

Generation of Oxygen-, Sulfur, Carbon-, Nitrogen- and Phosphorus-Centred Short-Lived Radicals Via One-Electron Oxidation with Stable Hydrazyl Radical

P. Ionita^{a,*}, B.C. Gilbert^b and A.C. Whitwood^b

^aInstitute of Physical Chemistry, Spl. Independentei 202, Bucharest 77208, Romania ^bUniversity of York, Department of Chemistry, York YO10 5DD, UK

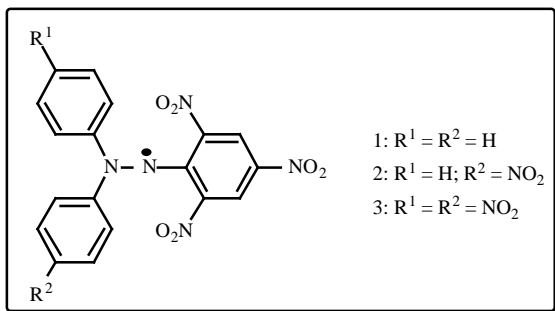
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Abstract: Using three readily-prepared free-radicals of DPPH type, with different oxidation potential, it is possible to generate, *via* one electron transfer or hydrogen-atom abstraction, short-lived radicals, characterised by the EPR spin-trapping technique. PBN, DMPO and DEPMPO were employed as spin-traps. The results show that DPPH and its congeners can be successfully employed for generation of short-lived oxygen-, sulfur-, carbon-, nitrogen-, and phosphorus-centered radicals.

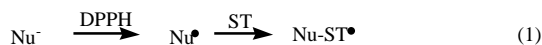
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INTRODUCTION

Previous work [1-5] show that 2,2-diphenyl-1-picrylhydrazyl radical (DPPH, **1**) and its congeners (NO₂DPPH, **2**; (NO₂)₂DPPH, **3**) can act as one electron oxidants, oxidizing *e.g.* the azide anion (N₃⁻) to the corresponding azido-radical (N₃[•]), which is subsequently trapped by a spin-trap (ST) as shown by EPR technique.

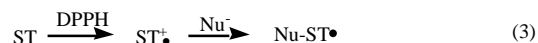


The usual process expected is described by eqn. 1: the hydrazyl radical abstract one electron from the nucleophile (Nu⁻), leading to the formation of short-lived radical Nu[•], which is trapped by a spin-trap (ST), forming the spin-adduct ST-Nu[•] [6].



However, the formation of the spin-adduct can be the result of some other processes, namely Forrester-Hepburn mechanism [7] (eqn. 2) or 'inverse spin-trapping' [8] (eqn. 3); in a previous paper we showed that genuine spin-adduct formation is observed (*n.b.* E⁰ for PBN is 1.47, and for DMPO is 1.62 V vs. SCE) [9]. The reactivity of these organo-soluble hydrazyl free radicals can be extended to water-soluble species using crown ethers as interphasic

carriers, for example transferring into the organic phase inorganic salts, as supramolecular complexes [1-5]. One advantage of this process is the activation of the 'naked' anion, due to the lack of its hydration.



While **1** is a weak oxidant (E⁰ = 0.30 V vs. SCE), **2** and especially **3** are more powerful oxidants (**2**, E⁰ = 0.49 V; **3**, E⁰ = 0.60 V); using different hydrazyl radicals we are able to tune the oxidation potential of the substrates [1]. In this paper we aim to establish that this kind of stable radicals (**1-3**) can be used for a variety of substrates.

In order to explore the possibility of generation of short-lived oxygen-, sulfur-, carbon-, nitrogen-, and phosphorus-centred radicals we chose as substrates sodium methoxide (**7**), potassium-*t*-butoxide (**8**), N-benzoyl-tyrosine-methylester (**9**), 2-mercaptopyrimidine (**10**), captopril (**11**), aniline (**12**), phenothiazine (**13**) and diphenylphosphine (**14**).

Different spin-traps show different selectivities in short-lived radical capture [6], so we used a range of spin traps including N-*t*-butyl-phenyl-nitron (PBN, **4**), 5,5-dimethyl-4,5-dihydro-3H-pyrrole-N-oxide (DMPO, **5**), and 5-diethoxyphosphoryl-5-methyl-4,5-dihydro-3H-pyrrole-N-oxide (DEPMPO, **6**), in order to scavenge the radicals formed.

RESULTS AND DISCUSSION

Oxygen-Centred Radicals: Reaction of 1-3 with Sodium Methoxide, Potassium *t*-Butoxide or N-Benzoyl-Tyrosine-Methylester in the Presence of Spin-Traps

Reaction of DPPH **1** with sodium methoxide, both in the presence or absence of spin-trap, led to the EPR spectra which correspond to the radical-anion **15** (Fig. 1), formed *via*

*Address correspondence to this author at the Institute of Physical Chemistry, Spl. Independentei 202, Bucharest 77208, Romania; Tel: +40213121147; Fax: +40213121147; E-mail: pionita@chimfiz.icf.ro

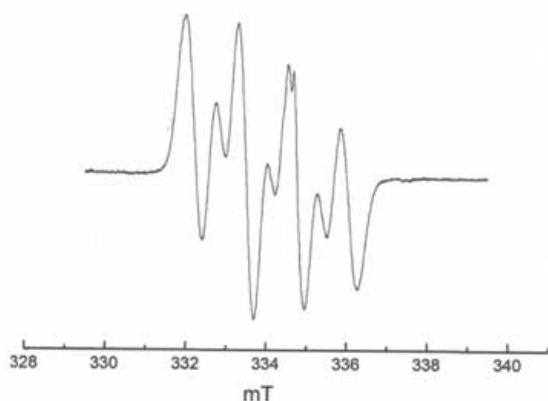
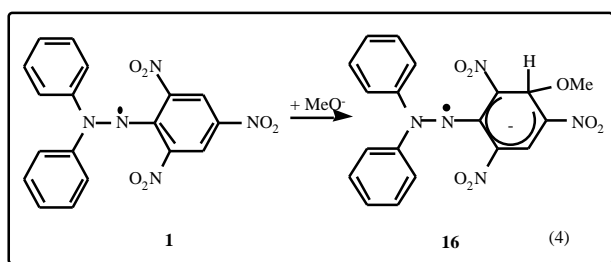
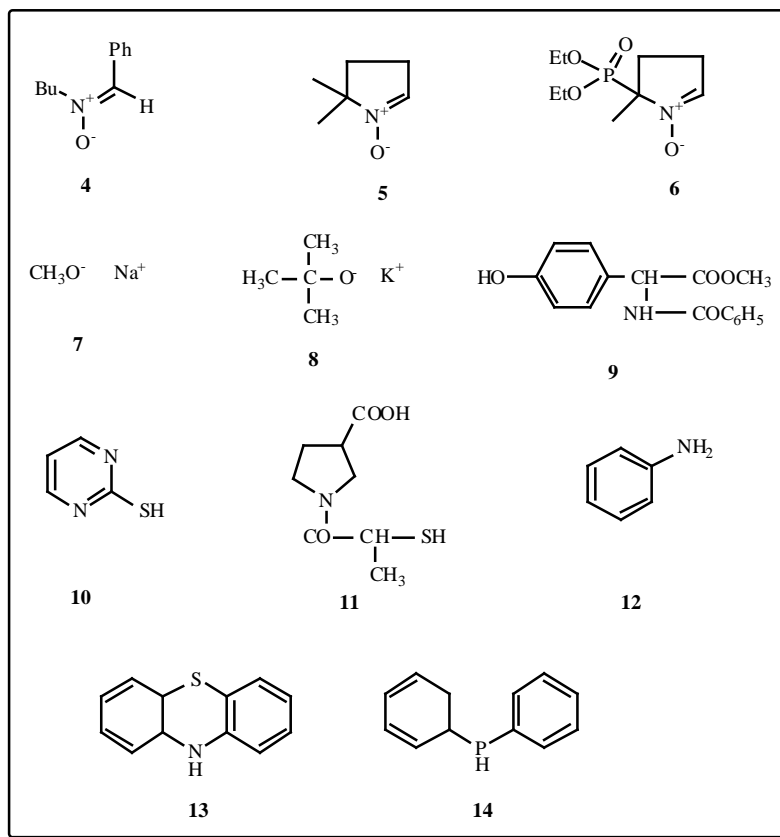
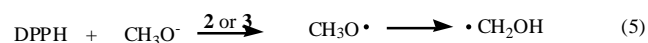


Fig. (1). EPR spectra of the Meisenheimer adduct **15**, showing the non-equivalence of the two nitrogen hyperfine splitting constants ($a_{N1}=1.248$, $a_{N2}=0.659$ mT)

nucleophile attack of sodium methoxide on the picryl moiety as shown in eqn. 4 (a Meisenheimer complex, similar to that observed for attack of cyanide anion) [5].

However, reaction of the nitro-substituted DPPH analogues **2** or **3** with sodium methoxide **7** led to the disappearance of the hydrazyl EPR spectra. The disappearance of **2** and **3** can also be monitored by colour change, from purple to yellow. In the presence of PBN, DMPO or DEPMPO gave EPR spectra containing signals from two nitroxide radicals, characteristic of the trapping of both alkoxy and carbon-centred radicals, (see Table 1) (for example, with DMPO the radical adducts have hyperfine splittings of a_N 1.415, a_H 0.761 and a_N 1.423, a_H 2.058 mT, respectively). These are assigned to the adducts formed by trapping $\text{MeO}\cdot$ and $\cdot\text{CH}_2\text{OH}$. Initial oxidation of methoxide generates $\text{MeO}\cdot$ which is followed by a solvent-assisted 1,2-hydrogen shift to give $\cdot\text{CH}_2\text{OH}$, see eqn 5.



Similarly, the reaction of potassium *t*-butoxide with **2** or **3** in the presence of spin-traps gave EPR signals from both oxygen and carbon-centred radicals. In this case, the initially formed ${}^t\text{BuO}\cdot$ can undergo β -scission to give a methyl radical and propanone, see eqn 6.

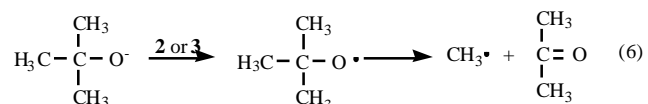


Table 1. EPR Data of the Identified Spin-Adducts^a

Substrate	Oxidant	4	5	6
Sodium methoxide 7	1 (-)			
	2 (+) 3 (+)			
Potassium t-butoxide 8	1 (-)			
	2 (+) 3 (+)			
Tyrosine derivative 9	1 (-)			
	2 (+) 3 (+)			
Mercapto- pyrimidine 10	1 (-)			
	2 (+) 3 (+)			
Captopril 11	1 (-)			
	2 (+) 3 (+)			
Aniline 12	1 (-)			
	2 (+) 3 (+)			
Phenothiazine 13	1 (-)			
	2 (+) 3 (+)			
Diphenyl- phosphine 14	1 (+)			
	2 (+) 3 (+)			

^a Hyperfine splittings in mT, ± 0.005 mT

The results can be explained as follow: sodium methoxide is a strong nucleophile and besides it cannot be oxidized by DPPH, so it will attack the polynitro-ring, forming the Meisenheimer complex (Scheme 1); in the case

of 2 or 3, the high power of oxidation led to the formation of oxygen (and carbon) centered radicals, which are trapped by STs.

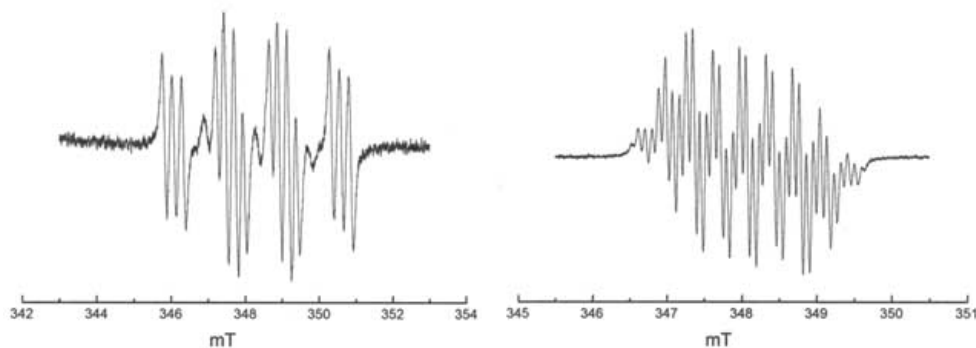


Fig. (2). EPR spectra of the PBN-aniliny spin adduct (left) and the phenothiazenyl free radical (right).

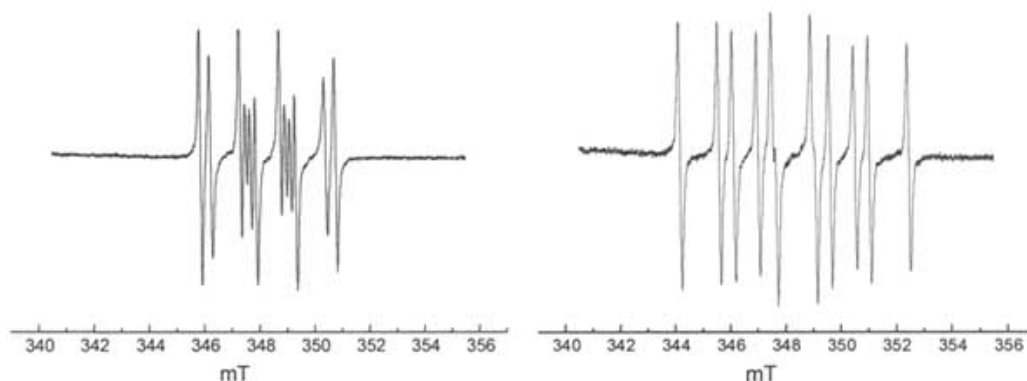


Fig. (3). EPR spectra of the PBN-diphenylphosphinyl spin adduct (left) and the DMPO-diphenylphosphinyl spin adduct (right).

We assume that the anion-radical in our case could be obtained only starting from the hydrazyl radical **1**. In the case of **2** and **3**, the oxidation barrier of the anion is passed by the hydrazyl radicals (E° for MeOH in DMSO is -0.368 and the calculated value for MeO⁻ in water is 1.10 V vs. NHE) [10]. Literature data [11] shows that aromatic radical-anions are possible intermediates in nucleophile aromatic substitution, strong EPR signals being recorded for a sample containing a mixture of a polynitrocompound and an alkoxide. However, tests run on the reduced counterparts of compounds **1-3** show no radical presence.

Use of phenol **9** as substrate gave EPR spectra solely from an oxygen-centred radical-adduct believed to arise from trapping of the appropriate phenoxyl radical.

Sulfur Centered Radicals. Reaction of 1-3 with 2-Mercaptopyrimidine or Captopril

1 does not react with 2-mercaptopyrimidine or captopril, even in the presence of STs (not strong enough to oxidize it), but **2** or **3** gave EPR spectra from the corresponding adducts of 2-mercaptopyrimidine or captopril-S-centered radicals, as judged by the EPR spin-adduct spectra of PBN, DMPO, and DEPMPO.

Nitrogen Centered Radical. Reaction of 1-3 with Aniline or Phenothiazine

Again, **1** cannot oxidize aniline or phenothiazine. The reaction with **2** and **3** led to the formation of the corresponding radicals (see Fig. 2 and 3). The phenothiazenyl radical is stable enough to be directly identified, without the presence of any STs.

Phosphorus Centered Radical. Reaction of 1-3 with Diphenylphosphine

It was shown that DPPH radical can oxidize the diphenylphosphine, leading to the corresponding phosphinyl radical, which has been trapped by PBN and DMPO [12, 13]. Our work used as well DEPMPO in the same purpose.

CONCLUSIONS

DPPH and its congeners can be successfully employed for generation of short-lived oxygen-, sulfur-, carbon-, nitrogen-, and phosphorus-centered radicals. These radicals were characterised by the EPR spin-trapping technique, using as spin-traps PBN, DMPO and DEPMPO.

EXPERIMENTAL

Generation of short-lived radicals was done as described previously [1]. In a typical experiment, to a solution of hydrazyl radical (10^{-4} - 10^{-3} M) and ST (10^{-4} - 10^{-2} M) in DCM was added about 5-10 mg of the nucleophile compound (for the methoxide or *t*-butoxide salts the presence of a crown ether is compulsory). The mixture was stirred by bubbling nitrogen, and the organic layer studied by EPR or UV-Vis. A rapid colour change has been observed, from violet to yellow-red, as the hydrazyl radical is reduced to the corresponding anion or hydrazine.

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