ON THE STRUCTURE OF ACYL NITROXIDES (NITROXONES). SPIN TRAPPING AMINOACYL

RADICALS WITH t-NITROSOBUTANE (t-NB) AND PHENYL t-BUTYL NITRONE (PBN)

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$\alpha$-Ketonitroxides (nitroxones) are relatively persistent nitroxides produced either from oxidation of hydroxamic acids (1) or by spin trapping (2). Since nitroxones are isoelectronic with semidiones (3) it is reasonable to assume that the carbonyl and nitroxyl functions are part of a planar $5\pi$-electron system (4,5). This assumption implies that the unpaired electron is delocalized over all four atoms of the $\pi$-system (4). Thus finite spin density
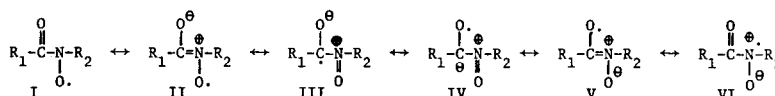


should exist on the carbonyl carbon (III). However no hyperfine splitting (hfs) is detected from hydrogens in the phenyl group of benzoyl nitroxides although Hückel MO calculations predict that significant spin density should exist in the aryl group if the nitroxone function is planar (6). When $R_1$=hydrogen, alkyl or perfluoroalkyl small hfs is sometimes detected from this group (Table 1). Certain cyclic nitroxones do provide substantial hfs from hydrogens in the $R_1$ position(5):
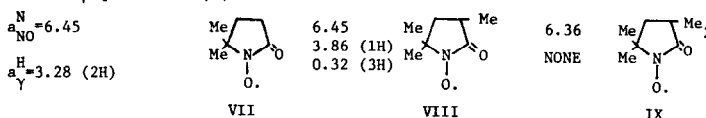


If these nitroxones are planar the hfs for the methyl group in acetyl t-butyl nitroxide should be about 2.2 G[**]. In fact no splitting is found. An explanation which can accommodate this fact is to propose that the nitroxone prefers to be nonplanar but not in an eclipsed conformation:
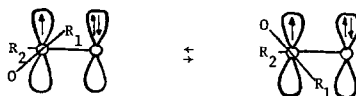


The following attempts to account for the ESR parameters of nitroxones:

1. When the N-hfs is 6.0-6.5 G the nitroxone is essentially planar and hfs from $R_1$ comes from finite spin desnity on the carbonyl carbon (see Table 1).

2. When the N-hfs is about 12 G (or larger) the nitroxone is nonplanar and approaches an eclipsed conformation. Hfs from $R_1$ comes from long-range interactions (see Table 1).

3. In intermediate cases the time-average dihedral angle between the plane containing the nitrogen p-orbital and the N-C bond and the plane containing the carbonyl and the C-N bond ($\theta_{NCO}$) is inversely proportional to the N-hfs.

The following results lend support to this proposal. When the aminoformyl radical is trapped by t-NB in a formamide-water mixture a triplet of doublets is obtained[+] (Figure 1). The doublets are absent in $D_2O$. The spectrum can be computer simulated using $a_{NO}^N$=10.38,

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** $a_\beta^H$ (Me) = $a_\beta^H$ (cyclic) $[\cos^2 \theta_{Me}/\cos^2 \theta_{cyclic}] \cong a_\beta^H$ (cyclic) 0.5/0.75

+ t-Butoxy radicals from thermal decomposition of di-t-butylperoxalate at room temperature were used to produce aminoacyl radicals from formamide; see e.g. reference 2 and 7.

$a_{NH}^{H}$=0.80, $a_{NCO}^{N}$<0.10, line width (LW)=0.68 G. Splitting from only one hydrogen is detected. Since the amido function must be strongly conjugated the hfs from the two amido hydrogens should be approximately equal if the nitroxone function is planar. A non-planar nitroxone function would give larger hfs from one amido hydrogen than the other because the "W-plan" arrangement of bonds and orbitals favors one hydrogen over the other (X):



$a_{NO}^{N}$=5.85, $a_{o,p,m}^{H}$=2.1 (2H), 0.7 (2H)

X                                            XI                                            XII
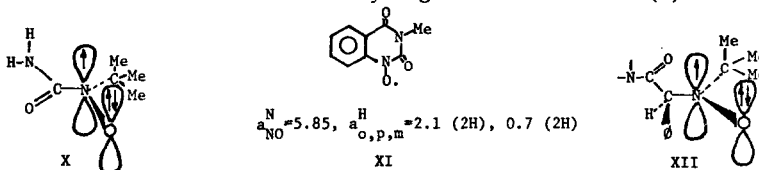
The N,N-dimethylaminoformyl adduct of t-NB can be made in the same way (8,9). A 12.12 G triplet is the major spectrum (Figure 2). The less persistent spectrum has been previously assigned to the adduct from methyl hydrogen abstraction (10,11). The main features of the major spectrum can be simulated using the constants reported by Holman and Perkins who used deuterated t-NB: $a_{NO}^{N}$=11.75, $a_{NCO}^{N}$=0.45, $a_{CH_3}^{H}$=0.6 (3H), LW=0.55 G$^*$. The N-methylaminoformyl adduct of t-NB gives the spectrum shown in Figure 3. From simulation: $a_{NO}^{N}$=10.60, $a_{CH_3}^{H}$=1.15 (3H), $a_{NH}^{H}$=0.58 (1H), LW=0.80 G. The spectrum obtained in N-methylformamide-$D_2O$ mixtures gives a 1:3:3:1 quartet: $a_{CH_3}^{H}$=1.15 (3H) G. The presence of hfs from one amido hydrogen when $R_1$=NH$_2$, from three methyl hydrogens when $R_1$=NMe$_2$ and from three methyl hydrogens greater than one amido hydrogen when $R_1$=NHMe all support the notion of a non-planar nitroxone.[**] Of interest is the report that the aromatic nitroxone shown above (XI) does not provide secondary nitrogen or methyl hydrogen splitting (12).

That long-range nitrogen and amido hydrogen splitting can be found if the dihedral angle is favorable is illustrated by the following examples. The aminoformyl adduct of PBN in a formamide-$H_2O$ mixture gives a spectrum consisting of a triplet of doublets split into quartets. The quartets disappear in a formamide-$D_2O$ mixture leaving a small 1:1:1 splitting: $a_{NO}^{N}$=15.29, $a_{CH}^{H}$=2.84, $a_{NCO}^{N}$=0.52, $a_{NH}^{H}$=0.52 (1H) G. The N-methylaminoformyl adduct of PBN in N-methylformamide gives a triplet of doublets with a 1:1:1 pattern due to another nitrogen splitting: $a_{NO}^{N}$=14.84, $a_{CH}^{H}$=2.71, $a_{NCO}^{N}$=0.65 G. In N-methylformamide-$H_2O$ the spectrum is somewhat different but no change is found in the presence of $D_2O$. The results from the N,N-dimethylaminoformyl adduct appear anomolous at first sight. The major spectrum consists of only a triplet of doublets:[+] $a_{NO}^{N}$=14.67, $a_{CH}^{H}$=5.98 G. It is proposed that in the aminoformyl and the N-methylaminoformyl adducts the H—N—C—N—O fragment has all atoms indicated in the same plane (XII). Since $\theta_{NCO}$ is quite small ($\theta_{NCO} \approx 10°$ based on a $a_{\beta}^{H}$=26 cos$^2 \theta_{NCH}$) the situation is favorable for long-range interactions. In the dimethylaminoformyl adduct perhaps because of the bulk of the groups attached, the bond to the amido nitrogen may not fall on this plane and the advantage of a small dihedral angle ($\theta_{NCO} \approx 0°$) is lost.

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$^*$ Holman and Perkins' experiments were in BrCCl$_3$. Results reported here are in DMF.

$^{**}$ A non-planar eclipsed conformation has been proposed for F-C-N-CMe$_3$ (9) but the relatively small fluorine hyperfine splitting ($a_{NO}^{N}$=12.15, $a_{CO}^{F}$=0.7 gauss) seems anomalous.

$^+$ The minor spectrum is due to an adduct from a carbon-centered radical: $a_{NO}^{N}$=14.54, $a_{CH}^{H}$=2.58 G.

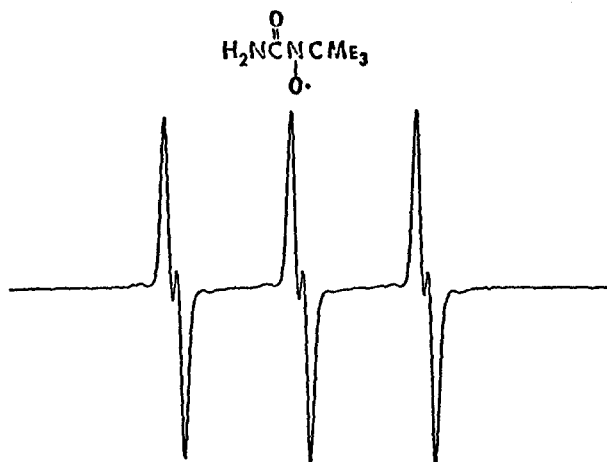$$\underset{\underset{\text{O}\cdot}{|}}{\overset{\overset{\text{O}}{\|}}{\text{H}_2\text{N}\overset{}{\text{C}}\text{N}}}\text{CMe}_3$$

FIGURE 1

$$(\text{CH}_3)_2\text{N}\underset{\underset{\text{O}\cdot}{|}}{\overset{\overset{\text{O}}{\|}}{\text{C}}}\text{NCMe}_3 \quad + \quad \text{H}\overset{\overset{\text{O}}{\|}}{\text{C}}\underset{\underset{\text{CH}_3}{|}}{\text{N}}\text{CH}_2\overset{\overset{\text{O}\cdot}{|}}{\text{N}}\text{CMe}_3$$

FIGURE 2

$$\text{CH}_3\text{NH}\underset{\underset{\text{O}\cdot}{|}}{\overset{\overset{\text{O}}{\|}}{\text{C}}}\text{NCMe}_3$$
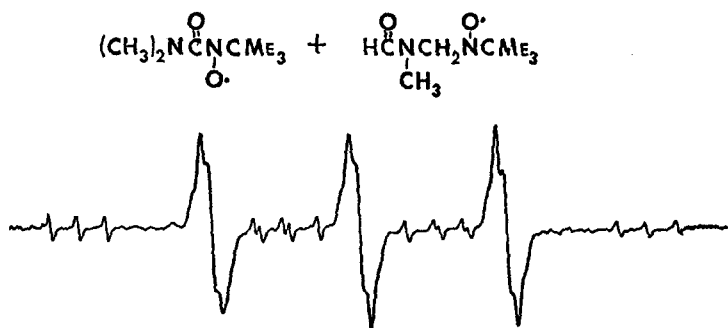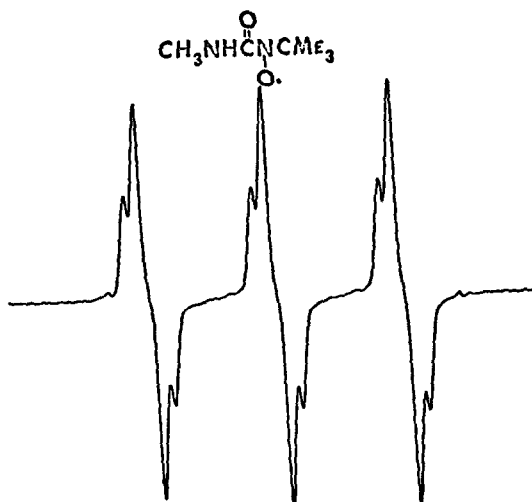
FIGURE 3

| Table 1 | α-Nitroxones | | $R_1-\overset{\overset{O}{\|}}{C}-\overset{\overset{O\cdot}{\|}}{N}-R_2$ | |
|---|---|---|---|---|
| $R_1$ | $R_2$ | $a_N$ | $a_{OTHER}$ | REFERENCE |
| $CF_3$ | t-butyl | 5.92 | 0.88 (3F) | 7 |
| 5-membered ring | | 6.45 | 3.28 (2H) | 5 |
| Br | t-butyl | 6.50 | 2.1 (Br) | 9 |
| Cl | t-butyl | 6.65 | 0.5 (Cl) | 9,13,14 |
| 6-membered ring | | 6.90 | | 5 |
| H | t-butyl | 6.96 | 1.35 (H) | 2,5 |
| $CH_3$ | phenyl | 7.18 | 0.23 (3H), 1.47 (3H), 0.62 (2H) | 1 |
| $CH_3$ | t-butyl | 7.83 | - | 2,5 |
| $C_6H_5$ | t-butyl | 7.90 | - | 2,5 |
| t-butyl | t-butyl | 7.96 | - | 2,5 |
| $CH_3O$ | t-butyl | 8.20 | 0.45 (3H) | 9 |
| $CH_3CH_2O$ | t-butyl | 8.25 | 0.45 (2H) | 9 |
| $C_6H_5NH$ | t-butyl | 10.25 | - | 15 |
| $NH_2$ | t-butyl | 10.38 | $a_N$=0.24, $a_H$=0.80 (1H) | this work |
| $CH_3NH$ | t-butyl | 10.60 | $a_H$=1.15 (3H), 0.58 (H) | this work |
| $(CH_3)_2N$ | t-butyl | 12.12 | $a_H$=0.70 (3H), 0.10 (3H) | this work |
| | | 11.75 | $a_N$=0.45, $a_H$=0.6 (3H) | 8,9 |
| F | t-butyl | 12.15 | 0.7 (F) | 9 |

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