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Synthesis and Spin Trapping Chemistry of a Novel Bicyclic Nitrone: 1,3,3-Trimethyl-6-azabicyclo[3.2.1]oct-6-ene-N-oxide (Trazon).

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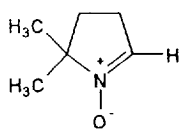
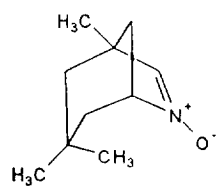
Abstract: Oxygen-centered and carbon-centered radicals are interesting possible intermediates within chemical and biological systems. In this communication the synthesis and use of a novel bicyclic nitrone 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-ene-N-oxide (Trazon) as a spin trapping compound is proposed. Trazon is a stable, crystalline solid with an excellent shelf life. The EPR spectra of Trazon spin adducts have similar EPR parameters as compared to 5-membered ring nitrones but there is extra information present in the form of hyperfine splitting from two β-hydrogens and two γ-hydrogens.

Since the first report in which 5,5-dimethylpyrroline-N-oxide (DMPO, **1**) was introduced as a spin trap for free radicals,[1] a growing number of nitrone spin traps based on DMPO have been synthesized and evaluated as spin traps.[2-5] In this communication we wish to report on the synthesis and electron paramagnetic resonance (EPR) spectral characteristics of a new bicyclic spin trap 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-ene-N-oxide (Trazon, **2**), a representative nitrone of a new class of bicyclic spin traps being developed in our laboratories (see reference 6 for synthetic procedure).



1



2

Hydroxyl spin adduct. The hydroxyl radical adduct of Trazon (Trazon-OH, **3**), was generated by exposing a 1% aqueous H_2O_2 solution of Trazon (50mM) to UV light for 5 seconds; the nitroxide shows a 1:2:1, 1:2:1, 1:2:1 spectral pattern (Fig. 1a). This pattern results from the hyperfine splitting (hfs) of two β-hydrogens coupling with the nitroxyl nitrogen: a_N = 15.0 G and $a_{\beta\text{-H}}$ = 9.7 (2H) G. The additional splittings can be accounted for by assuming long range "W" plan couplings, with a hfs of 1.1 and 1.0 G for one hydrogen each, probably from the *syn*-bridgehead and the C-4 *equatorial* positions.

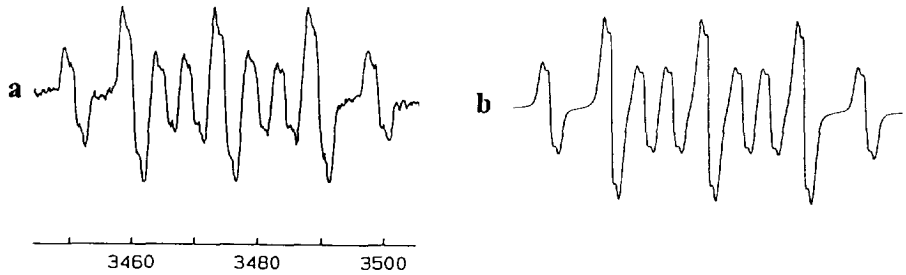
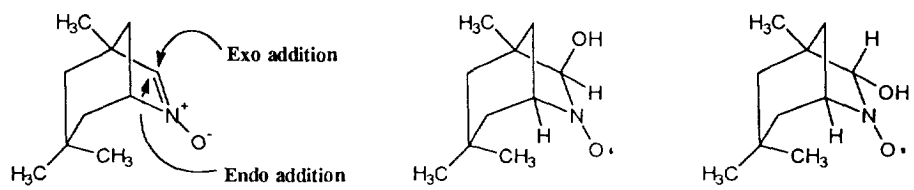


Fig. 1

a: EPR spectrum of Trazon-OH (photolysis of 1% aq. H_2O_2). b: Computer simulation of the EPR trace of Trazon-OH



3 **4**

The computer simulation with the above values generated the spectrum shown in Figure 1b. Although an EPR spectrum containing two sets of signals, one for the *exo* and the other for the *endo* adduct, could have been expected, this type of mixture spectrum was not observed even when the instrument was set on a higher gain setting. Either the spectrum is the same for **3** and **4** and the presence of a mixture of components cannot be distinguished by EPR, or only one stereoisomer is produced. This interesting spin trapping stereochemical problem is still being investigated.

Superoxide/hydroperoxyl spin adduct. In the case of the superoxide/hydroperoxyl radical adduct of Trazon, generated by illuminating a phosphate buffer solution containing riboflavin (2 mM) DETAPAC (1 mM) and Trazon (50 mM) with a 500 W projector lamp, the γ-hydrogen hyperfine splitting can be clearly seen. Again there is a 1:2:1, 1:2:1, 1:2:1 splitting pattern with the following hfs parameters: a_N = 14.7, $a_{\beta\text{-}H1}$ = 10.4, $a_{\beta\text{-}H2}$ = 9.1, $a_{\gamma\text{-}H1}$ = 1.8 and $a_{\gamma\text{-}H2}$ = 1.2 G (Fig. 2a). These values are very similar to those obtained for the DMPO-OOH spin adduct (a_N = 14.3, $a_{\beta\text{-}H}$ = 11.7 and $a_{\gamma\text{-}H}$ = 1.25 G). The computer simulation is shown in spectrum Fig. 2b.

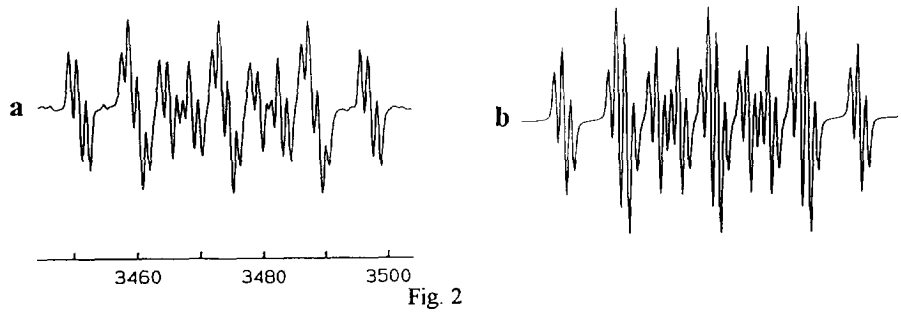


Fig. 2

a: EPR spectrum of superoxide/hydroperoxyl radical adduct of Trazon (Trazon-OOH) produced from riboflavin-DETAPAC system in phosphate buffer. b: Computer simulation of Trazon-OOH.

Phenyl spin adduct. When a benzene solution of phenylazotriphenylmethane (PAT) is warmed in the presence of Trazon, the resultant phenyl adduct of Trazon generated a spectrum having six sets of triplets with a 1:1 ratio of intensities. There is partial overlapping of the 2nd with the third set and the 4th with the 5th set. The hfs parameters were: a_N = 14.9 G, and $a_{\beta\text{-}H1}$ = 14.05, $a_{\beta\text{-}H2}$ = 8.5 G while the two γ-hydrogens have the same value's $a_{\gamma\text{-}H1} = a_{\gamma\text{-}H2}$ = 1.4 G (Fig. 3a). A computer generated simulation with the above values provides a good fit with the EPR spectrum (Fig. 3b).

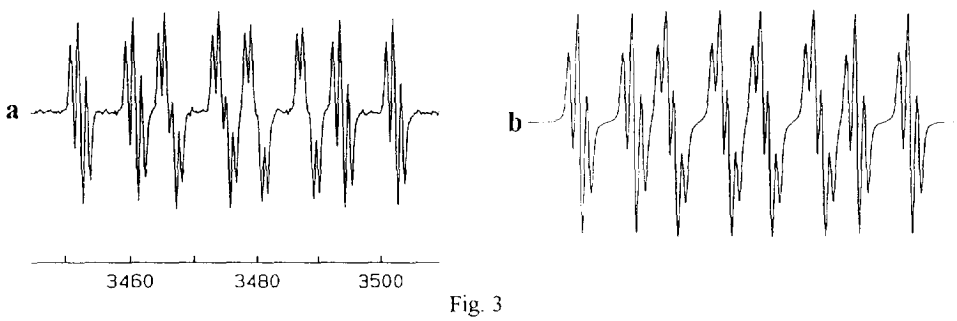


Fig. 3

a: Epr spectrum of the phenyl radical adduct of Trazon. b: Computer simulation of the EPR trace of the phenyl adduct of Trazon.

In conclusion we report the synthesis and spin trapping chemistry of a novel bicyclic nitrone, which is the first example of a new type of spin trap useful for spin trapping oxygen- and carbon-centered radicals. EPR parameters for a variety of additional examples are listed in Table 1.

TABLE 1

Hyperfine Splitting Constants of Trazon Spin Adducts[a]

Radical	Method	Solvent	a_N	$a_{\beta\text{-}H1}$	$a_{\beta\text{-}H2}$	$a_{\gamma\text{-}H1}$	$a_{\gamma\text{-}H2}$
Methyl	CH_3MgBr	C_6H_6	14.2	13.8	8.5	1.2	1.2
Ethyl	C_2H_5MgBr	C_6H_6	14.2	13.6	8.6	1.1	1.1[b]
Phenyl	PAT	C_6H_6	14.9	14.0	8.5	1.4	1.4
Hydroxyethyl	$(C_6H_5)_2CO + h\nu$	C_2H_5OH	15.4	14.8	9.2	1.4	1.4
2-Hydroxy-2-propyl	$(C_6H_5)_2CO + h\nu$	$(CH_3)_2CHOH$	14.8	17.7	8.8	1.4	1.2
Methoxyl[c]	$(C_6H_5)_2CO + h\nu$	CH_3OH	13.2	9.0	8.5	1.2	1.2
2-Cyanopropoxyl[c]	AIBN	C_6H_6	13.0	8.8	7.9	1.1	1.1
tert-Butoxyl	$[(CH_3)CO]_2$	C_6H_6	13.0	18.0	12.0	1.5	1.5
Hydroxyl	1% HOOH	H_2O	15.0	9.7	9.7	1.1	1.0
Hydroperoxyl	Riboflavin	H_2O	14.7	10.4	9.1	1.8	1.2

[a] In gauss at room temperature under nitrogen. [b] $a_{\gamma\text{-}H3} = 1.10$ G. [c] Assignment based on small a_N

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5. Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* **1995**, *60*, 5441 and references cited therein.
6. Experimental: To a solution of $Na_2WO_4\ 2H_2O$ (2.64 g, 8 mmol) and 1,3,3-trimethyl-6-azabicyclo[3.2.1] (obtained from Aldrich Chemical Co., 30.6 g, 200 mmol) in 40 mL of water was added a 30% H_2O_2 solution (45.5 mL, 440 mmol) at -5°C under nitrogen. After additional stirring for 10 min, $NaHSO_3$ and NaCl were added. The reaction mixture was then extracted with $CHCl_3$. Column chromatography on silica gel (ethyl acetate) followed by sublimation gave the nitrone **2** as a hygroscopic solid (25 g, 75%, m.p. 40 - 42°C). The compound exhibited IR, ^1H and ^{13}C-NMR and elemental analysis data consistent with the structure.

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