirical MNDO method[17] was applied to *Ia* – *Id* and various C-phenyl structures representing imines (*IVa*), imidates (*Va*), aldo nitrones (*VIa*), keto nitrones (*VIIa*) and alkoxy nitrones (*VIIb*).

TABLE I
^{13}C NMR chemical shifts (δ, ppm) and IR spectra ($\tilde{\nu}$, cm^{-1}) of nitrones *I* and related compounds[a]

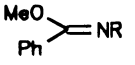
Compound	^{13}C NMR				IR	
	C(α)	N-C(CH_3)$_3$	CH_3C	CH_3O	C=N (or Ph)	NO
Ia	152.7	70.0	27.7	59.6	1 606 (m)	1 197
Ib	152.0	70.3	27.6	59.4	1 600 (vw)	1 200
Ic	151.9	72.2	27.8	59.9	1 603 (w)	1 201
IIa-E	174.2	70.5	27.1	62.5	1 610 (s)	1 023
IIa-Z	170.4	70.8	28.8	60.7		
IIb-E	174.1	70.6	26.7	62.7	1 619 (s)	1 020
IIb-Z	169.8	70.8	28.4	60.7		
IIc-E	172.4	72.0	26.8	63.3		
IIc-Z	172.7	71.8	26.4	63.8		
VIa	129.5	70.7	28.3			
Vb	157.5	57.3	29.9	52.3	1 675 (s)	
[b]	171.2	61.9	28.0	64.7		
[c]	169.6	61.6	28.3			

[a] All data from $CDCl_3$; [b] PhCON(t-Bu)OCH_3; [c] PhCON(t-Bu)OH.

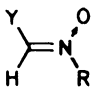
Geometries were optimized to give minimum heats of formation (see Experimental). Values for bond orders and charge densities for atoms of interest are given in Table III. From general principles there should be negligible π bonding between the α-methyl carbon and C(α) in *VIIa*, so that one can consider a calculated π bond order of 0.034 as



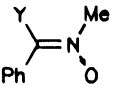
IV	X	R
a	Me	Me
b	H	t-Bu
c	H	Me
d	Et	Me
e	H	n-Bu



V	R
a	Me
b	t-Bu



VI	Y	R
a	Ph	t-Bu
b	Ph	Ph
c	Ph	Me
d	c-C_6H_{11}	Ph
e	COOMe	t-Bu



VII	Y
a - *Z*	Me
b - *E*	OMe
c - *Z*	(*E*)-CH=CHPh

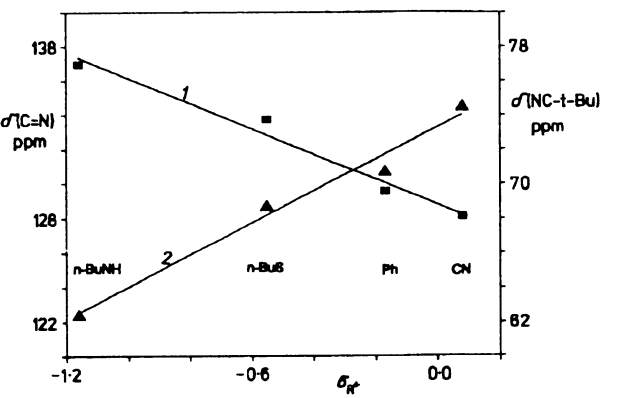
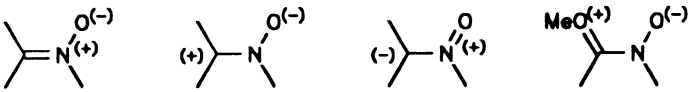


FIG. 1
Variations of ^{13}C chemical shifts for *III*, YCH=N(O)t-Bu. Curve *1*: C(α) shifts, left axis. Curve *2*: quaternary carbon of N-t-butyl shifts, right axis

insignificant. In agreement with a nearly orthogonal phenyl in *Ib*, as found[8] by MNDO calculations (twist angle 80°) and NOE, the π bond order between C(α) and C(1) of phenyl is 0.033 (not shown).

DISCUSSION

Various spectroscopic and reactivity properties of nitrones have been interpreted in terms of resonance structures *A* – *C* and, for a C-alkoxy nitrone[10], *D*. From dipole moment considerations Exner[4] suggested a hypervalent nitrogen due to the importance of both *A* and *C*.



A *B* *C* *D*

Empirical Correlations

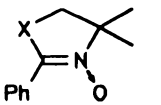
The well-documented upfield shift of C(α) of nitrones can be illustrated by the series imine, alkene, and nitrone with values of 155.1 ppm for imine[18] *IVb*, 137.0 ppm for styrene[13], and 129.5 ppm for nitrone *VIa* (PBN, Table II). The upfield shift of nitrones, in this case upfield of an alkene despite the electronegative atom and formal positive charge on nitrogen, has been taken as evidence of the importance of structure *C*. The range of chemical shifts reported for nitrones, however, is fairly large with values for

TABLE II
NMR chemical shifts (δ, ppm) and IR spectra ($\tilde{\nu}$, cm^{-1}) of nitrones[a] *IIIa* – *IIIe* and *VIa*

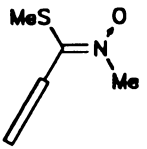
Compound	^{13}C NMR		^{1}H NMR α-H	IR	
	C=N	N–C(CH_3)$_3$		C=N	NO
IIIa	128.1	74.5	6.79	1 527	1 193
IIIb	133.7	68.6	7.38	1 545	1 205
IIIc			7.82		
IIId	137.0	62.5	7.24	1 670	1 160
IIIe			8.00	1 642	1 207
VIa	129.5	70.7	7.62	1 580	1 117

[a] All data from $CDCl_3$ solutions.

C(α) (in ppm) of 121.0 for carbomethoxy nitrone[19] *VIe*, 132.8 (3,4-dihydroisoquinoline N-oxide[20]), 137.3 for *VIIIa* (ref.[5]), and 146.3 for β-styryl nitrone[21] *VIIc*. Substitution of an oxygen or sulfur at C(α) extends the range even more downfield with chemical shifts of 142.9 (for α-methylthio nitrone *IX*, but the *E* isomer which has a conjugated phenyl[14]), 145.8 (cyclic oxazolidine[5] *VIIIb*), 150.1 (α-methylthio nitrone *IX-Z* with twisted phenyl[14]), and 150.0 (*Ib-E*, Table I). These are still upfield, however, from aldimine *IVc-E* (162.4) and ketimine *IVd-E* (171.5) ref.[18].

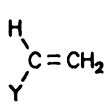


VIII	X
a	CH_2
b	O

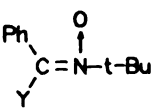


IX – Z

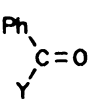
The present data indicate a high sensitivity of the chemical shift of C(α) of nitrones to substituents relative to the other sp^2 systems below, at least for substituting methoxy (Y = OCH_3) for hydrogen (Y = H). Illustrating this are the following values of $\Delta\delta = \delta(OCH_3) - \delta(H)$ (in ppm) which are positive, since the methoxy derivative is more downfield in each case.



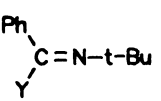
Δδ 30.3 (ref.[22])



Δδ 22.5



Δδ 10.0



Δδ 2.5

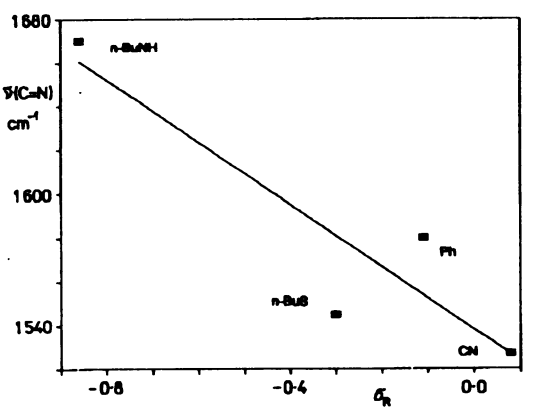


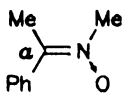
FIG. 2
Variations of $\tilde{\nu}$(C=N) for *III*, YCH=N(O)t-Bu, with group Y

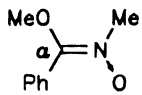
Comparison with Models

The effect on C(α) chemical shifts of adding an N-oxide oxygen to ketimines, aldimines, and imidates is shown in Table IV. In each case there is an upfield shift for the nitrone: 34 ppm for a keto nitrone, 25 – 27 ppm for aldo nitrones, and 5 – 16 ppm for C-alkoxy nitrones. Clearly there is a much smaller upfield shift for the C-alkoxy examples.

Using the ^{13}C shift of C(α) as a probe of the electron distribution changes induced by an N-oxide oxygen, one can view the smaller Δδ for C-alkoxy nitrones as reflecting less of an electron buildup at that position. It would thus appear that resonance form *C* is less important with a C-alkoxy group, which in effect tends to localize electron density in the π bond, presumably by electron repulsion with alkoxy lone pairs. The result is opposite to that found for the methoxycarbonyl nitrone *VIe-Z* which has a group that stabilizes electron density buildup at C(α) and has a chemical shift at 121.0 ppm(ref.[19]).

MO results support this conclusion. Adding an N-oxide oxygen to imine *IVa* to give keto nitrone *VIIa* increases the π electron density on C(α) from +0.116 to −0.169 (Table III) for a change of −0.285. In comparison, adding an N-oxide oxygen to imidate *Va* to give alkoxy nitrone *VIIb* increases the electron density at that site by the slightly lower value of −0.274.





VIIa ***VIIb***

relative to imine: relative to imidate:

$\Delta q_\alpha = -0.285$ $\Delta q_\alpha = -0.274$

ΔB.O. = −0.344 ΔB.O. = −0.295

Bond order changes are more significant. Compared to imine *IVa* with a C=N π bond order of 0.967 the value for keto nitrone *VIIa* is 0.623, or 0.344 lower indicating the importance of resonance form *C*. However, the decrease in π bond order for alkoxy nitrone *VIIb* relative to imidate *Va* is a *lower* value, 0.295, suggesting relatively less importance of *C* for the alkoxy nitrone. Resonance involving C-methoxy participation (*D*) does not seem important for *Ib*, since there is only a small, but not negligible, π bond order C(α)–O of 0.090, which is less than that of 0.123 for imidate *Va*. This low bond order suggests that the methoxy oxygen is more sp^3 in character than sp^2.

The unusual sensitivity of the C(α) chemical shift of nitrones to methoxy substitution (Δδ 22.5 ppm) relative to imines (2.5 ppm) may be due to a higher π electron density on C(α) of nitrones (−0.169 for *VIIa*) compared to imines (+0.116 for *IVa*). It seems that the higher electron density for nitrones would be more easily decreased by the

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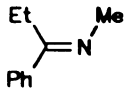
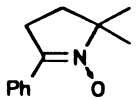
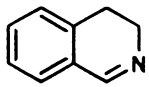
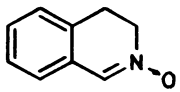
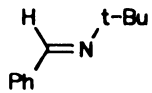
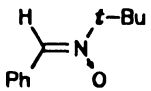
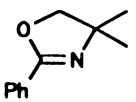
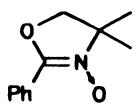
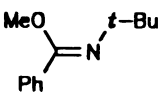
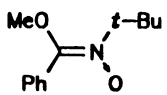
TABLE III
MNDO bond orders and charge densities

Compound		Bond orders			Charge densities				ΔH_f
						Nitrone			
		C=N	N → O	C–O[a] or C–C	C(α)	N	O	α-O[a] or α-C	
IVa-E	total:	1.914			+0.087	−0.290		+0.030	33.9
	pi:	0.967			+0.116	−0.140			
Va-Z	total:	1.843		0.980	+0.271	−0.349		−0.331	−2.39
	pi:	0.907		0.123	+0.123	−0.222			
VIIa-Z	total:	1.490	1.298	0.971	−0.149	+0.206	−0.424	+0.089	47.9
	pi:	0.623	0.350	0.034	−0.169	+0.774	−0.613		
VIIb-E	total:	1.462	1.272	1.001	+0.031	+0.177	−0.439	−0.293	13.5
	pi:	0.612	0.324	0.018	−0.151	+0.749	−0.635		
Ia-E	total:	1.469	1.270	1.002	+0.037	+0.183	−0.453	−0.290	−23.7
	pi:	0.619	0.321	0.091	−0.151	+0.749	−0.646		
Ib-E	total:	1.470	1.274	1.001	+0.035	+0.183	−0.451	−0.291	17.9
	pi:	0.620	0.322	0.090	−0.152	+0.750	−0.643		
Ic-E	total:	1.459	1.291	1.006	+0.009	+0.192	−0.438	−0.284	32.9
	pi:	0.609	0.340	0.090	−0.179	+0.765	−0.627		
Id-Z	total:	1.466	1.290	1.029	−0.016	+0.182	−0.427	−0.266	−13.3
	pi:	0.624	0.342	0.105	−0.159	+0.757	−0.627	−0.405	
VIa-Z	total:	1.524	1.294		−0.116	+0.213	−0.434		52.2
	pi:	0.655	0.347		−0.157	+0.780	−0.629		

[a] C–O and C–C denotes the atom connected to α-C other than phenyl.

TABLE IV
Effect of adding an N-oxide oxygen to imines and imidates on C(α) chemical shifts

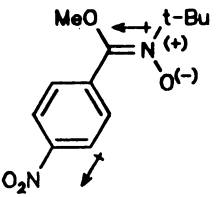
	Structure	C(α), δ(ppm)	Δδ, ppm	Ref.
IVd		171.5		18
			34.2	
VIIIa		137.3		5
X		159.8		20
			27.0	
XI		132.8		20
IVb		155.1		18
			25.6	
VIa		129.5		[a]
XII		162.2		5
			16.4	
VIIIb		145.8		5
Vb-Z		157.5		[a]
			5.5	
Ib-E		152.0		[a]

[a] Present work.

perturbation caused by an electronegative methoxy oxygen than electrons at the more positive site in imines.

Structural Variations within Nitrones

The trend of ^{13}C chemical shifts of C(α) of *Ia*, *Ib*, and *Ic* with the *p*-nitro derivative most upfield is called a reverse polar effect[16] since one would expect substitution of a nitro group, by removing electrons from connected carbon atoms, to cause a downfield shift. Instead, according to the field-induced π-polarization explanation[23] the field created by the substituent dipole induces a dipole in the π bond of the side chain in the direction indicated for the present case in *XIII*.

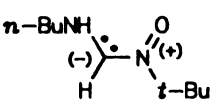


XIII

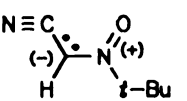
Because of an orthogonal phenyl, this localized polarization should be more important than an extended polarization[23,24] involving the aromatic ring, as concluded for twisted α-alkylstyrenes[23].

In agreement with this model the MNDO charge densities at C(α) for *Ia*, *Ib*, and *Ic* are +0.037, +0.035, and +0.009, with less positive charge, hence relatively more electron density, for the *p*-nitro derivative, thereby explaining its upfield shift. Also, the positive part of the induced dipole could explain the normal downfield shift of the tert-butyl quaternary carbon.

For C-heteroatom substituted nitrones *III* a reverse substituent effect was also observed on the chemical shifts of C=N carbons (Fig. 1, curve *1*) in that electron-withdrawing groups (e.g., C≡N) give more upfield shifts. A possible explanation of the data is analogous to one offered by Olah[25] for iminium ion ^{13}C shifts and by Suda[13] for nitrones. In the present system the downfield shift for *IIId* may be due to the decreased importance of *IIId-C* for the π-donating n-BuNH group. With the π-accepting CN group the relative importance of *IIIa-C* increases and causes an upfield shift.



IIId – C



IIIa – C

The above resonance forms can also be used to explain the $\tilde{\nu}$(C=N) trend in Fig. 2. Destabilization of *IIId-C* by n-BuNH results in more double bond character to C(α)–N and a higher frequency, while stabilization of *IIIa-C* by CN decreases the π bond order giving a lower frequency.

Removing the N-oxide oxygen of *Ia* – *Ic* from conjugation by protonation causes C(α) to move downfield by ca 20 ppm (see Table I), presumably by decreasing the importance of the resonance form corresponding to *C*. To our knowledge, this is the first report of ^{13}C chemical shifts of nitrone salts.

Relevance to Cycloadditions and Electrochemistry

The present MO calculations provide insight to the reported enhanced reactivity of 4,4-dimethyl-2-phenyloxazoline N-oxide, a cyclic C-alkoxy nitrone, which underwent cycloaddition with phenylisocyanate 76,000 times faster than the corresponding pyrroline N-oxide[5]. Enhancements, though smaller, were also observed for reaction with dimethyl acetylenedicarboxylate, and for the 2-methyl derivatives[9] with these dipolarophiles. There was also a tendency for these C-alkoxy nitrones to give a "reversed" regioselectivity with electron-deficient alkynes[5,9,10] and alkenes[9].

It had been suggested[10,26] that electron-donating groups on the dipole might increase the HOMO energy so that the nitrone HOMO-dipolarophile LUMO interaction might become dominant thereby leading to reversed regioselectivity according to frontier MO theory[27]. Consistent with this explanation offered for the observed regioselectivity[9,10] and enhanced rates[5,9] of C-alkoxy nitrones, we found a higher HOMO energy (–8.4 eV) for alkoxy nitrone *Ib* compared to PBN *VIa* (–8.8 eV). In particular, it was also suggested[9] that electron donation by a C-alkoxy oxygen should increase the coefficient on the N-oxide oxygen leading to a greater difference in coefficients on C and O termini and hence the reversed regioselectivity. These C and O coefficients in the HOMO for *Ib* are –0.60 and +0.66, respectively, a difference of 0.06 (neglecting signs), while for *VIa* they are essentially the same, –0.67 and +0.68, respectively.

While in the correct direction to explain enhanced reactivity and reversed regioselectivity, these MO differences seem small. It is therefore of interest to note that calculated total atomic charges for C(α), N, O atoms of the 1,3 dipole of PBN are negative at *both* termini, with values of –0.12, +0.21, and –0.43, respectively. However, for alkoxy nitrone *Ib* these values have unlike signs at termini, with values of +0.035, +0.18, and –0.45, respectively. A contributing factor to enhanced rates and regioselectivity of C-alkoxy nitrones may therefore be stronger coulombic attractions[27] in transition states involving C-alkoxy nitrones with asymmetrically substituted dienophiles. Another possibility suggested for enhanced rates of these C-alkoxy nitrones[5] is a favored two-step process[28].

Cyclic voltammetry of model compounds *IVb*, *Vb*, *VIa* and alkoxy nitrone *Ib* in acetonitrile have peak potentials[29] that give the following order for ease of oxidation and reduction:

Imidate < Imine < Aldo nitrone < Alkoxy nitrone.

Aromatic hydrocarbons exhibit the same behavior in that one more easily oxidized is also more easily reduced[30]. For oxidation, $E_{p(a)}$ values correlate well with HOMO energy levels, as shown in Fig. 3. The slope of 0.98 is close to the value of 1.0 expected for reversible systems.

In the case of reduction, a similar plot of $E_{p(c)}$ for the same series showed no relationship with LUMO energy of the neutral molecule. This result is different from polarographic reduction of various heterocyclic amine N-oxides which did give (ref.[31]) a linear relationship for $E_{1/2}$ for the first reduction wave in DMF. Another approach was attempted based on reports that reduction of aldehydes[32], azines[33], and aromatic hydrocarbons[34] correlated with the MO energy difference between neutral molecule and radical anion. MNDO calculations of the anions of *Ib*, *IVb*, *Vb*, and *VIa* were therefore carried out, using the half-electron method[35], to see if there was a correlation of $E_{p(c)}$ with electron affinity *A* defined as the difference of heats of formation of the anion and neutral molecule[34]. However, there was no apparent relationship for the present series. It was found that the difference $E_{p(a)} - E_{p(c)}$ does correlate with the difference $\varepsilon_{LUMO} - \varepsilon_{HOMO}$ (see Fig. 4), as reported for heterocyclic amine N-oxides[36].

It is of interest to note that the HOMO energy of imidate *Vb* is lower than that of imine *IVb* (see Experimental) as expected for addition of an electronegative atom. However, the same substitution has the opposite effect on the HOMO of alkoxy nitrone *Ib* which has a *higher* energy than that of nitrone *VIa*. It would seem on this basis that the ROC=N(O)R function has unique, not "additive", electronic properties.

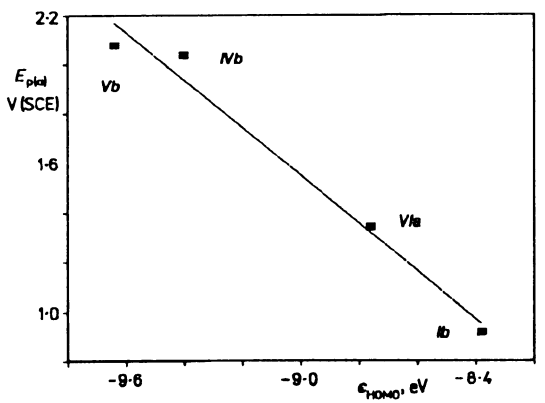


FIG. 3
Dependence of anodic peak potential of alkoxy nitrone *Ib* and model compounds *IVb*, *Vb*, and *VIa* on HOMO energy

CONCLUSIONS

^{13}C NMR and IR spectroscopy and MO calculations have given information about the electronic nature of the acyclic RO–C=N(O) grouping. For a C-aryl system, the upfield shift of C(α) of an imidate N-oxide vs the corresponding imidate is less than the usual upfield shift of an imine N-oxide compared to an imine. This suggests that there is less buildup of electron density on C(α) in the case of C-alkoxy nitrones. MNDO charge density and π bond order calculations for model systems confirm localization of the C=N π bond by an α methoxy group.

For nitrones containing an α heteroatom (nitrogen or sulfur), phenyl, or cyano group the shift of C(α) moved downfield for π-donating groups and upfield for π-accepting groups. This reverse substituent effect as well as C=N stretching frequencies can be readily explained by π bond localization by electron-donating groups. Since these nitrones are sterically much different from the C-aryl nitrones, it would appear that this phenomenon may be general for acyclic nitrones.

Two types of substituent effects on C(α) chemical shifts were observed. One was an reverse effect for C-aryl-C-methoxy nitrones which can be explained by polarization of the C=N π bond by the substituent. The other concerned a high sensitivity to substitution of OMe for H at C(α) for nitrones compared to aldehydes and imines. MO calculations on examples of the nitrone and imine systems give a higher electron density for the nitrone, which may thus be more easily perturbed by the methoxy group.

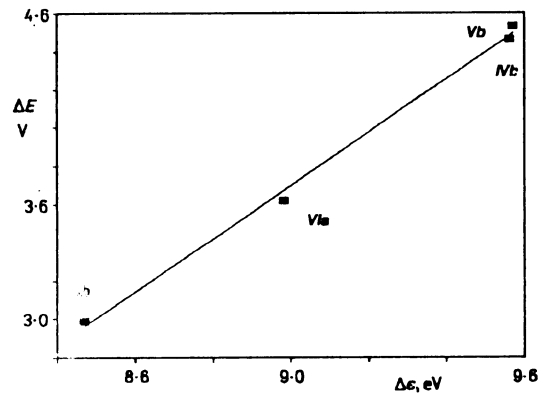


FIG. 4
Relationship between the differences $E_{p(a)} - E_{p(c)}$ (ΔE) and $\varepsilon_{LUMO} - \varepsilon_{HOMO}$ ($\Delta\varepsilon$) for alkoxy nitrone *Ib* and model compounds *IVb*, *Vb*, and *VIa*

This research was supported by an NSF Chemical Instrumentation Grant (CHE-8406088) and by an equipment grant from the W. M. Keck Foundation. We especially want to thank Professors Václav Horák, Charles F. Hammer and Miklos Kertesz for valuable discussions.

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