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α-2,6-DIFLUOROPHENYL-N-*TERT*-BUTYLNITRONE: A SPIN TRAP FOR DISTINGUISHING DIFFERENT TYPES OF ALKYL RADICALS BASED ON LONG-RANGE FLUORINE HYPERFINE SPLITTING

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α-2,6-Difluorophenyl-N-*tert*-butylnitrone (F_2PBN) was synthesized and evaluated. A number of alkyl adducts of F_2PBN were studied by ESR/ENDOR. An additional hyperfine splitting (a triplet of doublets of doublets) is reported. The existence of two (one large, one small) F-hfsc's from the ortho-fluorine atoms in the phenyl ring of most alkyl adducts was confirmed by ENDOR spectroscopy.

KEY WORDS: Spin trapping, ESR, ENDOR, long-range fluorine hyperfine splitting.

ABBREVIATIONS:PBN–α-phenyl-N-*tert*-butylnitrone;F_2PBN–α-2,6-difluorophenyl-N-*tert*-butylnitrone; F_5PBN–α-pentafluorophenyl-N-*tert*-butylnitrone; hfsc–hyperfine splitting constant; hfs–hyperfine splitting; BOOB–di-*tert*-butyl peroxide.

DEFINITIONS: primary radical: $-CH_2\cdot$; secondary radical: $>CH\cdot$; tertiary radical: $->C\cdot$

INTRODUCTION

Phenyl-N-*tert*-butylnitrone (PBN) was proposed as a general purpose spin trap some 20 years ago[1] and this suggestion has been widely accepted.[2] The advantages of PBN for use in biochemical systems is based on its low toxicity and the persistence of the spin adducts of carbon-centered radicals. However a disadvantage of PBN is that the ESR spectra of the alkyl adducts are all quite similar with little change in N- and β-H hfsc's. Although deuteration of the *tert*-butyl and phenyl groups of PBN permits resolution of the γ-H hfs for primary radical adducts, the same interaction does not seem to be detectable either by ESR or ENDOR for secondary radical adducts.[3] Since secondary alkyl radicals are thought to be the most likely intermediates in free radical reactions of unsaturated fatty acids and their esters, a need exists to develop spin traps which can distinguish secondary alkyl radicals from other carbon-centered radicals. Results with 2,6-difluorophenyl-N-*tert*-butylnitrone, F_2PBN, indicate that this spin trap may be able to function in this capacity.

RESULTS AND DISCUSSION

Simple alkyl adducts of PBN-type spin traps can be produced from organometallic

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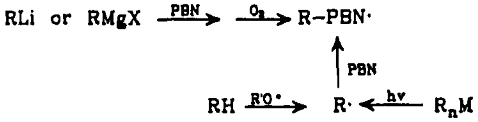
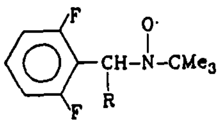
*Taken from the M.Sc. Thesis "An ESR/ENDOR Spin Trapping Study of α-2,6-Difluorophenyl-N-*tert*-Butylnitrone" by Yee-Lai Eunice Chan, 1988, University of Guelph, Guelph, Ontario.

compounds either by photolysis (organolead, silver, mercury or tin), or by nucleophilic addition followed by air oxidation of the anionic addition product (organolithium or organomagnesium Grignard)[1] or by hydrogen atom abstraction using an oxygen-centered radical (*tert*-butoxyl or triplet benzophenone):



ESR spectra obtained by these methods from most alkyl adducts of F_2PBN (I) give 12-line patterns composed of a triplet of doublets of doublets (see Figure 1 for a typical example).



I

From ENDOR spectroscopy it is possible to show that one doublet comes from a β-H hfs (ENDOR doublet centered on 14.5 MHz[4]) and one F-hfs (ENDOR doublet is centered on 13.7 MHz). Inspection of Table I shows that the primary alkyl adducts

TABLE I
ESR Hyperfine Splitting Constants of Carbon-Centered Adducts of F_2PBN[a-b]

Adduct	a_N	a_H^{β}	a_F^{δ}	$a_F^{\delta'}$	Solvent
PRIMARY π-RADICALS					
Methyl*	14.69	6.06	(0.73)		Benzene
Ethyl	14.40	5.66	1.70		Benzene
n-Propyl	14.39	5.57	1.87	(0.37)	Toluene
n-Butyl	14.31	5.66	1.88	(0.24)	Toluene
n-Pentyl	14.37	5.65	1.83		Toluene
Benzyl	14.40	4.10	2.05	(0.36)	Benzene
Allyl	14.43	5.49	1.72	(1.44)	Benzene
SECONDARY π-RADICALS					
Isopropyl	14.22	3.77	3.77	(0.17)	Benzene
Cyclopentyl	14.30	5.36	2.70	(0.30)	Toluene
Cyclohexyl	14.27	3.70	3.70	(0.34)	Toluene
sec-Butyl	14.61	7.81			Toluene
	15.43	6.32	1.3		H_2O/EtOH
TERTIARY π-RADICAL					
tert-Butyl	13.64	5.03			Benzene
	15.33	6.67	1.62		H_2O
σ-RADICALS					
Vinyl	14.78	4.05	(0.25)		Benzene
Phenyl†	14.25	4.41			Toluene

[a] All the ESR spectra were recorded at room temperature and the hfsc's are given in Gauss.

[b] Entries in () indicate values (2.81 MHz = 1 Gauss) obtained by ENDOR in toluene at approximately 200 K.

$^{*}a^{\beta}_{\text{C-13}} = 3.81$ G

†This spin adduct has been reported before - see ref.[5]

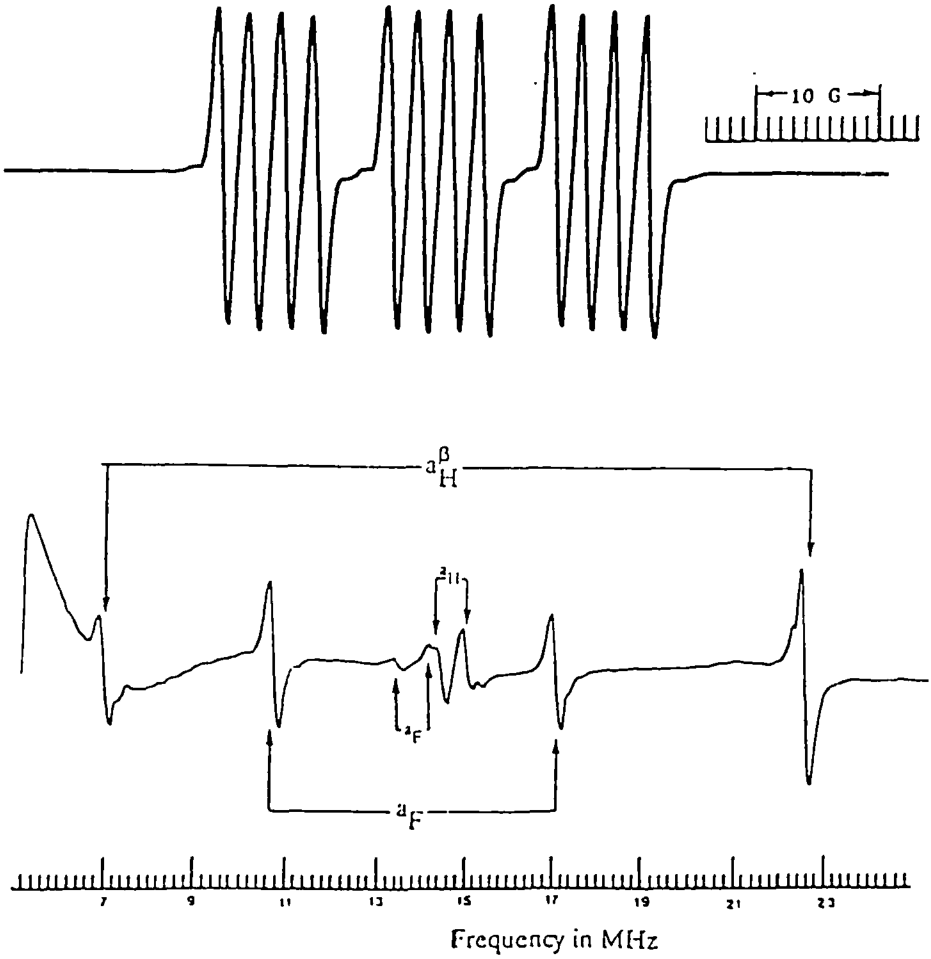


FIGURE 1 (a) ESR spectrum obtained from the anion addition of cyclopentylmagnesium chloride to F_2PBN in toluene air oxidation. (b) ENDOR spectrum obtained in toluene at 190 K of the cyclopentyl adduct of F_2PBN.

with linear carbon chains (i.e. with more than two carbons) provide one F-hfs in the range of 1.7–2.1 G, secondary alkyl adducts (with short or cyclic carbon chain e.g. iso-propyl, cyclopentyl or cyclohexyl) give one somewhat larger F-hfs (2.7–3.8 G), while those adducts with bulky carbon groups exhibit no detectable F-hfs in toluene and small (~ 1.6 G) F-hfs in polar solvents (e.g. *sec*-butyl, *tert*-butyl). Vinyl and methyl spin adducts give one very small F-hfs detectable by ENDOR spectroscopy only. The phenyl adduct provides no detectable F-hfs.[5] Evidence for the presence of the second fluorine in the spin adduct is accounted for in most cases as a very small F-hfs only detectable by ENDOR spectroscopy. These differences can be used to help assign structures to the spin adducts obtained from spin trapping experiments.

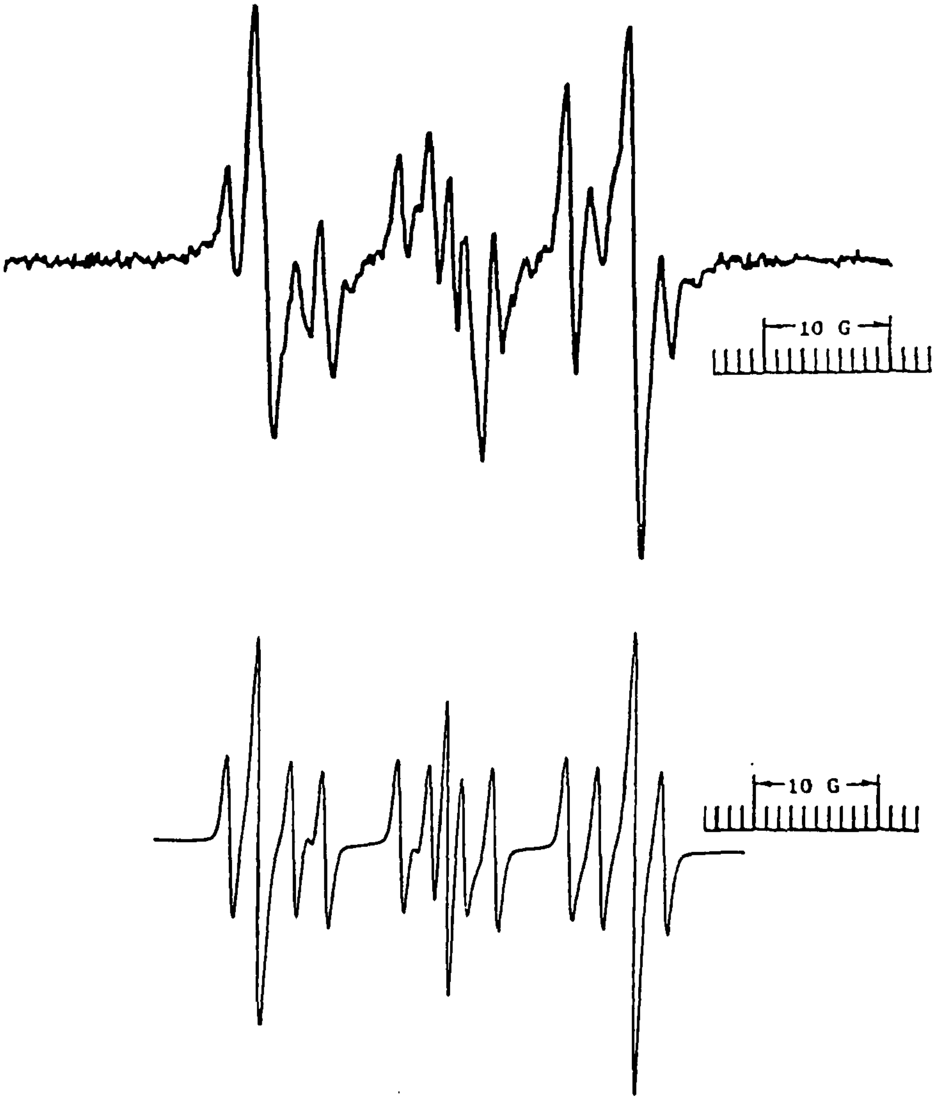


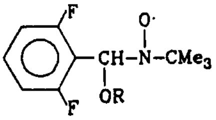
FIGURE 1 (a) ESR spectrum obtained from the photolysis of BOOB and cyclopentane in the presence of F_2PBN in toluene. (b) Computer simulation of (a) using the following parameters: (i) pentyl-F_2PBN·: N(1) = 14.3 G; H(1) = 5.4 G; F(1) = 2.7 G; (ii) tert-butoxyl-F_2PBN·: N(1) = 13.7 G; H(1) = 5 G; (iii) Di-tert-butyl aminoxyl: N(1) = 16 G.

ESR spectra obtained for different oxyl or peroxyl adducts (II) do not change significantly with structure although peroxyl addition products, in general, have smaller hfsc's than oxyl adducts (Table II). In no case is an additional doublet due to F-hfs observed in an oxyl or peroxyl adduct.

TABLE II
ESR Hyperfine Splitting Constants of Oxygen-Centered Adducts of F_2PBN[a]

Adduct	a_N	a_H^β	Solvent	Radical Source
Hydroxyl	15.4	5.20	Water	H_2O_2 + hν
Superoxide/Hydroperoxyl	14.87	5.42	Water	KO_2 + H_2O
Benzoyloxyl	12.91	3.13	Benzene	benzoylperoxide + hν
n-Butoxyl	13.55	5.88	Benzene	n-butylnitrite + hν
tert-Butoxyl	13.71	4.99	Benzene	BOOB + hν
2-Cyano-2-propyloxyl	13.2	4.0	Benzene	AIBN + O_2
Ethyloxyl	13.39	5.48	Toluene	trimethyllead acetate
tert-Butylperoxyl	13.17	2.82	Benzene	*tert*-butylhydro-peroxide
2-Cyano-2-propylperoxyl	12.21	2.15	Toluene	AIBN + O_2
Cumylperoxyl	13.07	3.42	Toluene	cumylhydro-peroxide

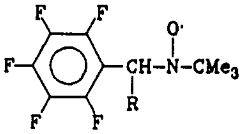
[a] All the ESR spectra were recorded at room temperature and the hfsc's are given in Gauss.
AIBN = azoisobutyronitrile



II

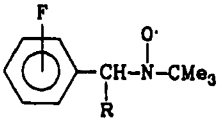
Thus in spin trapping studies where both carbon-centered and oxygen-centered radicals are trapped, F_2PBN could provide additional information for assignment. Most alkyl adducts are expected to give additional hfsc from the aryl fluorines whereas oxyl adducts will produce only triplets of doublets due to the normal N- and β-H hfs in PBN adducts.

Results with alkyl adducts of α-pentafluorophenyl-N-*tert*-butylnitrone (F_5PBN) are very similar to that of F_2PBN. F_5PBN also provides additional F-hfs in some alkyl adducts of F_5PBN (III).



III

However, the introduction of *one* fluorine atom substituent into the phenyl ring of PBN (i.e. α-2-fluorophenyl-N-*tert*-butylnitrone and α-3-fluorophenyl-N-*tert*-butylnitrone) (IV) is not enough to bring about detectable F-hfs and does not lead to any significant change in a_N or a_H^β for the derived adducts. Also no additional F-hfsc is observed in the alkyl adducts of these nitrones.



IV

The origin of the unusual F-hfs is of interest. We attribute the detection of *two* (one large, one small) F-hfsc's from the ortho-fluorine atoms in the phenyl ring of most alkyl adducts to long range hyperfine splitting brought about by slow rotation of the 2,6-difluorophenyl group. The same long range hyperfine splitting may be the origin of different small proton hfsc's from the phenyl hydrogens in the phenyl adduct of PBN as detected by ENDOR spectroscopy in deuterated PBN.[3] Further studies are underway.

Acknowledgements

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