

Use of Nitroso Compounds as Scavengers for the Study of Short-Lived Free Radicals in Organic Reactions

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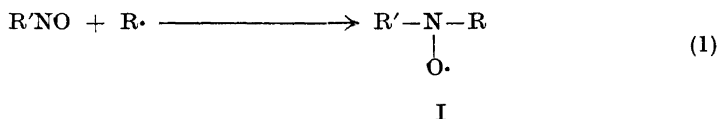
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Nitroso compounds have been used for the trapping and detection of short-lived radicals. The ESR-spectra of the nitroxide radicals formed can advantageously be used for structural elucidation and for reaction mechanism studies.

The usefulness of the nitroxide method is demonstrated by trapping of the intermediate short-lived free radicals which appear in the oxidation of carboxylic acids and aliphatic alcohols with lead tetraacetate, in the α -acetoxylation of ketones with lead tetraacetate, and in the reaction between OH-radicals and a number of organic compounds.

It has been shown that nitroso compounds are effective traps for free radicals¹⁻⁷ (eqn. (1)). In connection with a structural investigation of some nitroxide radicals⁵ we became increasingly aware that this property could advantageously be used for mechanism studies. Thus, a short-lived radical can be transformed into new and more stable species, the ESR-spectrum of which can be recorded without using flow methods or an extremely low temperature. Magnetic nuclei on the α - and in certain cases on the β -carbon atoms lead to informative secondary structures of the main triplet due to the ¹⁴N nucleus of the nitroxide group.



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R' is chosen so that it does not give rise to any hyperfine splittings. 2-Methyl-2-nitrosobutanone-3 and *t*-nitrosobutane have been used in this work. The nitroso compound and the nitroxide radicals formed must be reasonably stable in the reaction medium, and this requirement is met within a wide range of pH, and also in the presence of strong oxidative reagents such as lead tetraacetate and ceric ions.

At room temperature 2-methyl-2-nitrosobutanone-3 is present mainly as an inactive dimer, which has to be split into the monomeric state either thermally or by irradiation with UV light before any reaction according to eqn. (1) can take place.^{5,6} The equilibrium of *t*-nitrosobutane is shifted more towards the monomer as compared with 2-methyl-2-nitrosobutanone-3, and at room temperature the former scavenger is therefore able to react directly without any previous irradiation.⁷ At lower temperature, however, irradiation has to be performed in order to activate the scavenger, even in the case of *t*-nitrosobutane.

Irradiation of a solution containing the nitroso scavengers produced also the symmetric nitroxide radical, R'₂NO•, by splitting off •NO and trapping of the radical R'•. The ESR-spectra of the symmetric nitroxide radicals here concerned exhibited a single ¹⁴N triplet without any secondary splittings. In most cases the concentration of the symmetric nitroxide radicals was rather small, but sometimes their presence gave rise to overlapping peaks which hampered the interpretation of the spectra of unsymmetric nitroxide radicals.

The splitting constant *a*^N of the nitroxide radicals varies widely from about 7 to 28 gauss, depending upon the nature of R and R' (I, eqn. (1)) but is almost constant within each series of derivatives (see Table 1). *a*^N varies somewhat with the solvent, *ca.* 1 gauss, and was found to be larger in polar solvents (Table 2; *cf.* also Ref. 8).

The usefulness of the nitroxide method for the trapping of intermediate short-lived radicals is demonstrated here in the case of the oxidative decarboxylation of carboxylic acids with lead tetraacetate, the α -acetoxylation of

Table 1. *a*^N for nitroxide radicals (R-NO•-R').

| R | R' | <i>a</i> ^N in gauss | Refs. |
|------------------------------|------------------------------|--------------------------------|-----------|
| Alkyl | Alkyl | <i>ca.</i> 14.5-16 | 10, 11 |
| Aryl [⊖] | Alkyl | <i>ca.</i> 11.5-12.5 | 1, 11, 15 |
| Phenyl | Phenyl | 9.7 | 9 |
| COR R-C- COR | COR R-C- COR | <i>ca.</i> 13 | 5 |
| Acyl | Alkyl, aryl | <i>ca.</i> 7 - 8.5 | 3, 12, 13 |
| Alkoxy | Alkyl | <i>ca.</i> 27 - 28 | 2 |
| Alkoxy | Aryl ^a | <i>ca.</i> 14 - 15 | 2, 14 |

^a 2- and 2,6 substitution forces the ring out of plane and changes the *a*^N to *ca.* 17 and 25 gauss, respectively, *i.e.* near the value for the alkoxy-alkyl series.

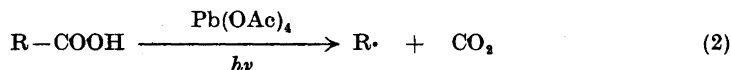
Table 2. Splitting constants, a^N , in different solvents.

| Solvent | $[(\text{CH}_3)_2(\text{COCH}_3)_2\text{C}]_2\text{NO}\cdot$ | $(t\text{-Bu})_2\text{NO}\cdot$ |
|---------------------------------|--|---------------------------------|
| H ₂ O | 15.02 | 16.97 |
| H ₂ O/DMSO 1:1 | 14.95 | 16.68 |
| MeOH | 14.41 | 16.09 |
| DMSO | 14.41 | 15.56 |
| HOAc | 14.40 | — |
| EtOH | 14.31 | 15.93 |
| CHCl ₃ | 14.16 | 15.85 |
| CH ₂ Cl ₂ | 14.16 | 15.65 |
| C ₆ H ₆ | 13.98 | 15.30 |

ketones by lead tetraacetate and ceric ions, the oxidation of aliphatic hydroxyl compounds with lead tetraacetate, the reaction of photochemically generated OH-radicals with a number of organic compounds and the homolytic fission of some organometallic compounds.

OXIDATIVE DECARBOXYLATION OF CARBOXYLIC ACIDS WITH LEAD TETRAACETATE

This reaction, which is known to proceed via radicals,¹⁶ eqn. (2)



was tested first. In accordance with expectation nitroxide radicals were formed on irradiation by UV light of a solution of lead tetraacetate, the carboxylic acid and the nitroso compound in methylene chloride or chloroform. At -40°C , the radicals R \cdot were trapped as unsymmetric nitroxide radicals (see Table 3). Fig. 1 shows the ESR-spectrum obtained with propionic acid. The secondary splittings from trapped ethyl radicals constitute a large triplet (1:2:1) further split into a narrow quartet (1:3:3:1).

The ESR-spectra obtained at room temperature were completely different and exhibited in most cases a secondary doublet splitting. The a^N values

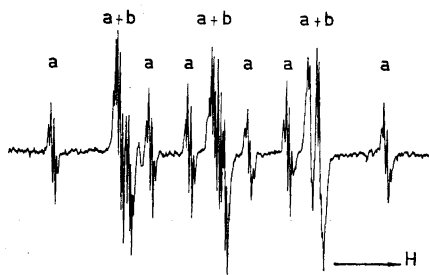


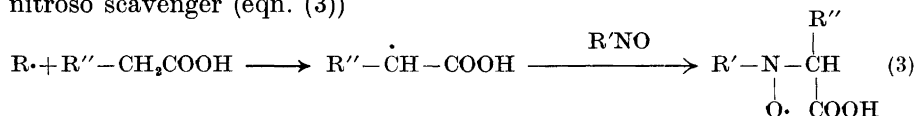
Fig. 1. ESR-spectrum of the nitroxide radicals formed by trapping of the radicals produced in the lead tetraacetate oxidation of propionic acid at -35°C . Scavenger: 2-methyl-2-nitrosobutanone-3. Solvent: CH₂Cl₂. Two radical species have been trapped. Spectrum caused by trapped: a) CH₃-CH₂ \cdot radicals, b) CH₃- $\dot{\text{C}}\text{H}$ -COOH radicals.

Table 3. Nitroxide radicals formed by trapping of the radicals produced in the lead tetracetate oxidation of carboxylic acids. Scavenger: 2-methyl-2-nitrosobutane-3. The samples were irradiated by UV light *in situ* in the ESR-cavity.

| Acid | Temperature -40°C | | | | Temperature +25°C | | | | |
|---------------|---|-----------------------------|---|---|---------------------------------|--|-----------------------------|---|-------------------------------|
| | Radical R=(CH ₃) ₂ CCOCH ₃ | a _N ^H | a _α ^H in gauss | a _β ^H in gauss | Solvent | Radical R=(CH ₃) ₂ CCOCH ₃ | a _N ^H | a _α ^H in gauss | Solvent |
| Acetic | $\dot{\text{R}}\text{NO}-\text{CH}_3$ | 15.4 | 12.9 (q) | — | CH ₃ Cl ₂ | $\dot{\text{R}}\text{NO}-\text{CH}_3$ | 15.1 | 12.2 (q) | CHCl ₃ |
| Propionic | $\dot{\text{R}}\text{NO}-\text{CH}_2-\text{CH}_3$ | 14.9 | 10.4 (t) | 0.51 (q) | » | $\dot{\text{R}}\text{NO}-\text{CH}_2\text{COOH}$ | 12.9 | 4.99 (t) | HOAc |
| Isobutyric | $\dot{\text{R}}\text{NO}-\text{CH}(\text{CH}_3)_2$ | 14.7 | 1.66 (d) | 0.1 (m) | » | $\dot{\text{R}}\text{NO}-\text{CH}(\text{CH}_3)\text{COOH}$ | 12.9 | 2.1 (d) | C ₆ H ₆ |
| Isovaleric | $\dot{\text{R}}\text{NO}-\text{CH}_2\text{CH}(\text{CH}_3)_2$ | 14.9 | 10.6 (t) | 0.62 (d) | » | | | | |
| Octanoic | $\dot{\text{R}}\text{NO}-(\text{CH}_2)_6\text{CH}_3$ | 14.8 | 10.3 (t) | 0.67 (t) | » | $\dot{\text{R}}\text{NO}-\text{CH}(\text{CH}_2)_5\text{CH}_2\text{COOH}$ | 12.9 | 4.9 (d) | C ₆ H ₆ |
| Phenyl acetic | $\dot{\text{R}}\text{NO}-\text{CH}_2\text{Ph}$ | 14.7 | 8.32 (t) | — | » | | | | |

d = doublet, t = triplet, q = quartet, m = multiplet

were slightly smaller than those of the nitroxide radicals obtained at -40°C (Table 3). These radicals are obviously produced by abstraction of one α -hydrogen atom from the acid, and the coupling of the secondary radical with the nitroso scavenger (eqn. (3))



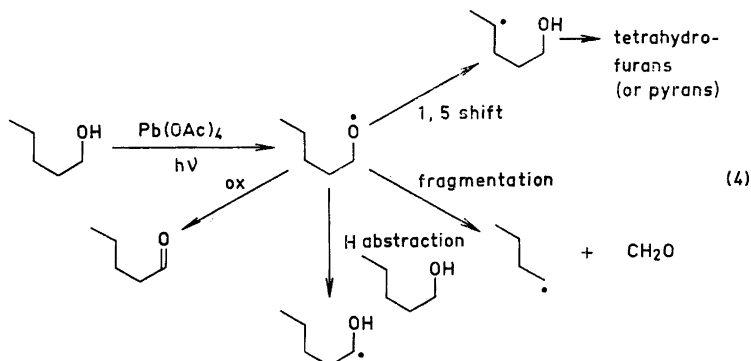
The results obtained with the carboxylic acids are in agreement with those of Heusler *et al.*¹⁷ who carried out the decarboxylation at -180°C , and recorded the spectra of the primary and secondary radicals directly.

α -ACETOXYLATION OF KETONES BY LEAD TETRAACETATE

Radical¹⁶ as well as ionic mechanisms have been proposed for the α -acetoxylation of ketones by lead tetraacetate (see Ref. 16 for a review). The absence of dimers has been used as an argument in favour of an ionic mechanism, and in cases where small amounts have been detected, *e.g.* 7.5 % from acetyl acetone,¹⁸ their formation is thought to proceed *via* carbonium ions, *i.e.* $\text{CH}_3\text{COCH}^+\text{COCH}_3$.¹⁶ We can now present evidence that radicals appear during the oxidation, and this fact in combination with dimerization supports the radical mechanism. Certainly, the first step of the reaction constitutes a one-electron transfer from the ketone to Pb^{4+} . The radicals from the lead tetraacetate oxidation of 1,3-dicarboxyl compounds were trapped by 2-methyl-2-nitrosobutanone-3 at room temperature. The spectra of the nitroxide radicals exhibited the expected secondary doublet splitting from trapped radicals of the structure $\text{R}^1\text{-CO-}\dot{\text{C}}\text{H-CO-R}^2$ (for acetyl acetone: $a^{\text{N}}=13.2$ g, $a^{\text{H}}=3.53$ g). This reaction can also be carried out by ceric ions.^{5,19}

OXIDATION OF ALIPHATIC HYDROXYL COMPOUNDS BY LEAD TETRAACETATE

This reaction gives a variety of products formed *via* several postulated secondary radicals (eqn. (4)),



and the presence of more than one radical species is indicated by the overlapping spectra recorded from several alcohols. Some of the reactions are favoured for certain alcohols. Thus, the oxidation of methanol at -70°C in methylene chloride gave rise to methoxy radicals which were trapped by the nitroso scavenger 2-methyl-2-nitrosobutanone-3 (see Fig. 2). The nitroxide radicals

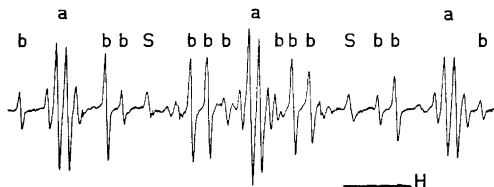



Fig. 2. ESR-spectrum of the nitroxide radicals formed by trapping of the radicals produced in the reaction between methanol and lead tetraacetate in CH_2Cl_2 at -70°C . Scavenger: 2-methyl-2-nitrosobutanone-3.

- a) Quartets (1:3:3:1) from nitroxide radicals formed from $\text{CH}_3\text{O}\cdot$ radicals derived from methanol.
 b) Lines originating from nitroxide radicals formed from $\text{CH}_3\cdot$ radicals derived from lead tetraacetate.
 S) Lines caused by the symmetric nitroxide radical derived from the scavenger.

Table 4. Nitroxide radicals formed by trapping of the alkoxy radicals produced in the lead tetraacetate oxidation of alcohols. Scavenger: 2-methyl-2-nitrosobutanone-3. Solvent: methylene chloride. Temperature: -70°C . The samples were irradiated by UV light *in situ* in the ESR-cavity.

| Alcohol | Trapped radical | Splitting constants in gauss a^{N} | a_{α}^{H} |
|---------------------|---|--|-------------------------|
| Methanol | $\text{CH}_3\text{O}\cdot$ | 29.4 | 1.4 (q) |
| Methanol- d_4 | $\text{CD}_3\text{O}\cdot$ | 29.4 | unresolved |
| Ethanol | $\text{CH}_3\text{CH}_2\text{O}\cdot$ | 28.9 | 1.1 (t) |
| Propanol | $\text{C}_2\text{H}_5\text{CH}_2\text{O}\cdot$ | 29.1 | 1.3 (t) |
| Isopropanol | $(\text{CH}_3)_2\text{CHO}\cdot$ | 28.5 | unresolved |
| Butanol | $\text{C}_3\text{H}_7\text{CH}_2\text{O}\cdot$ | 29.1 | 1.3 (t) |
| Isobutanol | $(\text{CH}_3)_2\text{CHCH}_2\text{O}\cdot$ | 29.2 | 1.4 (t) |
| <i>s</i> -Butanol | $(\text{C}_2\text{H}_5)_2\text{CHCHO}\cdot$ | 28.7 | unresolved |
| <i>t</i> -Butanol | $(\text{CH}_3)_3\text{CO}\cdot$ | 27.0 | — |
| Pentanol | $\text{C}_4\text{H}_9\text{CH}_2\text{O}\cdot$ | 29.0 | 1.3 (t) |
| 2-Methylbutanol | $(\text{C}_2\text{H}_5)(\text{CH}_3)\text{CHCH}_2\text{O}\cdot$ | 29.1 | 1.5 (t) |
| 3-Methylbutanol | $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{O}\cdot$ | 29.0 | 1.3 (t) |
| 2-Methyl-2-butanol | $(\text{CH}_3)_2(\text{C}_2\text{H}_5)\text{CO}\cdot$ | 27.2 | — |
| 2-Methyl-2-pentanol | $(\text{CH}_3)_2(\text{C}_3\text{H}_7)\text{CO}\cdot$ | 27.1 | — |
| Octanol | $(\text{C}_7\text{H}_{15})\text{CH}_2\text{O}\cdot$ | 29.0 | 1.2 (t) |
| Cyclohexanol |  | 28.5 | unresolved |

t=triplet, q=quartet

formed exhibited the large nitrogen splitting constant characteristic for alkoxy-nitroxide radicals (*cf.* Table 1). Alkoxy radicals were also trapped from a number of other alcohols. The splitting constants of the nitroxide radicals formed in these reactions are collected in Table 4. The alkoxy radicals derived from tertiary alcohols were found to give rise to nitroxide radicals with somewhat smaller a^N values as compared with those derived from primary and secondary alcohols.

The oxidation of 2-phenyl-ethanol-1 gave rise to nitroxide radicals with a secondary triplet (1:2:1), $a^H=8.2$ g and $a^N=14.7$ g, indicating the presence of the radical $\text{Ph}-\dot{\text{C}}\text{H}_2$ from the fragmentation path $\text{Ph}-\widehat{\text{C}}\text{H}_2-\text{CH}_2-\widehat{\text{O}}$.

At room temperature, aliphatic primary alcohols with a carbon chain of more than four atoms were found to give rise to secondary doublets very probably as the result of the abstraction of a hydrogen atom from a methylene group *via* a 1,5-shift. This interpretation was supported by the result obtained with hexanol-1,1- d_2 . The ESR-spectrum observed in this case exhibited also the doublet splitting found with a sample of non-deuterated hexanol indicating that the hydrogen atoms on carbon atom 1 are not involved.

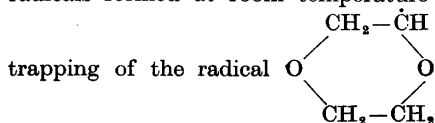
In this connection it will be emphasized that radicals are also formed from $\text{Pb}(\text{OAc})_4$, very probably by photolysis. These radicals give sometimes rise to a more or less disturbing background of nitroxide radicals. The radicals derived from $\text{Pb}(\text{OAc})_4$ include methyl radicals * (see Fig. 2) and a species of unknown origin which forms a nitroxide radical exhibiting a doublet splitting of about 2 gauss. No radicals could be detected from methylene chloride or chloroform.

TRAPPING OF SHORT-LIVED RADICALS FORMED IN THE REACTION BETWEEN ORGANIC COMPOUNDS AND OH-RADICALS

As the nitroxide method consumes only small quantities of the parent material, as compared with flow-methods, it was thought that the former method could be used in the study of the short-lived radicals formed in the reaction between organic compounds and OH-radicals. (For a review on flow-methods for generating radicals by abstraction with OH-radicals, see Ref. 20). In the experiments described here the nitroxide radicals were produced by UV irradiation of a solution containing the parent material, the nitroso scavenger and H_2O_2 .⁶ After being generated by the light-induced cleavage of H_2O_2 , the OH-radicals react with the organic substance, and radicals are formed which are eventually trapped as nitroxide radicals stable enough to be detected by ESR-spectroscopy. By this technique the radicals formed in the reaction between OH-radicals and some alcohols, ketones, and ethers were trapped. The results are generally in agreement with those obtained with the flow-methods,²⁰ and indicate the formation of radicals by abstraction of α - or β -hydrogen atoms. Thus, the radical $\cdot\text{CH}_2\text{OH}$ from methanol gave rise to a nitroxide radical with $a^N=13.9$ g, $a^H=5.57$ g (1:2:1). From acetone the

* Methyl radical are also observed with samples of $\text{Pb}(\text{OAc})_4$ recrystallized from benzene, and virtually free from acetic acid otherwise present for stabilization of lead tetraacetate.

Fig. 3. ESR-spectrum of the nitroxide radicals formed at room temperature by



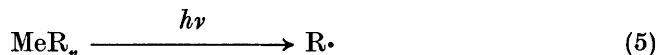
produced in the reaction between photochemically generated OH-radicals and 1,4-dioxane. Solvent: CHCl_3 . Scavenger: 2-methyl-2-nitrosobutanone-2.



radical $\cdot\text{CH}_2\text{COCH}_3$ was trapped. The splitting constants were: $a^{\text{N}}=14.1$ g, $a^{\text{H}}=7.60$ g (1:2:1). In these experiments the scavenger was 2-methyl-2-nitrosobutanone-3. The nitroxide radicals formed by trapping of the radicals produced in the reaction between OH-radicals and 1,4-dioxane is shown in Fig. 3.

HOMOLYTIC FISSION OF METAL-CARBON BONDS

Irradiation by UV light of organometallic compounds produces radicals which could be trapped by the nitroso scavengers



Me = Pb, Hg, Sn

Alkyl radicals were easily trapped at room temperature. By carrying out the reaction at -70°C in methylene chloride it was also possible to trap aryl radicals derived from tetraphenyl lead, bis-(*p*-dimethylaminophenyl) mercury, bis-(*p*-methoxyphenyl) mercury, bis-(*o*-methoxyphenyl) mercury, and tetraphenyl tin.

CONCLUSIONS

The advantage of the nitroxide method over flow methods for the detection of short-lived radicals is mainly connected with the much smaller consumption of material. Indeed, very small amounts only are needed. The nitroxide method is very simple to handle, and the reaction can in many cases be performed at room temperature. However, there are also some limitations inherent to the method. The main interaction of the unpaired electron involves the nitrogen (and oxygen) atom of the nitroxide group, and the secondary splittings caused by the trapped radical are therefore rather small, as compared with the hyperfine structures of the untrapped radical. This situation will imply a reduction of the information available, and might sometimes reduce the efficiency of the method as regards the elucidation of the structure of the radicals concerned. Further, the nitroxide radicals have been found to be unstable in the presence of an excess of redox reagents such as SH-compounds and certain metal ions.

EXPERIMENTAL

Many of the compounds used were commercial preparations which were used as supplied or after purification. 2-Methyl-2-nitrosobutanone-3 was prepared as described by Aston *et al.*,²¹ and *t*-nitrosobutane according to Emmons.²²

The ESR-spectra were obtained as described elsewhere.^{5,6}

The radicals were prepared by dissolving the parent substance together with the nitroso scavenger in the appropriate solvent and adding the oxidizing reagent. Irradiation of the samples was performed *in situ* by a high pressure mercury lamp (Osram HB-200).

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